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State of Knowledge on Molecular Adaptations to Exercise in Humans: Historical Perspectives and Future Directions

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Abstract

For centuries, regular exercise has been acknowledged as a potent stimulus to promote, maintain, and restore healthy functioning of nearly every physiological system of the human body. With advancing understanding of the complexity of human physiology, continually evolving methodological possibilities, and an increasingly dire public health situation, the study of exercise as a preventative or therapeutic treatment has never been more interdisciplinary, or more impactful. During the early stages of the NIH Common Fund Molecular Transducers of Physical Activity Consortium (MoTrPAC) Initiative, the field is well-positioned to build substantially upon the existing understanding of the mechanisms underlying benefits associated with exercise. Thus, we present a comprehensive body of the knowledge detailing the current literature basis surrounding the molecular adaptations to exercise in humans to provide a view of the state of the field at this critical juncture, as well as a resource for scientists bringing external expertise to the field of exercise physiology. In reviewing current literature related to molecular and cellular

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processes underlying exercise-induced benefits and adaptations, we also draw attention to existing knowledge gaps warranting continued research effort.

Introduction

To date, regular physical activity (bodily movement which results in energy expenditure) is one of the most efficacious methods of improving and maintaining human health. Physical activity impacts a wide variety of physiological systems and improves health and health-related quality of life across a wide variety of clinical conditions. In particular, physical exercise [a subset of physical activity that is planned, structured, repetitive, and performed with the intent to improve health or fitness (301)] demonstrates the greatest benefits; these often present in a linear, dose-dependent fashion (1396). The health benefits of physical exercise are wide-ranging, impacting numerous physiological systems and influencing the progression of chronic conditions including (but not limited to) cardiovascular disease (CVD), neurocognitive decline, psychological disorders, musculoskeletal disorders, metabolic syndrome, type 2 diabetes (T2D), some forms of cancer, and all-cause mortality (968, 1342). Thus, it is well-established that exercise is a powerful intervention to improve various aspects of health throughout the lifespan.

Despite the tremendous health value of exercise, several challenges persist in harnessing the full potential of exercise as a therapeutic for the individual and in reducing healthcare-related costs at the societal level. Unfortunately, only a minority of individuals meet minimum guidelines for exercise participation in the United States and in developed countries worldwide (1056, 1333). Compounding this problem, a significant portion of individuals do not even receive basic exercise/physical activity recommendations from their healthcare provider(s) (572, 940), despite increasing evidence that inactivity and physical deconditioning should be considered as a unique risk factor in medical decision making (657, 776). Given these issues, implementation of successes from exercise clinical trials into clinical practice and community programs has remained largely elusive.

In addition to focusing efforts on increasing adherence/implementation, a significant opportunity exists to understand how exercise improves health (74). While it is known that exercise impacts a vast array of physiological functions and pathobiological risks, many questions remain regarding the cellular and molecular mechanisms driving these effects. A pharmaceutical that fully mimics the wide-ranging benefits of exercise across physiological health and other domains of wellness is unlikely to exist (248, 483, 536, 1397). Still, because of its multipotent effects on the body’s organ systems, exercise has been proposed by several investigators as a “polypill” for improving health (406, 1006, 1442). As outlined previously (74), opportunities surrounding an enhanced understanding of the mechanisms underlying the health benefits of exercise may lead to improving exercise prescriptions based on individual characteristics that influence the extent of exercise adaptations (i.e., “exercise responsiveness”), optimization of exercise as a therapy, and development or repurposing of adjuvant pharmaceuticals to enhance exercise tolerance in the presence of a comorbid condition.

In view of these expansive opportunities, the National Institutes of Health (NIH), via the NIH Director's Common Fund, recently funded a landmark study known as the Molecular Transducers of Physical Activity Consortium (MoTrPAC) (1146). The stated aim of MoTrPAC is to: "catalogue the biological molecules affected by exercise in people, to assemble a comprehensive map of the molecular changes that occur in response to movement and, when possible, relate these changes to the benefits of physical activity. This molecular map will contain the many molecular signals that transmit the health effects of physical activity, and indicate how they are altered by age, sex, body composition, fitness level, and exposure to exercise. The program also aims to develop a user-friendly database that any researcher can access to develop hypotheses regarding the mechanisms whereby physical activity improves or preserves health, facilitating investigator-initiated studies and catalyzing the field of physical activity research (1146)." The MoTrPAC study is expected to generate an abundance of new data related to the fundamental molecular biology of human physiologic responses to exercise in several body tissues. Still, this endeavor is only getting underway; thus meaningful outputs of the study remain years away. The objectives of the present article are thus to assemble a compendium of the current state of knowledge surrounding the biological responses and adaptations to exercise in humans, to provide a comprehensive contextual resource for newcomers to the field, and to outline potential opportunities for advancing the field in the decades to come.

A Brief History of the Field

Exercise as ancient medicine

The history of exercise physiology overlaps considerably with that of human medicine. In a recent review of the contributions of ancient civilizations to the American College of Sports Medicine's ongoing "Exercise is Medicine" initiative (1312), Charles Tipton (a recognized leader in the field of exercise physiology) stated that physicians in many early civilizations prescribed exercise, believing that it could promote health and avoid diseases. This belief is thought to date back nearly 3000 years BCE. Evidence suggests that "medical gymnastic" breathing exercises were often prescribed in China during this period (1312). In approximately 7th century BCE, ancient Indian physician Susruta declared that exercise "should be taken daily," depending on the health and state of the individual (1313). Interestingly, even in these early days, excessive exercise was warned against, for fear of exhaustion or even death (1312). Nonetheless, the fact that bodily movement was touted as prevention for disease and promotion of healthy aging across geographies and ethnic groups demonstrates the fundamental human "drive to move." Thus it is not surprising, as later philosophers famously noted, that disease follows when this drive is resisted or ignored.

Historians seem to agree that the ancient Greek and Roman civilizations contributed most significantly to the foundation of the field. Herodicus (ca. 500 BCE) is often called the "Father of Sports Medicine" for his approach to integrate physical fitness (e.g., Greek gymnasiums) with medicine (116, 455). Hippocrates (460–370 BCE), a contested student of Herodicus, continued this practice and is credited with composing a detailed exercise prescription to aid a diseased patient. Ultimately, Galen (130–210 CE), a Greek physician who lived in the Roman Empire, drew from the teachings of his forebears and created a

lasting impact on the world's culture by imprinting exercise into prescription for numerous diseases (116). He described the "naturals" (healthy bodily processes), "nonnaturals" (external stimuli such as activity and diet that bring peace and health), and the "contra-naturals" that disrupt them. Galen also distinguished exercise from movement in general by its vigorous nature requiring noticeable exertion, a critical distinction relevant to describing and prescribing exercise versus general physical activity guidelines. Galen's influence is believed to have lasted at least 14 centuries (1312).

The Renaissance

Medical advancements throughout the Renaissance period (sometimes called the Scientific Revolution) greatly enhanced the understanding of human health. In 1543, Andreas Vesalius published the first human anatomy text, *De Humani Corpus Fabrica*. This text, along with Vesalius' other contributions, is credited with revolutionizing the medical community's understanding of cardiovascular, neural, and musculoskeletal anatomy (152, 887, 936). His unique approaches to dissection, comparative anatomy, and pedagogy (1196) earned him the moniker "Father of Modern Anatomy" and are believed to have been pivotal in surgical practice (1349). Shortly thereafter, Santorio Santorio (1561–1636), his name often written as variations on this theme, studied the basics of human metabolism (364). He famously constructed a life-size balance and tracked changes in his body mass with perturbations brought on by daily living (291). Through this work, Santorio laid the foundation for studies of metabolism, nutrition, and dietetics, and he further contributed to exercise physiology through his documentation of perspiration (291). The Scientific Revolution period also saw William Harvey publish insights into the mechanics of the human circulatory system in 1628's *De Motu Cordis* (1009, 1170) and Antonie van Leeuwenhoek's invention of the microscope, allowing observation of fine microstructures [most pertinently to exercise, the sarcolemma and striations of whale skeletal muscle fibers (1087)]; thus new knowledge began to advance the teachings of Galen and the ancient world.

Enormous contributions to the field came from Antoine Lavoisier (1743–1794), a Frenchman recognized as the Father of Modern Chemistry and Combustion. Lavoisier is partially credited with the discovery of oxygen, an element he termed "oxigene," along with his contemporaries Joseph Priestly and William Scheele (1182, 1183). He also designed the first proper calorimeter in 1784, which he put to good use the next decade in what is considered the first true exercise physiology experiment (672). Tracking consumption of oxygen, Lavoisier demonstrated a sizable (more than tripled) increase in resting respiration when a subject continually pressed a foot pedal (1416). His wife reportedly observed, sketched (Figure 1), and took notes on all experiments, aiding in Lavoisier's rise to prominence as an innovative scientist (1416). Unfortunately, since his research violated (much less debunked) the prevailing phlogiston theory (based on a concept that toxic gas was expelled rather than life-giving oxygen inhaled), Lavoisier was executed as the French Revolution raged on in 1794.

The golden age of discovery

Spurred on by recently acquired knowledge, researchers in the 1800s continued to progress down the path toward establishing exercise physiology as a distinct discipline, then referred

to as physical education, hygiene, or bodily exercise. Physiologist Claude Bernard (1813–1878) led the way, with his discoveries related to digestion, metabolism, circulation, and the nervous system engendering the concept of “le milieu intérieur,” or internal environment that all bodily systems strive to maintain despite constant fluctuations in the external environment (269). This idea eventually developed into the concept of homeostasis, now a central tenet of exercise physiology. Bernard called particular attention to the nervous system as the central regulator of the interior milieu.

Concurrently, knowledge of the workings of the cardiovascular system was improved with Adolph Fick’s application of physic principles to cardiac dynamics, enabling a better understanding of gas exchange and, eventually, the measurement of cardiac output (1186). Fick’s observation that, if the amount and concentration of a substance carried in blood are known, the volume of blood can be calculated (1346) is aptly applied to exercise physiology in an equation linking oxygen uptake to the product of cardiac output and the arteriovenous oxygen difference, that is, = oxygen consumption (Vo_2) = cardiac output (Q) ÷ arteriovenous oxygen difference ($a–vo_2$). Further insight came from studies in energy expenditure conducted by chemist Wilbur O. Atwater and physicist Edward B. Rosa. Through his career, Atwater (1844–1907) conducted hundreds of studies related to metabolism (some at rest, others during cycling exercise), famously running a calorimeter continuously for days with lab staff rotating through the role of test subject. Atwater’s work in combustion help determines the caloric value of macronutrients, with clear implications for exercise metabolism and sports nutrition (193). This series of breakthroughs highlight the integrative nature of exercise as an activity involving multiple body systems. Thus it is not surprising that, even today, we continue to identify mechanisms of cross talk between body tissues in response to exercise.

Work physiology in the early 20th century

The turn of the century brought on an era of interest in human performance and resilience, and several notable researchers rose to prominence during this time. For example, John Scott Haldane (1860–1936) examined conditions that challenge the limits of respiratory physiology (e.g., altitude, deep diving, air composition of sewers and mines) (1417). Haldane is likely best known for developing an apparatus to quantify gas exchange (513). Decades later, the device would be optimized by Per Scholander (1164) and others (1187), providing more efficient measurement, greater portability, and overall increased accuracy in assessing metabolic processes.

Great strides were made during this time in the Scandinavian region, with the charge led by August Krogh (1874–1949), sometimes considered the Father of Exercise Physiology (61). Trained in zoology and physics in Denmark, Krogh imbued his work in human physiology with this knowledge, which allowed him a unique perspective on existing and arising scientific problems. This, in combination with his skills in “visual thinking” (1093) enabled him to design and build innovative tools to facilitate research, including a microtonometer (806), a magnetically braked cycle ergometer, and a balance impressively precise enough to detect changes in body mass down to approximately 2 g (1093). During his training and later career, Krogh worked closely with his wife Marie in the study of respiration

and oxygen dynamics (605, 1163). Together they published a series of papers entitled the "Seven Little Devils," so named because they refuted the mechanism of active gas exchange proposed by Krogh's mentor, Christian Bohr (464). Namely, the Kroghs demonstrated that simple diffusion was responsible for gas exchange by optimizing the measurement of partial pressure of oxygen in the alveolar air and arterial blood. Marie went on to elaborate on the plasticity of this system during periods of high demand (e.g., muscular work and/or low oxygen availability) to earn her doctoral degree in 1914 (1163), while August continued to study the mechanics of oxygen delivery and earned 1920s Nobel Prize in Physiology or Medicine after elegantly demonstrating that muscle capillaries open and close based on tissue needs, that is, capillary recruitment (1093). Krogh himself trained a number of notable individuals that shaped the Scandinavian future of exercise physiology, including a trio of motivated individuals he nicknamed "The Three Musketeers" (1214), which included Erik Hohwü Christensen, Marius Nielsen, and Erling Asmussen. Krogh's profound influence led to an Institute at the University of Copenhagen dedicated in his name in 1970 (1214).

Exercise physiology as a so-named discipline had still not yet taken shape, but textbooks such as the Physiology of Bodily Exercise and the Physiology of Muscular Work had begun to be published and would receive repeated revisions in their subsequent iterations. A notable contributor during this period was Archibald Vivian (A.V.) Hill (1886–1977), a so-called "giant" in the field of exercise physiology (94). Hill specialized in skeletal muscle thermodynamics, mechanics, and metabolism, laying the groundwork for understanding the various biochemical energy systems and setting into motion a "Revolution in Muscle Physiology" (565). Hill's collaborative work in muscle heat production with biochemist Otto Meyerhof earned the Nobel Prize in 1922 (94). Hill is also credited with the concept of maximal oxygen consumption (Vo_2max) as a plateau in oxygen uptake despite increased workload (95). This measurement went on to be not only a robust correlate of endurance performance but the most powerful independent predictor of frailty and mortality (954), further linking exercise capacity to human health.

Biographers of Hill consistently comment on his light-hearted nature and enjoyable approach to his work. He famously made bold conjectures (731) and even "challenges" to the field (567), appreciating that scientific hypotheses are made to be disproven to lead to breakthroughs (94). Hill himself conceded, when questioned why he bothered studying athletes, exercise, and muscles, that the work was "amusing" (94). Pursuing his amusement, Hill set into motion the field of applied exercise physiology. In this realm, Hill enjoyed studying athletes because he viewed them as exemplars of the limits of human performance and could repeat their performances with consistency. His conjecture that exercise physiology, due to its integrative, complex, and fascinating nature, might recruit bright minds from other disciplines (94, 409) has proven itself time and again as the field enters the era of interdisciplinary team science.

The study of athletes was further expanded by the legendary Harvard Fatigue Laboratory (HFL), which set out to build a fundamental understanding of physiological stresses endured by industrial workers and army soldiers (409). During their two-decade tenure in the basement of Harvard University's Business School, the HFL team generated over 300 scientific publications (650, 1314), including series entitled "Blood as a Physicochemical

System” and “Studies in Muscular Activity”. The HFL was founded in 1927 by Lawrence J. Henderson and led by David Bruce Dill, who served as director of research. Initially assembled to elucidate the mechanisms underlying fatigue in the industrial worker, the HFL team quickly came to appreciate that no population better demonstrated fatigue exposure and resilience than athletes (1157). They took advantage of their location, studying blood gas composition and hemodynamics in Boston marathon runners, such as seven-time victor Clarence DeMar.

As American culture changed and World War II loomed, the HFL focus shifted from industry to military physiology, necessitating examination of various environmental challenges. The facilities enabled the research team to reproduce these with chambers designed to simulate high altitude and extreme cold and heat (409), supplemented by field research projects such as desert walks, altitude exposure, and artic simulations. HFL researchers established the precedent of subjecting themselves to many of their experiments (in fact, with relatively little effort, it is possible to discern which members of the HFL staff participated as subjects, since many publications include individual subject initials in data tables). The advantages of this practice were several (among them convenience of access and demonstration of feasibility/fairness of protocols), but, most importantly, this practice allowed the HFL to create a consistent and robust database for internal validation of repeated measurements and comparisons across conditions (650).

Upon its dissolution in 1947, the HFL propelled its staff into leadership positions across the United States, and they continued to be productive researchers and mentors. Some estimate that most American exercise physiology laboratories can “trace their lineage to the Fatigue Lab in only two or three academic generations” (650). Fittingly, the HFL’s reputation is held in high esteem, its scientific prowess bolstered by legends of treadmill-running laboratory dogs (650) and the infamous 40-40-40 Club, membership in which was reserved for those who could tolerate the extreme challenges of −40 °C, 40,000 ft, and walking 40 miles in 12 h (107, 650).

The modern era

The 1950s brought Watson and Crick’s discovery of the chemical structure of DNA, the establishment of the American College of Sports Medicine, and Roger Bannister’s record-setting mile under four minutes. The field was poised to take advantage of all three, with renewed interest in human health and performance and a scientific direction toward a Molecular Revolution that continues to advance. Skeletal muscle in particular began to receive notable attention (516). Hugh E. Huxley’s sliding filament theory, published in 1954 (616), provided a mechanical perspective on the workings of contractile elements actin and myosin in skeletal muscle (1408). Not long after, Johannes Bergström introduced the muscle biopsy technique to extract muscle tissue from living individuals (112), enabling much of the field’s foundation in mechanisms of exercise adaptations. This contribution allowed our understanding to extend beyond more accessible tissues such as blood and has been optimized (279, 378) and enriched over time with the growing appreciation for the various roles of skeletal muscle in metabolism and signaling.

A frontrunner in the studies of muscle biology was Bengt Saltin (1935–2014), a trainee of one of August Krogh's Musketeers, Erik Hohwü-Christensen (1156). Throughout his career, Saltin examined human performance, adaptations to training, and maladaptations to unloading in the context of the cardiovascular and skeletal muscle systems. He was notably interested in the mechanisms underlying such phenomena (including, but not limited to, skeletal muscle fiber type composition and selective use of energy pathways), many of which remain relevant in today's research landscape (658). Saltin served as head of the Copenhagen Muscle Research Center (CMRC), established with funds to encourage Danish leadership in international collaboration and aimed to understand mechanisms of skeletal muscle physiology. Due to funding restrictions in Denmark, it did not last more than a decade (1994–2004), but it has left a lasting impact on the field. Studies during its heyday and in the years that followed truly blended exercise physiology with medicine (660), realizing the ideals of early historians and physicians such as Susruta and Hippocrates. For instance, a team of CMRC alumni, led by Bente Pedersen, coined the term "myokines" after identifying that muscle-derived IL-6 was upregulated and secreted during contractile activity and had notable interactions with other tissues to influence glucose metabolism (1020).

Several visiting scholars from the U.S. collaborated with the CMRC, including David Costill and Phil Gollnick (78, 1156). Costill is credited with popularizing the Bergström muscle biopsy technique in the U.S., applying it to the investigation of metabolism during aerobic exercise (280). The lay articles that accompanied his scientific publications made performance- and health-related research accessible to nonacademicians and helped to endorse the American Running Boom of the early 1970s. Gollnick took a basic science approach to the mechanisms underlying exercise, supplementing human work (471) with research in animal models (48). Contemporary John Holloszy's contributions to exercise and aging provided a basic understanding of metabolic pathways involved in training and detraining (509), enabling a more complete understanding of carbohydrate bioenergetics that support exercise (583). These researchers directed 20th century exercise physiology in the United States, and the current research landscape continues to be shaped by their direct academic descendants.

A major motivator for increased understanding of skeletal muscle exercise biology was the more widespread use of the muscle biopsy sampling technique in human subjects research. Key molecular mechanisms of muscle adaptation, often first revealed in preclinical studies, have proven instrumental in guiding human research in this direction. Notably, Frank Booth and colleagues investigated the influence of immobilization on muscle contractile protein balance in a rat model, highlighting the complex relationship between transcription and translation of actin (1401). This work in a prolific line of research led by Booth (928, 1304) laid the groundwork for a better understanding of the molecular regulation of synthesis of muscle proteins such as actin and cytochrome C during periods of loading and unloading. Others such as Williams and colleagues (1432) built on this, investigating transcriptional dynamics of muscle mitochondrial proteins.

These discoveries eventually led to the "Transient mRNA Hypothesis," which states that long-term changes in protein abundance are the result of short-term exercise-induced increases in encoding messenger RNA (833, 986). Since early evidence generated by Neufer

and Dohm (970), subsequent studies in both animals and humans have supported this (358, 732, 1033, 1049), forming the basic understanding of how acute responses beget stable adaptations to chronic exercise training. While these studies laid important groundwork for future research into muscle size and strength adaptations characteristic of resistance exercise (730), the dynamics of muscle gene transcription and translation influence all exercise outcomes reliant on production of new proteins, including key adaptations to aerobic exercise training. For example, transiently increased expression of genes encoding factors related to mitochondrial biogenesis (1033), lipoprotein lipase (1176), and other metabolic pathways (564) are critical molecular events in skeletal muscle that may form the basis of adaptations to long-term aerobic exercise.

The Human Genome Project and MoTrPAC

At the turn of the millennium, a battle between government- and industry-based efforts (1219, 1380) to sequence the full human genome resulted in an enormous amount of publicly available data that could be used to guide future hypotheses. In perspective allowed by our 20-year vantage point, this momentous event has become an inflection point in molecular biology research, subsequently leading to an explosion of knowledge based on transcriptomics, proteomics, and epigenetics that continues to grow steadily today. The application of these so-called ‘omics data sets to exercise and physical activity was spearheaded by leaders such as Claude Bouchard. Today, we continue to apply molecular mapping and data modeling to understand fitness (143), responsiveness to exercise training (1308), or genetic proclivity to be physically active (802).

Despite the growing volume of molecular data sets collected from exercise studies, the ability to carry out clinical trials directed toward developing exercise-based treatments for disease continued to be constrained by limited knowledge of its mechanisms of action based on data from appropriately sized human trials. Highlighting this critical information gap, a collaboration of leading researchers in the field, led by Dr. Darrell Neufer, came together to summarize current knowledge and the potential of exercise trials for discovery of actionable targets to promote human health (969). Perhaps motivated by this, Dr. Francis Collins, current NIH Director and a key scientist in the Human Genome Project, leveraged the NIH Invited Exercise Community gathering as a platform to address this need. Under Dr. Collins’ direction, the NIH eventually directed Common Fund resources toward the MoTrPAC initiative. Clearly, this level of support from a scientific giant highlights the need to develop this area of scientific inquiry, as well as its potential impact on public health. Ongoing initiatives such as MoTrPAC and the worldwide Athlome Project (1055) will bolster the available knowledge base in the context of exercise, leading to continued expansion of knowledge in healthy populations and providing a reference map to allow more mechanistic characterization of the influence of exercise training in chronic disease.

Section summary

Exercise physiology continues to permeate new avenues of human health, following our tendency to be fascinated by the infinitely large (e.g., the frontiers of space) and intricately small (e.g., regulation of gene expression by methylation or acetylation). In addition to emerging ‘omics platforms that survey the transducers of exercise, the field

is invigorated by examination of different physiological stressors such as unloading (in bedrest or spaceflight), aging, chronic disease, and the continual drive to test the limits of human performance (589). Throughout human history, exercise has always been viewed as medicine, and we continue to understand its mechanisms of action, optimize its prescription, and apply its power. At this prospective inflection point in the trajectory of the field, we acknowledge the historical figures on whose shoulders we stand and review the knowledge amassed in their wake.

Important Considerations in Exercise Research

To provide adequate context for an understanding of molecular adaptations to exercise, we first briefly overview key considerations for conducting and interpreting exercise research. While these may be common understanding for those in the field, we intend to include this information for all readers, regardless of familiarity with these tenets of exercise research. Through this objective, this article may guide new and talented investigators in other areas of expertise toward continuing to develop the breadth of knowledge related to exercise in humans.

Exercise and physical activity

Whereas physical activity (PA) is classically defined as energy expenditure from bodily movement (208), exercise is a subcategory of PA that is planned, structured, repetitive, intentional (208), and typically paired with a goal or desired outcome. Most commonly, exercise is divided into aerobic exercise (AE) and resistance exercise (RE). AE usually involves repeated movement cycles (e.g., running, swimming, cycling) and is defined based on the large contribution of oxidative phosphorylation to bioenergetic metabolism. RE is so named due to movements being performed against a load, ranging from body weight to external weighted equipment (e.g., bars, dumbbells, elastic bands). While the primary outcomes for AE and RE tend to involve cardiorespiratory fitness and muscle mass/strength, respectively, both modes have numerous benefits for multiple physiological systems due to a unique set of challenges imposed by each. While performance-focused individuals typically adopt a training regimen that specifically optimizes their goals (259), combined training in AE and RE provides a range of benefits to maximize overall health, that is, reducing morbidity and mortality risk throughout aging (699). Thus, exercise guidelines of most major public health organizations and governments emphasize combined AE and RE training. For example, the CDC/American College of Sports Medicine (ACSM) recommends 150 min/week of moderate AE or 75 min/week of vigorous AE, combined with 2 days/week of RE. Soberingly, however, less than 5% of American adults actually meet these criteria (1048, 1333).

Regular exercise promotes maintained or enhanced cardiorespiratory fitness (CRF), a strong predictor of health and mortality in adults (954). CRF is measured as maximal or peak oxygen consumption (Vo_2max or Vo_2peak) and expressed as a rate (mL O_2/kg/min or liters O_2/min). Briefly, Vo_2max refers to the concept introduced by A.V. Hill and reflects a true physiological ceiling in oxygen uptake, which may be attained by different means depending on the individual. Vo_2peak refers to the highest measured rate of oxygen

consumption given the experimental parameters (e.g., mode of exercise, test protocol used) (495, 1060). In determining CRF, the most important factor is participant effort, which may be assessed based on classical criteria (356) including a true plateau in rate of oxygen uptake with increasing workload, maximum heart rate (HR) above age-predicted target, respiratory exchange ratio >1.1, blood lactate >8 mmol/liter, and maximal perceived exertion. Notably, the appropriate thresholds for these test termination criteria are under continued consideration. Vo_2max improvements of 4% to 13% have been reported following as little as two weeks of training (55, 539, 633, 1217, 1424). Remarkably, highly trained athletes may demonstrate Vo_2max values 40% to 50% greater than their untrained counterparts (639, 1206). Even more dramatic benefits of continued exercise are apparent in advanced age (196, 499, 1323), as Vo_2max undergoes age-related decreases in sedentary adults (197, 1282, 1283). However, Vo_2max does not increase indefinitely with continued training, as some have revealed that adaptability in Vo_2max is partially genetically constrained (136, 137, 1308).

Accelerometry

For many years, prior to the development of accelerometer technology, objective assessment of physical activity outside the laboratory in free-living settings remained a challenge for the field. Accelerometry aids in describing and quantifying PA in a relatively unbiased and reproducible manner, in terms of its type (e.g., leisure time, occupational), intensity (e.g., light, moderate, high), duration, frequency, and timing. Accelerometers are easy to use (for both researcher and participant) and have high sensitivity for detection of change (911). Despite these benefits, accelerometry data are not represented consistently in the literature. Montoye and colleagues recommend reporting 12 key elements for complete PA assessment (910): accelerometer brand, model, and placement on body, number of days worn, number distributed and mode of distribution, validity considerations such as minimum number of days and min/day necessary to declare validity, criteria for determining accelerometer was not worn, and determining noncompliance, and data metrics such as data epoch length and outcomes of interest derived from raw data. Researchers are encouraged to strive for completeness in data reporting, including how the specific limitations of the chosen device may influence study findings.

Exercise dose

Several variables contribute to the overall amount, or dose, of an exercise stimulus. Factors including intensity, duration, and frequency interact to determine the overall stress of exercise, leading to differential activation of molecular transducers across physiological systems. Chronic exposure to a given exercise dose facilitates long-term adaptation.

Intensity—Intensity is a metric of work or power necessitated by exercise such that higher intensity will require higher energy expenditure. In RE, intensity may be defined based on workload relative to maximum, which is usually measured as the maximum load lifted one time (as one-repetition maximum, or 1RM, Table 1). Intensity dictates the burden on skeletal muscle cells (myofibers). In humans, myofiber subtypes are defined based on the predominant isoform of the contractile protein myosin, including type I (smallest, slow, oxidative), type IIa (larger, faster, more glycolytic), and type IIx (fastest, most fatigable)

(1159). These fiber types are innervated by type-specific motor neurons, whereby a motor neuron and all the myofibers it innervates comprise a motor unit. The sequential firing of motor units based on the size of the motor unit (a concept termed the “size principle”) was introduced in the 1960s by Elwood Henneman (554). This enables incremental muscle contraction, with the smallest (type I) motor units possessing the lowest activation threshold and thus typically engaged before the larger, more powerful (type II) motor units. Due to this relationship, tissue-level adaptations are usually specific to the muscle under load or tension and the contraction intensity/demand that defines the proportion of motor units recruited up to maximum (i.e., all motor units activated).

For AE, using HR as a reference point for intensity assumes that demand on the cardiovascular system reflects the overall physiological stress. This metric can be easily and quickly collected, facilitating exercise prescription and periodization. In addition to representing intensity relative to maximum HR (HRmax), intensity is often expressed as a percentage of HR reserve (HRR, calculated as HRmax − HRresting), a robust reflection of cardiovascular reserve (1275, 1276). To define target exercise HR, a given HRR percentage is added to HRresting. Common training regimens based on intensity include moderate-intensity continuous training and interval training [e.g., high-intensity interval training (HIIT), or sprint interval training] which typically involves short periods of high-intensity work followed by longer periods of low- to moderate-intensity recovery. Physiologically, moderate and HIIT elicit both central (i.e., cardiovascular) and peripheral benefits, and both regimens can lead to similar improvements in Vo_2max (550, 931).

Intensity is the primary determinant of energy utilization throughout exercise (1115). Whereas carbohydrate-based stores such as muscle glycogen are preferentially used in high-intensity activities, low- or moderate-intensity exercise permits sufficient time for utilization of fats, which are more energy-rich due to their high carbon bond composition. Elegant studies by Romijn and colleagues using a stable isotope infusion design demonstrated differential contributions to overall energy expenditure in men (1115) and later women (1116) at a range of exercise intensities. Interestingly, at all intensities, the absolute energy derived from plasma sources is identical, whereas the skeletal muscle component (glycogen and intramuscular triglycerides) changes depending on intensity. These and other works (123, 278) highlight the importance of skeletal muscle glycogen for maintenance of exercise intensity. Alternatively, increasing available carbohydrate exogenously (283) may supplement declining muscle glycogen stores in activities performed at a high intensity for a longer duration.

Duration—Duration is the other major determinant of energy utilization during and after exercise. The length of a single exercise session (i.e., duration) may last anywhere from several seconds (e.g., 100 m sprint) to ≥24 h (e.g., ultra-endurance running). When intensity is held constant (i.e., “steady-state” exercise), prolonged duration facilitates a shift toward fatty acid utilization. By manipulating intensity and duration, it is possible to control the total session work output and thus influence the mechanical and metabolic adaptations enforced by the training regimen. For example, by the end of a 2 h cycling bout at 65% of Vo_2max, >60% of overall energy expenditure is derived from fat sources (1115). Thus,

adaptations in fatty acid cycling and fat oxidation enzymes are typically seen with moderate intensity AE training (238).

Frequency—In RE, frequency is generally described as the number of sessions per body part or per week within the shortest training cycle. Two recent systematic reviews and meta-analyses describe the impact of RE frequency on outcomes such as muscle strength (497) and hypertrophy (1169). Briefly, overall training volume is the primary driver of differential responses (187, 1169, 1303): the frequency of sessions over which this volume is accrued may be less important (985). Conversely, when volume is not matched, an increase in frequency increases overall exercise dose, leading to greater improvements with RE (1168). An important consideration of exercise frequency is recovery time (i.e., time elapsed between exercise sessions), which may differ based on muscle group exercised (497, 1246), biological characteristics [e.g., sex (610, 612), age (387)], and lifestyle factors such as sleep and diet patterns.

In general, patterns in AE frequency mirror RE such that adaptations (196, 489) and health benefits (361) are dependent on overall dose rather than frequency of sessions. Importantly, this dose-response relationship diminishes at very high volumes: thus, some evidence supports an ideal range of 2 to 3 sessions per week (1166). While there is some debate regarding whether higher lifetime AE load actually contributes to negative health outcomes, such as cardiac events [reviewed in (362)] and mortality (1166), these findings may be influenced by factors such as exercise intensity and eccentric loading component. In terms of performance, AE frequency and/or duration may be manipulated to peak for competition in a process known as “tapering” (1215). The taper period is typically designed such that overall intensity is maintained while dose is reduced by approximately 25% to 50% (824). In young healthy males, tapering results in increased type IIa myofiber size and power along with significantly improved performance (824, 947, 1319).

Effects of biological sex

Biological sex, defined by a given sex chromosome complement or sex hormone profile, plays an important role in adaptations or acute responses to exercise. To date, much research has focused on exclusively male populations (1051), whether because of availability of male participants as members of exercise laboratories or perceived complications introduced by hormonal fluctuations throughout the menstrual cycle (275, 655, 848, 1095, 1270, 1428). While these within- and between-sex differences do exist and are biologically meaningful, the general consensus is that it is necessary to continue to study both males and females to best characterize these differences and their potential impacts on performance, health, and disease. A feasible practice may be to recruit participants of both sexes and perform independent downstream statistical analyses. However, it remains important to reconcile any differences revealed to increase our understanding of relevant processes contributing to sex-specific patterns.

In the context of exercise, research has revealed some key differences in physiological properties between the sexes (Figure 2). Briefly, differences in skeletal muscle (611, 612, 1105, 1113, 1413, 1455), cardiovascular (8, 326, 499, 667, 854, 1419), endocrine (218,

491, 713, 1105, 1242, 1415), and metabolic (202, 328, 1287, 1288) phenotypes have been observed. Importantly, many key adaptative outcomes to exercise training appear to be similar between the sexes (4, 103, 593, 612, 849, 1220, 1415, 1464), although the underlying mechanisms may be different (2, 507). Despite these interesting findings, the area of sex-specific responses to exercise generally remains poorly defined and is clearly an area warranting extensive future investigation.

Section summary

A rapidly progressing field has outlined numerous controllable factors that influence the magnitude, direction, and target system/tissue of adaptation to exercise training. It remains necessary to consider carefully the influence of these variables in study findings and to shift attention toward existing knowledge gaps. In particular, a focus on equalizing the imbalance between all-male and sex-matched research is of utmost importance as the field of exercise prescription research migrates toward a more individualized strategy. Furthermore, due to emerging evidence from genetics and genome-wide association studies (GWAS), the potential influences of race and/or ethnicity warrant significantly more attention. These factors should be viewed in light of potential for discovery. For instance, ongoing efforts such as the MoTrPAC initiative will leverage variability in human exercise biology to build a comprehensive and diverse molecular map of acute responses and adaptations to exercise.

Current Evidence of Exercise as Medicine

A continually growing body of evidence strongly supports that exercise has multiple long-term benefits across the entire lifespan, from the womb until late life (Figure 3). Exercise improves general health and fitness, psychological well-being, social interaction, etc., enhancing every dimension of quality of life while reducing the risk of chronic disease and mortality (1034, 1144) through a range of mechanisms. Yet in the midst of overwhelming evidence to suggest that exercise is essential to preserve health, most adults are still inactive (1400), a sobering statistic that costs an estimated $53.8 billion worldwide. Concerningly, prevalence of inactivity is higher among older adults, women, many racial and ethnic minority groups, and individuals with an underlying chronic disease (335, 1400). Regardless of age, sex, race, ethnicity, or fitness level, habitual exercise and an active lifestyle are cornerstones for maintenance of physical independence, health, and well-being (1034, 1048). Furthermore, exercise has shown promising results as a preventative and/or rehabilitative strategy for a wide range of diseases by improving the function of numerous body systems.

General health maintenance

Gestation and early life—In the absence of obstetric or medical contraindications, exercise is considered safe during pregnancy (303–305, 346, 858, 1027, 1070, 1143) and is recommended for its wide-ranging benefits in maternal and neonatal outcomes (1027, 1144). Exercise reduces the risk of pregnancy complications such as preeclampsia, gestational hypertension, and gestational diabetes (164, 305). Sustained maternal cardiorespiratory fitness and gestational weight management protect against risk of postpartum CVD, T2D (106, 506, 524, 717, 1027), and obesity (1028). In addition to controlling maternal

gestational weight (1301) and associated risks (82, 304, 859), exercise during pregnancy reduces the likelihood of high gestational weight (macrosomia) in infants (1388), an outcome associated with numerous health defects throughout life (242, 1388). Evidence is still insufficient regarding the benefits of exercise for cesarean section, labor duration, and high-birth weight fetus delivery (164, 858). Nevertheless, neonates whose mothers exercise during pregnancy demonstrate birth weight within normal range and attain higher scores on the Apgar scale [a gauge of responsivity in neonates (306, 858, 1071, 1143)] than counterparts of sedentary mothers. Furthermore, exercise may reduce the risk of postpartum depression (303, 1070), a common psychiatric disorder affecting approximately 10% to 15% of women during/after pregnancy (101, 167).

Childhood and adolescence—Multiple studies demonstrate exercise-induced improvements in cardiorespiratory fitness, muscle mass, and strength in children and adolescents (102, 245, 381, 488, 769, 770, 952, 1436). A potential countermeasure to combat the dramatic increase in childhood obesity prevalence in recent years (740), exercise is an effective weight management strategy (698, 771, 772, 1202, 1347). Concerningly, obese children have a doubled risk of becoming obese adults (740, 1151) and premature death (765). Exercise, however, can decrease the metabolic burden of obesity independent of weight loss (6, 310, 771, 772). Furthermore, regular exercise alleviates the severity of pulmonary deficits associated with childhood asthma, a common disorder limiting both maximal lung function and exercise tolerance (797, 800, 823, 898, 1036, 1395).

In children and adolescents, HIIT is a time-effective intervention to elicit cardiovascular health effects (189, 268, 353, 1083, 1121, 1418). Further, concurrent training in AE+RE (as encouraged by many organized sports) may have synergistic effects in children and adolescents, improving strength, power, CRF, and sports performance (445). Provided that it is properly designed, RE has positive effects on skeletal mass and bone development during childhood and youth (102, 488, 952), in addition to increasing muscle strength, power, endurance, and neuromuscular control (777). Further evidence suggests RE training may reduce the risk of sports-related injuries in youth (102, 381, 488, 777, 952). Remarkably, children and adolescents that undertake RE show greater gains in strength compared to adults in the initial stages of RE, benefits that are carried into adulthood (419).

A critical component of normal health, neurodevelopment during childhood and adolescence is commonly affected by disorders such as attention deficit/hyperactivity disorder (ADHD) [affecting 8% to 10% of children (972)] and autism spectrum disorder (ASD) [affecting approximately 2% of children (69)]. Notably, moderate-to-vigorous AE may alleviate the severity of characteristics associated with these disorders, for example, response inhibition, response time, cognitive control, attention allocation, cognitive flexibility, processing speed, and vigilance (322, 972). In children with ASD, exercise attenuates deficits in social skills, language and communication, cognition, and attention (393, 651, 1317), in addition to improvements in blood lipid profile, parent-perceived quality of life (1317), and motor control (146). Importantly, these studies demonstrate safety in addition to efficacy, highlighting the potential utility of exercise to treat and manage functioning in neurodevelopmental disorders (393, 1317). In these populations as well as neurotypical children and adolescents, exercise appears effective at improving domains of cognition,

metacognition, self-esteem, enhanced self-concept, and increased life skills (26, 322, 527, 561, 592, 1029).

Adulthood—Exercise throughout the lifespan promotes optimal functioning of most (if not all) physiological systems. During adulthood, higher CRF is associated with lower risk of premature mortality and lower incidence of CVD, respiratory disease, and colorectal cancer (1247). Furthermore, a prospective cohort study of >500,000 adults aged 40 to 69 years found that both CRF and grip strength (a physical performance measure of muscle strength) were negatively associated with mortality (699), indicating that both cardiovascular and skeletal muscle function are important indicators of general health in middle-aged adults (941). Certainly, other physiological systems play a role in determining overall health status. For instance, failure to reach peak bone mass is predictive of skeletal fragility and fracture risk in later life (1334), whereas exercise has positive effects on bone mass and morphology (323, 486).

Regularly assessed vital signs (e.g., blood pressure, heart rate variability) can serve as important biomarkers of health, and exercise appears to have a positive influence on these in adults (272, 619, 620, 700, 796, 944). Endocrine indicators of health are also easily accessible in circulation and provide valuable insight into system functioning. Due in part to drastic hormonal changes during perimenopause and eventual menopause, adult females are more likely to undergo a more precipitous rate of muscle and bone mass declines, contributing to heightened risk of falls and fractures (1211), in addition to an array of other chronic conditions. Exercise interventions may forestall the declines in muscle, bone, and metabolic health (211, 510, 1152), positively impacting physical capacity in mid-life. Furthermore, the combination of exercise with adjuvant hormone replacement therapy is under study.

Beyond maintenance of physical health, regular exercise promotes mental wellness in adults (229, 485, 528, 743, 1266). Mood and anxiety disorders are increasingly common in this age range (556). While the estimated prevalence of depression and anxiety are 4.4% and 3.6%, respectively (425), many adults live with both disorders simultaneously (425), and it is estimated that approximately 50% of U.S. adults will experience a mental health disorder at some point during adulthood (689). In a large cross-sectional study of 1.2 million adults, exercise was associated with lower self-reported mental health burden, regardless of age, race, gender, household income, educational level, and exercise type (229). In contrast, cessation of regular exercise is associated with increased depressive symptoms in healthy adults (919). These effects are particularly pronounced in females, a subpopulation generally at higher risk for developing a mental health disorder during adulthood (77, 425, 556).

Healthy aging—Aging is a process shared by all living things and involves a complex series of biological changes that lead to a general decrease in physiological resilience (i.e., ability to tolerate and recover from stressors) and increased vulnerability to adverse events (380, 573). Even in the absence of chronic disease, the generally downward trajectory of aging varies across individuals, likely as an integrated result of genetic, epigenetic, environmental, behavioral, and other factors (39). Nevertheless, there is overwhelming evidence that regular engagement in exercise has potent antiaging effects (173, 1025),

protecting the function of most physiological systems, including cardiovascular, respiratory, immune, and musculoskeletal (70, 131, 140, 307, 408, 595, 615, 798, 915, 1293). In fact, skeletal muscle tends to be a tissue of aging and exercise research focus, due to its steady decline in mass and function with age, in combination with its critical roles in movement, metabolic homeostasis, and support of the immune system. Maintenance of skeletal muscle function with aging reduces the risk of falls, which often result in injury, onset of disability, and loss of independence in older adults (179, 336, 421, 442, 515). In a systematic review and meta-analysis in >20,000 older adults, exercise reduced the risk of falling by 21% (1192), a robust effect given the high fall risk with advancing age (49).

Those who age "successfully" enjoy a long health span, or lifespan free of chronic disease (1173); habitual exercise appears to be a critical component of successful aging (39, 129, 416, 735, 1235, 1371). A recent study by Gries et al. in aging men and women who reported engaging in lifelong exercise demonstrated that individuals were biologically nearly 30 years "younger" than their calendar ages, based on a range of maximal CRF parameters (499). A rapidly expanding area of research sampling lifelong exercisers continues to demonstrate preserved cardiovascular health (196, 1193), mitochondrial health (499, 1323), skeletal muscle mass and performance (219, 498), and muscle endocrine function (327, 757) in the face of aging. At this time, much of the research is focused on AE-trained older adults, but continued research is necessary to examine the potential benefits of RE and/or concurrent training throughout the lifespan. Furthermore, the benefits of lifelong training for other domains of health (e.g., cognition, mental health) represent an emerging knowledge gap (447, 448).

Musculoskeletal diseases

Musculoskeletal diseases encompass a collective group of conditions that affect locomotor organs and tissues (muscles, bones, joints, tendons, ligaments, etc.). Musculoskeletal diseases affect 20% to 33% of people globally, and rates increase with advancing age (1444), accounting for approximately $213 billion in annual health care expenses in the US alone (1340). Clinical symptoms include pain and mobility limitations, together contributing to decreased engagement in physical activity and increased likelihood of disability (1340, 1444). Exercise may be used as both primary and secondary prevention to prevent the onset or reduce the clinical burden of this class of diseases. Here, we focus on four prevalent musculoskeletal disorders: sarcopenia, osteoarthritis, rheumatoid arthritis, and osteoporosis.

Sarcopenia—Sarcopenia is a multifactorial neuromuscular disease clinically characterized by age-related declines in skeletal muscle mass and sometimes associated with decrements in strength and function (231, 287, 922, 1032, 1267). Multiple operational definitions of sarcopenia exist, leading to difficulty in accurately assessing its prevalence in the population (171, 288, 1105). After muscle mass peaks around age 30 to 40 years, it naturally declines with advancing age (~10% per decade) (287, 337, 726), and strength losses occur at a faster rate (~2%–4% per year). Lower limbs are usually more dramatically affected (337, 482, 726, 805, 828). Consequences of low muscle mass may be exacerbated by complications including incomplete muscle mass recovery following illness, infection, or hospitalization (289).

Exercise is one of the best-studied and most effective countermeasures for sarcopenia. Despite heterogeneity across studies in age range and exercise mode, consistent improvements are seen in total skeletal muscle mass, strength, and other functional outcomes in sarcopenia (821, 1377). RE, in particular, is a potent stimulus for reversal of sarcopenia, given its positive impact on muscle hypertrophy (163, 289, 337) and muscle protein synthesis (72). While the degree of hypertrophy is highly variable across individuals, all individuals garner multiple positive adaptive responses to training (249). On the other hand, AE can improve exercise tolerance and metabolic function through enhanced oxidative enzyme capacity and heightened insulin sensitivity (581, 749). These adaptations occur through increased mitochondrial biogenesis (1108, 1145), reduced low-grade inflammation (153, 337, 752, 857), and improved skeletal muscle plasticity (752).

Osteoarthritis—Osteoarthritis (OA) is characterized by structural changes in articular cartilage, subchondral bone, ligaments, capsule, synovial membranes, and periarticular muscles (53, 608, 926, 1022) that are often accompanied by chronic pain and mobility impairment. OA affects 10% to 13% of noninstitutionalized adults in the United States (252, 1475) but the prevalence doubles to approximately 25% in individuals ≥65 years (1475). In addition to age, factors such as sex, race, ethnicity, bone density, obesity, joint structure and mechanics, nutritional factors, and genetic predisposition also influence the incidence of osteoarthritis (53, 816, 926, 1254, 1370, 1475). Due to their biomechanical roles as weight-bearing structures, the hip and knee joints are most commonly affected (53, 926). Many individuals with OA elect to undergo joint replacement surgery to alleviate pain, swelling, stiffness, and crepitus of the affected joint (926). OA contributes substantially to emergency hospital costs (1209) and affects >250 million people worldwide (609).

Regular exercise is recommended to prevent, manage, and “prehabilitate” OA (81, 750, 966, 1343). Evidence from multiple systematic reviews suggests that, when exercise is properly prescribed, pain and stiffness are reduced without damage to cartilage or synovial tissue (91, 150, 844, 973, 1034) or accelerated OA progression (91, 844, 973, 1414). In addition to improving general functioning, flexibility, and muscle strength, exercise can enhance mood and quality of life (91, 92, 119, 206, 222, 325, 668, 795, 1307). Furthermore, exercise yields similar or large effect sizes in comparison to pharmacologic treatments such as nonsteroidal antiinflammatory drugs (81, 418). In a network meta-analysis of 9134 patients with knee and hip OA in 103 randomized controlled trials, AE training was the most beneficial intervention for managing pain and improving performance (468), although a range of other modalities have been examined for their effects on muscle strength, walking speed, weight management, and quality of life. For instance, several systematic reviews and meta-analyses indicate that benefits are conferred from activities such as AE, RE (91, 1387), combined flexibility and strength programs (149, 468, 754, 795, 966, 1111, 1470), yoga (754, 1470), Tai Chi Chuan (222, 794), aquatics (90, 822), and proprioceptive training (646, 1225). The optimal prescription likely varies based on an individual’s needs, preferences, and symptoms.

Rheumatoid arthritis—Rheumatoid arthritis (RA) is a chronic autoimmune disease that affects approximately 1% of the adult population and is characterized by degenerative

arthritis in synovial joints, including proximal (e.g., hands and wrists), intervertebral (cervical, lumbar), and other joints (e.g., hips, knees, ankles, toes, shoulders, etc.) (890, 1430). RA is clinically characterized by inflammation, deformation of the affected joint(s), pain, stiffness, and fatigue that lead to progressive deteriorations in mobility, functional ability, and quality of life (890, 1430), as well as hospitalization and disability in many individuals (227). Concerningly, RA-associated changes in lean and fat body mass are associated with increased CVD risk (57, 890, 892, 894, 1430). A range of pharmacologic and nonpharmacologic RA treatment options are available (1430), but the most intensive involve a combination of conventional synthetic and biological disease-modifying antirheumatic drugs and are costly to patients and health care systems (227).

Exercise interventions have consistently been demonstrated as a cost-effective and sustainable treatment with multiple general systemic benefits and positive impacts on RA symptomology. These include aerobic fitness (540), strength (67, 613), functional ability (67, 613, 1430), cardiovascular health (286, 892), fatigue (298, 681, 1354), and inflammatory burden (60, 891). Furthermore, evidence from prospective observational and experimental studies demonstrates that exercise promotes positive effects on pain (68), cognition (1184) and quality of life in individuals with RA (68). Practically, higher fitness is inversely associated with number of hospital admissions and length of hospitalization (893), and higher physical activity level time is associated with lower 10-year CVD risk (391, 895) in individuals with RA.

Osteoporosis—Osteoporosis is a systemic skeletal disorder characterized by reduced bone mass and disruption of bone microarchitecture, increasing the susceptibility to bone fragility, osteoporotic fractures, and mortality (558, 670, 711, 1147, 1449). Osteoporosis is common among older adults, especially postmenopausal women (1001, 1449); its current prevalence is expected to increase with the growth of the aging population and the concerted action of multiple risk factors that contribute to osteoporosis pathophysiology (746). Existing pharmacotherapies have side effects and transient benefits at best; thus, adherence to pharmacologic regimens is poor (692, 874). Fortunately, exercise boosts bone health (874, 1152) across a range of individuals and exercise prescriptions (479, 1240, 1472–1474).

RE is particularly well-studied as a high-impact, weight-bearing exercise modality to modulate adverse outcomes associated with osteoporosis. Whether performed independently, progressively, or as part of a multimodal intervention, RE improves bone health across a range of ages, including the high-risk postmenopausal female demographic (479, 1240, 1472, 1473). Exercise interventions modulate osteoporosis adverse outcomes through improvements in bone mineral density (479, 1473), fall risk factors (e.g. sway velocity and anterior-posterior sway range)(1405), fear of falling (1240) and fall-related injuries (1472), while improving muscle strength, functional mobility, balance and quality of life (1177, 1240). Exercise volume is associated with positive and stable changes in bone density (479). Exercise may also be used as a primary prevention strategy: it has been suggested that achieving 10% higher peak bone mass in young adulthood can delay the onset of osteoporosis by 13 years and reduce subsequent risk of lifetime fracture risk by

50% (100, 1252). However, the appropriate exercise mode must be carefully considered: non-weight-bearing activities may provide little to no benefit on bone structure (100).

Cardiovascular diseases

CVDs are a class of conditions affecting the health of the heart and vasculature and are the global leading cause of death (1445). General risk factors for CVD include but are not limited to obesity, dyslipidemia, inflammation, and oxidative stress. Most premature deaths attributed to heart attack and stroke could theoretically be prevented with early detection and management and/or effective prevention via preservation of CRF. Conversely, increasing CRF through exercise reduces the risk of CVD and all-cause mortality (718, 845, 1255).

Hypertension—Hypertension, clinically defined by elevated blood pressure, is incredibly common, affecting >40% of the adult population worldwide (785, 916, 1097). Physiologically, high blood pressure is the end-product of disturbances in systemic vascular resistance and/or on cardiac output due to numerous circulating and vasoactive factors, many stemming from chronic hyperactivation of the sympathetic nervous system. Hypertension increases the load on not only the peripheral vasculature but also organs such as the heart, kidneys, and brain (172, 804, 1097). Hypertensive patients have an increased risk of cardiovascular and cerebrovascular morbidity and all-cause mortality (172, 192, 384, 392, 511, 512, 641, 1047, 1097, 1180, 1260, 1420). Most patients use one or a combination of antihypertensive medications, but long-term use of pharmacotherapies increases the likelihood of side effects (502, 1298). In contrast, regular exercise has multiple acute and chronic benefits for management of high blood pressure.

Habitual exercise is associated with reduced side-effects, optimization of pharmacologic treatment, and prevention or postponement of development of hypertension (636, 916, 1047, 1097, 1100, 1420). In addition, physical exercise positively impacts office and ambulatory blood pressure, a continuous measurement of blood pressure over hours (140, 194, 207, 1097). A single bout of AE and RE consistently decreases 24 h ambulatory blood pressure (191, 272) as well as office blood pressure for up to 2 h postexercise, a phenomenon known as postexercise hypotension (194, 207). The magnitude of the blood pressure-lowering response varies with exercise dose, and the optimal strategy to maximize postexercise hypotension is still not identified (1097).

Coronary heart disease—Coronary heart disease (CHD) is a cardiovascular pathological condition characterized by ischemic cardiomyopathy via narrowing or blockage of the coronary arteries, commonly due to atherosclerotic plaque constriction (1022). CHD has a long asymptomatic development phase but frequently leads to major acute cardiovascular events (e.g., myocardial infarction, sudden cardiac death) (766). While prevalence of CHD is higher in males across age ranges, advancing age reduces this sex difference (294, 1185). Primary and secondary preventative strategies include lifestyle changes, optimal medical care, myocardial revascularization, use of antiplatelet agents (415), and regular exercise (417, 459).

The UK Biobank, a large, longitudinal cohort study, showed that strength and fitness were inversely associated with incident CHD and atrial fibrillation in adults genetically

predisposed to develop CVD (1306). Similarly, a study in U.S. veterans demonstrated a relationship between higher CRF and lower incidence of major cardiovascular events (718). Given the broad range of cardiovascular benefits across exercise modes, it appears that most types of activity exert a protective effect (417, 475, 580, 1010, 1356). Some have reported clinically relevant cardiovascular preconditioning benefits detectable immediately after a single exercise bout (1011, 1302).

Exercise-based cardiac rehabilitation after an acute ischemic event is the cornerstone for secondary prevention of CHD; this practice reduces cardiovascular (38) and all-cause mortality risks (853) by 26% and 13%, respectively. Despite remarkable benefits, only 62% of patients are referred to cardiac rehabilitation at the time of discharge after an acute event, and an even smaller fraction actually attend one or more sessions (339). Finally, evidence suggests that precaution should be taken when prescribing high-intensity interventions in high-risk CHD patients due to an acutely elevated risk of events (417, 580).

Heart failure—In heart failure (HF), cardiac muscle progressively weakens, resulting in compromised blood delivery throughout the body. HF may be further classified based on its etiology, potentially resulting from either pressure overload associated with hypertension (888) or volume overload associated with valvular defects (e.g., mitral valve regurgitation) (255, 902). Further discrimination includes the anatomical site (e.g., left or right HF) (723) and the discernment of whether ejection fraction is reduced (HF-REF) or preserved (HF-PEF) (706). HF affects >5 million Americans (~12%) (939, 1352), is more common in individuals >70 years (1174, 1352), and requires vigilant monitoring to continually optimize treatments to its progression (1281). HF patients also have poor respiratory muscle strength and endurance, cardiopulmonary perfusion, and skeletal muscle function (255, 1022). Prognosis is grim in that most HF patients do not survive five years after diagnosis (1372), while others become reliant on ventricular assist device implantation or heart transplant (255, 1174, 1372).

Exercise, particularly aerobic, is an effective primary prevention strategy (210, 1433): stratification of high-risk individuals into fitness-based quintiles supports an incrementally protective effect of CRF (1022). In contrast, low fitness is a strong independent predictor of adverse outcomes (957). Additionally, lower CRF in young adulthood is associated with left ventricular dysfunction and higher prevalence of subclinical abnormalities and other complications in late life (115, 1003), suggesting that primary prevention is critical. Nonetheless, exercise-based cardiac rehabilitation has beneficial effects on prognosis, functional capacity, and quality of life in individuals with HF (255, 271, 1002). Even in patients with ventricular assist devices (7, 537, 673) and heart transplant (37), evidence supports that both short- and long-term training interventions are safe and effective.

Metabolic diseases—Metabolism, the cell-level process of converting nutrients into energy, is fundamentally disrupted in the cluster of conditions known as metabolic diseases, a leading cause of death worldwide (19). Lifestyle habits, such as meeting the recommended exercise levels (1048), have numerous effects on prevention and management of metabolic diseases, sometimes demonstrating a stronger impact on metabolic risk factors and mortality than achieved by pharmacotherapies (955).

Obesity—Across the lifespan, overweight and obesity are common conditions, and prevalence across all age ranges has been steadily increasing throughout the last century (698, 771, 772, 1347, 1446). While its primary feature is excessive amount of body fat, obesity results from a range of etiologies including genetic, environmental, and endocrine factors. In both children (740) and adults (265), obesity contributes to a broad range of comorbidities, including (but not limited to) T2D, hypertension, nonalcoholic fatty liver disease, obstructive sleep apnea, and dyslipidemia. Obesity and its network of associated pathologies constitute a substantial economic burden (1446), in addition to impairing quality of life and increasing mortality.

Regardless of age, sex, race, and exercise type, regular physical exercise is an effective weight-loss and weight-management intervention (771, 772). Three months of AE or RE significantly reduces body fat percentage, waist circumference, and visceral, subcutaneous and intrahepatic adipose while simultaneously improving insulin sensitivity and skeletal muscle mass in obese adolescents (771, 772). Even independent of weight loss (310), exercise training promotes meaningful changes in body composition and a favorable metabolic profile. Illustrating this, a prospective study tracked the development of CVD risk factors in >100,000 adults across an approximately 6 year period (855). In comparison to those who decreased physical activity rates over time, the individuals that increased or maintained habitual exercise patterns demonstrated lower rates of hypertension, T2D, and hypercholesterolemia regardless of whether they lost, gained, or maintained weight (855). While weight loss may be a strong and visible motivator for individuals, it may be of clinical import to communicate that not all interventions result in a change in overall body weight to temper expectations appropriately. Changes in other easily measurable parameters (e.g., body fat percentage, waist-to-hip ratio) may be a better reflection of health and may provide incentive to continue an exercise regimen.

Diabetes—Currently, more than 13% of U.S. adults are affected by diabetes, and prevalence has been rising in children and adolescents as well (212). In 2017, diabetes was the seventh leading cause of death in the United States and demanded a total estimated cost of $327 billion (212). The majority of cases are diagnosed as T2D (175), a condition characterized by impaired function of insulin-producing pancreatic beta cells caused by a combination of insulin resistance, relative insulin deficiency, and abnormal fat and protein metabolism (30, 1022). On the other hand, type 1 diabetes results from autoimmune destruction of the beta cells. Both conditions manifest as hyperglycemia (high blood glucose); in T2D, development of hyperglycemia is progressive and insidious, which may cause classic diabetic symptoms to be overlooked before more severe complications arise (637). In comparison with nondiabetics, individuals with T1D or T2D have two to four times higher risk of co-morbidity (e.g., hypertension) and mortality (257, 466, 704, 1022). Furthermore, low CRF is a strong independent predictor of all-cause mortality in both T1D and T2D (138, 257, 803, 1411).

As part of lifestyle change therapy (637), exercise has been shown to improve insulin sensitivity, fasting insulin, and glycated hemoglobin (HbA1c), a classic marker of long-term blood glucose regulation, in children, adults, and older adults (257, 261, 347, 386, 637, 1202). Impressively, metabolic benefits of exercise are brought about quickly (e.g., within

a week of vigorous AE training (705)), and a single bout may have effects on whole-body insulin sensitivity that persist for up to 96 h (704). Higher intensity or longer-duration training amplifies the stability of these positive changes (138, 704, 811, 1268, 1434). Meta-analyses including both AE and RE demonstrate positive effects of exercise on glucose sensitivity (704), glycemic control (811), and inflammation and oxidative stress (803). RE may also augment overall physical functioning through increased skeletal muscle mass and bone mineral density (257, 261, 637, 803, 811). Preclinical studies suggest that exercise may improve pancreatic beta cell mass and function (290). Exercise also exerts immunomodulatory benefits on pancreatic beta cells and systemic inflammation in T1D (256, 257).

Dyslipidemia—Dyslipidemia includes a number of lipoprotein metabolism disorders, primarily elevated blood levels of total cholesterol (hypercholesterolemia) and/or triglycerides (hypertriglyceridemia) which are major risk factors for atherosclerotic CVD (724, 1022). More than 13% of U.S. adults ≥20 year have high total cholesterol and 18% have low levels of protective HDL cholesterol (199), an inverse risk factor for metabolic and CVD (19, 785, 1022, 1047). High total cholesterol levels have been associated with obesity, breast cancer (178), diabetes-associated morbidities (984), Alzheimer's disease (AD) (1457), stroke (882), and CHD (142). Through its influence on rates of cholesterol synthesis, transport, and clearance (351), regular exercise can reduce total cholesterol, triglycerides, and LDL cholesterol and increase protective HDL (724, 939, 1022, 1099, 1258, 1420). These effects reduce reliance on pharmacological treatments: the National Health and Nutrition Estimation Survey estimates that a 15% reduction in LDL cholesterol can reduce the need for antidyslipidemic drugs in 5% to 14% of the population (199). Given that dyslipidemias are a risk factor for many cardiovascular and metabolic diseases, exercise-induced improvements in blood lipid profile positively affect a range of outcomes to reduce overall health risk.

Metabolic syndrome—Metabolic syndrome (MetS) is astoundingly prevalent, affecting one in every three U.S. adults ≥40 years (14). While international criteria differ (19, 962), MetS is generally described as a multifactorial cluster of five key factors: central adiposity, dyslipidemia, insulin resistance, glucose intolerance, and hypertension. MetS is a major contributor to CVD risk (1191), a precursor for other metabolic chronic conditions (312), and an emerging epidemic of its own. Despite being at elevated risk for a coronary event, individuals with MetS do not exhibit symptoms of cardiovascular dysfunction. Thus, primary prevention via exercise is likely the most effective treatment option for MetS (331).

The benefits of exercise for each of the subcomponents of MetS are well-studied; thus it is logical that exercise reduces overall risk of MetS. As recently reviewed (953), increasing exercise and/or higher CRF positively impact MetS incidence and prevalence, while low fitness and/or physical activity is associated with higher incidence of MetS (350, 625, 679, 953, 1262, 1469). Meeting at least the recommended exercise guidelines (1048) can help prevent the development of MetS in later life (71, 312, 953). Through its impact on MetS factors, habitual exercise can also reverse MetS: Katzmarzyk et al. (676) found that >30% participants diagnosed with MetS at baseline were no longer affected after a 20 week AE

intervention. The exercise intervention significantly decreased triglycerides, blood pressure, and waist circumference, while improving HDL cholesterol and fasting plasma glucose.

Cancer

Cancer is the second leading cause of mortality in the United States, with approximately 1.8 million new cases and 600,000 deaths expected in 2020 alone (1200). The risk of developing an invasive cancer is dependent on intricate and compounded risk factors such as genetic predisposition, environmental exposure to DNA-damaging agents, and lifestyle factors. It has been estimated that 40% to 60% of cancers can be prevented by modifying factors such as obesity, smoking, and physical inactivity (1230). Given the prevalence and ambiguous, complex origins of cancer, the development and/or combination of effective therapeutic approaches to prevent, treat, and manage it are of great public health importance. The relatively young field of exercise oncology is targeted at leveraging exercise to offset treatment-related side effects and improve quality of life in cancer patients. Early trials focused on AE in breast cancer patients (438, 712, 1263), and promising results in this population spurred exercise interventions in other cancers. Collective evidence supports that AE and RE elicit improvements in symptom-related outcomes such as exercise tolerance, quality of life, fatigue, and overall function (9, 439, 1175).

Many cell survival pathways targeted by chemotherapy are also critical for protecting the heart (221). Exercise may alleviate the cardiotoxic burden of chemotherapy and other cancer drugs, as was first demonstrated in 2006 in a preclinical study using treadmill running in rats (239). In a subsequent breast cancer case study, AE prior to and throughout treatment resulted in reduced fatigue and improved functional capacity (324). In further support, adverse side-effects such as hemodynamic shifts, depression, soreness, and pain were significantly less prevalent in individuals performing vigorous AE before every chemotherapy session than those undergoing usual care (703). Furthermore, exercise may be associated with changes in the tumor microenvironment, including tumor treatment sensitivity, induction of antitumor immunity, reductions in inflammation, and increases in antioxidative capacity (52, 578). While poor vasculature and permeability of solid tumors often pose a challenge for treatment, exercise can expand vessel density and tumor perfusion, improving the efficacy of anticancer agents (52). Ongoing research is needed to consider the range of cancer types, chemotherapeutic agents, and exercise modalities (299).

Cancer patients, including pediatric patients, are now living longer after treatment (901). Unfortunately, long-term side effects of toxic treatments are a growing concern, contributing to a rising burden of cancer treatment-related disease (e.g., CVD, HF) even 30 years after treatment (299). Given its short-term cardioprotective effects in individuals undergoing chemotherapy, long-term exercise could have a role in reducing the risk of treatment-related adverse outcomes. In support, a prospective study in 2973 breast cancer patients found a dose-dependent protective effect of physical activity during recovery on CVD risk (654). Similar findings have been reported in testicular cancer (299). Finally, a recent meta-analysis by McTiernan et al. reported that physical activity was inversely related to both all-cause and cancer-specific mortality in survivors of breast, colorectal, and prostate cancers (878). Despite promising evidence that exercise is necessary before, during, and

after cancer treatment, greater insight into molecular mechanisms driving exercise-induced improvements in tumor biology, cardiotoxicity, and long-term survival is needed. This will continue to guide the field of exercise oncology toward developing and optimizing specific exercise prescriptions for individuals with cancer (965).

Neurodegenerative diseases

Neurodegenerative diseases are on the rise in the rapidly aging population (1453), with today's prevalence rates expected to triple 2050 (158). Associated dementia is a major public health concern, projected to cost $2 trillion globally in the next decade (971). Dementia is highly debilitating, demolishing an individual's independence and quality of life while placing immense emotional and financial strain on their family and caregivers. The current and projected economic burden of neurodegenerative disease and dementia prompted a call-to-action in 2015 (1453) for research directed at modifying progression of neurodegenerative diseases As there are currently no cures or specific biomarkers for these conditions, the impact of lifestyle factors such as exercise is of great research interest (367, 454, 873). While most exercise research focuses on the most common neurodegenerative disorders, dementia exists in numerous forms with wide variability in pathology, presentation, and progression.

Alzheimer's disease—AD is the most common neurodegenerative disease: clinical AD affects approximately 4% of older adults worldwide (394) and preclinical AD or mild cognitive impairment (MCI) impacts significantly more at an earlier life stage (158). Postmortem AD brains show neurofibrillary tangles and plaques made of the peptide amyloid-β, but the current best biomarker is a single nucleotide polymorphism in apolipoprotein E4 (ApoE4), shared by over 50% of adults living with AD (1137). ApoE4 genotype may be relevant to exercise adaptation: in a longitudinal study of 1646 older adults, habitual exercise is associated with lower risk of dementia in only noncarriers (389). Conversely, a study by DeMarco et al. (321) found that acute exercise heightened brain function in young female ApoE4 carriers but not in noncarriers, an area warranting further investigation in older populations. Nevertheless, physical activity reportedly reduces the incidence of AD by approximately 40% to 50% (168, 504) and higher levels of regular exercise may be associated with reduced amyloid-β burden (161, 162). In older adults with MCI, short-term RE (154) and AE (1295) training mitigate reductions in volume and plasticity of key brain regions impacted in dementia and AD. Furthermore, important changes are sustained up to one year following the cessation of training (154). In a sophisticated study examining the relationship between regular exercise (reported as step-count) and gene expression in the hippocampal brain region, Berchtold et al. (108) found that physical activity promoted transcriptional patterns of genes primarily associated with mitochondrial health, synaptic plasticity, and neuromuscular communication that were inversely related to cognitive impairment and AD. Thus, exercise may target critical signaling pathways that are dysregulated in AD and dementia, representing a potential mechanistic strategy for preservation of cognitive function.

Parkinson's disease—The second most prevalent neurodegenerative disorder (affecting ~1% of adults over age 65 year) is Parkinson's disease (PD), which stems from death

of dopaminergic neurons in the substantia nigra of the midbrain. PD is considered a neurodegenerative movement disorder: the first symptoms of PD are not detectable until most of these neurons have died (122) but predominantly manifest as motor function abnormalities (tremor, bradykinesia) in addition to deficits in senses, sleep quality, mood, and cognition. Some cases of PD are accompanied by abnormal accumulation of α-synuclein into Lewy bodies in the brain. Lewy body dementia (LBD), a separate but overlapping type of dementia often manifests in so-called “Parkinsonian” symptoms (47, 1441). Perhaps due to this complexity, exercise training studies in populations with exclusively LBD are lacking (626), highlighting an existing knowledge gap.

A prevailing theory is that motor symptoms of PD take years to manifest because of a physiological tolerance threshold for loss of nigrostriatal dopamine, below which motor function is compromised (122). In a longitudinal study of nearly 200,000 cross-country skiers, Olsson et al. demonstrated that exercisers lived longer before onset of PD, suggesting that AE may fortify this “motor reserve” (991). In populations with moderately advanced PD, RE may restore skeletal muscle size and strength to levels found in healthy adults, in addition to reducing the severity of nonmotor symptoms (29, 682). Furthermore, relative motor unit activation (the degree of neuromuscular “effort” relative to maximal contraction that is required to perform a task) is improved with RE in PD (682, 683). Regular exercise also can improve balance and gait speed (1205), although the lasting effects of such interventions are not presently clear (1386, 1441). Large cohort studies suggest that an exercise regimen started in middle-age may reduce risk of PD (17). Mechanistically, this may be linked to higher insulin sensitivity (861), reduced neuroinflammation (873), or acutely elevated activity of the substantia nigra (685) in individuals who exercise regularly. Ongoing research is investigating whether beginning exercise shortly after diagnosis may delay PD progression or the need for dopaminergic medication (1158). Finally, limited data exist as to the effects of exercise on MCI and dementia in PD, which are highly common in its later stages (552).

Section summary

Overall, strong evidence supports that exercise has beneficial effects for organ function in both health and disease, reducing overall risk of morbidity and mortality. A range of disorders and diseases are becoming increasingly prevalent as our population grows steadily more sedentary (213, 1447). Physical activity, whether recreational or structured exercise, promotes the preservation of multiple physiological systems, including musculoskeletal, cardiovascular, neurological, and metabolic function. Some have referred to exercise as a “polypill,” that can not only mimic but outperform pharmaceutical interventions (955) with little to no side effects and at lower cost. Nevertheless, there is a tendency of clinicians to prioritize pharmacologic treatments over exercise (953). Thus, research efforts should be directed at understanding the molecular mechanisms driving exercise-induced improvements in physiological function to provide evidence-based guidance for clinicians (1146). In the general public, behavioral interventions targeting individuals, groups, and/or communities are absolutely necessary to build exercise habits and facilitate a society in which a physically active lifestyle is commonplace.

Current and Emerging Methodologies for Biospecimen Assessment

Much of our current knowledge surrounding the molecular mechanisms mediating the effects of exercise in humans comes from analysis of biospecimens collected at various time points before, during, and after chronic training (i.e., adaptation) or a single acute bout of exercise (i.e., short-term response/transient effect). While exercise is a robust physiological stimulus affecting nearly every system, this article and MoTrPAC clinical studies focus on tissues most accessible in humans: skeletal muscle, blood, and adipose. MoTrPAC and countless independent investigations utilize animal models to capture molecular activity in inaccessible human tissues such as brain, liver, heart, and so on; these preclinical studies continue to provide mechanistic clarity regarding important pathways underlying exercise adaptation.

Skeletal muscle

Skeletal muscle biopsy considerations—The first percutaneous needle was created by Guillaume-Benjamin Duchenne in 1865 allowing the sampling of skeletal muscle, which resulted in the discovery of Duchenne Muscular Dystrophy (226). This sampling method was further adapted by Jonas Bergström, (112) and further modified by Evans et al. in 1982 with the application of suction through the trocar, increasing the yield of biopsy specimens by approximately four-fold (378, 1289). Since then, the Bergström needle has been used to sample primarily the vastus lateralis due to its large size, subcutaneous location, and distance from major neurovascular structures. In addition to the vastus lateralis, the deltoid, anterior tibialis, soleus, gastrocnemius, trapezius, biceps, and triceps have also been sampled (109, 281, 446, 473, 825, 837). While it is advantageous to sample the vastus lateralis muscle, some technical controls should be implemented whenever possible, as the distribution of type I and II myofibers (and thus the molecular characteristics of the sample) may differ depending on participant demographics (sex, age), dominant leg (right or left), location along the muscle, and depth sampled (788–792).

In addition to the widely used Bergström needle, other sampling needles such as the microbiopsy needle, the Well-Blakesley conchotome, the myotome, the Polly-Bickel needle, and others have been introduced (555, 995). The microbiopsy needle has been reported to reduce the invasiveness of the muscle sampling procedure due to its smaller diameter, while negating the need for skin and fascial incisions to gain access to the muscle (538, 606). Anecdotal reflection from a participant perspective indicates a preference for the microbiopsy procedure (606). The microbiopsy needle typically yields a short and wide muscle specimen (~70–90 mg), compared to approximately 50 to 400 mg of long and thin muscle tissue obtained from a standard Bergström needle biopsy. As such, the optimal approach should be carefully considered in light of downstream research objectives that may be particularly reliant on a given arrangement of myofibers within the bundle and total tissue yield required.

Regardless of the instrument chosen for extraction of the biospecimen, tissue processing should be performed according to research objectives. First, it is necessary to remove any blood, fat, fascia, and connective tissue from the biospecimen, as these may contaminate the sample and influence downstream results. Timing is of the utmost importance: dynamic,

transient effects such as phosphorylation (182, 451), methylation (89), etc. necessitate preferential allocation of tissue for proteomics and metabolomics (1125). Homogenate analyses (such as these and other ‘omics) actually capture a variety of cell types in addition to skeletal myofibers (1127). In contrast, single-fiber analyses reveal enriched biological signatures that may be diluted by a homogenate approach (1091). In terms of tissue allocation, a longer bundle may be better suited for teasing apart and clipping individual myofibers for fiber type-specific analyses, whereas a wider bundle may provide extensive surface area better suited for histological analyses. Most commonly, fibers are oriented transversely, such that slicing the mounted specimen with a cryostat yields a cross-sectional view of the myofibers within the bundle (945). Alternatively, longitudinal muscle sections may be preferable for visualization of certain subcellular structures at high resolution, such as sarcomeric structures and mitochondria.

Histological staining and imaging—Tissues designated for histology can be preserved immediately by submersion into a fixative such as glutaraldehyde or formaldehyde and subsequently used for methodologies including transmission electron microscopy (TEM) (453). TEM is considered to be a gold standard methodology for skeletal muscle imaging, allowing the detection of changes in microstructures such as mitochondria, including volume, density, number, and morphology (1190). Imaging techniques continue to evolve. Focused ion beam-scanning electron microscopy (FIB-SEM) has allowed detection of myofiber-type specific differences in mitochondrial morphology following 3D reconstruction of human vastus lateralis single myofibers and muscle sections (180, 293).

Obtaining TEM and FIB-SEM images in combination with the analysis process can be very time consuming and costly. The more widely used alternatives include confocal, light, or fluorescence microscopy. Biopsy samples are preserved through a controlled freezing technique to limit the expansion of intracellular water and prevent freeze-fracture artifacts in the tissue (739). Briefly, samples are mounted in a water-soluble embedding medium such as optimal cutting temperature compound mixed with tragacanth gum, submerged in isopentane cooled with either liquid nitrogen or dry ice, and frozen for long-term storage at −80 °C or below.

These commonly used methods can prepare muscle for staining ranging from hematoxylin and eosin to more complex co-staining procedures (e.g., neutral lipid stain, oil red O, and immunohistochemical co-stains) (834, 945, 1190). These techniques can be applied to detect myofiber type-specific phenomena, such as changes in oxidative capacity measured through cytochrome C oxidase expression, and changes in lipid droplet associated proteins before and after sprint interval training (1190). Confocal images of sectioned or single muscle fibers enable in-depth analysis of mitochondrial morphological changes in relation to skeletal muscle intramyocellular lipid stores (733).

Finally, laser capture microdissection (LCM) is an advanced method in which specific myofiber populations are physically excised. While technical barriers exist, a major strength of LCM is the ability to perform both targeted and high-throughput ‘omics analyses on a relatively smaller amount of muscle tissue than required by other applications. Illustrating the efficiency of data collection, Murgia and colleagues reported the detection

of >2000 proteins in approximately 2 h of measurement time (949). Combining LCM with downstream gene and protein analysis has enormous potential for characterizing differences between myofiber populations, for example, based on myosin heavy chain isoform (1265) or abundance of another target of interest (949).

Single myofiber physiology—Skeletal muscle fibers may be assessed for parameters such as contractile force, shortening velocity, and power in the absence of nervous system input and physiological fluctuations in calcium availability. Briefly, for this approach, myofiber bundles are permeabilized in a skinning solution, and then individual myofibers are teased out and tied between a force transducer and motor arm. To determine maximal shortening velocity, the myofiber is submitted to a slack test (355): the myofiber is slackened by moving the motor arm, and time to redevelop force (whereby the slack is alleviated) is calculated and averaged at four settings along the length of the myofiber. Another commonly performed assay relies on measurement of the relationship between force and shortening velocity at a series of fiber lengths to calculate theoretical maximal velocity and power (405). Single myofiber physiology experiments have aided in illustrating fundamental differences in contractile properties between myofiber types, such as approximately five-fold higher power in pure type IIa than type I myofibers (437, 1321). These techniques have also enabled detection of intricate changes in the myofiber contractile apparatus that arise from exercise training (405, 1320, 1325, 1328), aging (498, 1321), and unloading (1425, 1426).

Muscle satellite cell culture—Mature skeletal muscle contains satellite cells, a pool of stem-like cells that facilitate remodeling and regeneration in response to stress (534, 1039). This regenerative potential and the mechanistic impact of biochemical and mechanical perturbations on muscle satellite cells can be assessed in vitro using cell culture models. In isolating satellite cells from human skeletal muscle biopsies, the surface marker cluster of differentiation (CD)56 (also known as neural cell adhesion molecule, or NCAM) is often used to differentiate satellite cells from fibroblasts and other cell types in the specimen (12). Alternatively, animal-derived cell lines such as C2C12 (mouse) or L6 (rat) cell lines may be employed. Some evidence suggests variation in the basal expression of metabolic, proliferative, and developmental genes across species (3), potentially complicating the translatability of cell culture experiments.

Throughout a controlled period of growth in a cultured environment, muscle satellite cells differentiate into myoblasts and eventually fuse into multinucleated myotubes (1244). Notably, myotubes can be stimulated to contract, mimicking exercise in the absence of systemic or neural influences with the use of methodologies such as electrical pulse stimulation (EPS) (148, 375), pulsed forskolin and ionomycin (276, 1232), 5-aminoimidazole-4-carboxamide-1-β–ribofuranoside (AICAR), and caffeine (203). These stressors allow recapitulation of some of the intermyofibrillar adaptations to an exercise-like stress, such as accretion of contractile protein (148), bioenergetic adaptations underlying metabolic flexibility (1232), and myokine production and release (435). While administration of these biochemical stressors provides mechanistic insight into key pathways underlying myocellular adaptations, it is important to note that they are only able to

partially capture the impact of exercise exposure and often cannot mimic the characteristic multisystem elevation in cellular energy demand.

Blood

Many of the beneficial effects of exercise are the integrated result of multiple physiological systems engaging in cross-tissue communication. In this regard, the circulatory system is important facilitator of tissue cross talk via delivery of signaling molecules, cells, and other structures between tissues. A primarily relevant example of this is myokines such as IL-6, which is secreted from glycogen-depleted skeletal muscle and acts in a paracrine fashion on the liver to stimulate glucose release in support of continued muscle contraction (1026, 1249). Exercise-induced myokine secretion facilitates adaptations including hypertrophy (myostatin, IL-4, -6, -7, and -15), and osteogenesis (IGF-1, FGF-2), fat oxidation, insulin sensitivity, and anti-inflammation (IL-6) (1018). In addition, lipids (e.g., 12,13-dihydroxy-9Z-octadecenoic acid, or 12,13-diHOME) and metabolites (e.g., succinate) can also serve as circulating signaling molecules during and after exercise. Arteriovenous balance studies of the forearm, leg, and splanchnic bed [classically been used to examine fuel metabolism during exercise (15)] allowed the characterization of the temporal release of IL-6 from the leg following acute exercise (1250) and can be a powerful approach to identify other novel factors released from tissues of interest.

A developing area in the context of exercise biology is the production, release, and packaging of proteins and microRNAs (miRNA) into secretory vesicles such as extracellular vesicles (EVs), microvesicles (1018), and exosomes (444, 594, 793, 959). These signaling factors are thought to convey molecular factors underlying a range of systemic adaptations to exercise; thus, much remains to be learned by characterizing their contents and identifying the tissue of origin (751). Many of the standard biochemical workflows used to analyze tissue homogenate and single myofibers (e.g., protein immunoassay, targeted gene expression, other ‘omics) can also be applied to secretory vesicles. For instance, combining EV isolation with mass-spectrometry, Whitham et al. identified 322 proteins that were significantly increased immediately after exercise and 3 at 4 h postexercise time point (1423). Continued research into EVs and related species released in response to exercise may prove to be a powerful resource in designing integrative disease therapies.

Leukocytes, the circulating cells of the immune system, are also involved in mediating the beneficial effects of acute and chronic exercise. Acute exercise induces a temporal shift toward increased circulating natural killer cells and neutrophils (1479). Leukocyte (e.g., neutrophil and monocyte) infiltration into peripheral tissues such as skeletal muscle plays a critical role in repair and regeneration following exercise (843) and long-term hypertrophy (422). Beyond a standard complete blood count with differential, flow cytometry can be used to study leukocyte redistribution, alterations in expression of cell surface markers, and changes in leukocyte function with exercise (1082). Leukocytes can be sorted into specific populations for follow-up analyses using flow cytometry or via incubation and centrifugation in specific collection tubes coated with preservative chemicals.

Adipose

Adipose tissue was classically perceived as a relatively inert organ for storage of triglycerides; however, it is now recognized as an endocrine organ (687) displaying phenotypic diversity across adipocyte subpopulations (e.g., white, beige, brown) with distinct metabolic and functional roles (463). As the body's major energy reservoir, adipose tissue plays a key part in whole-body metabolism, with dysfunction contributing to pathologies such as obesity, T2D, dyslipidemia, and insulin resistance. Excess accumulation of upper body adipose in particular is linked to increased risk for CVD (413, 481). Dysfunction in adipose tissue is characterized by larger, metabolically inflexible adipocytes, immune cell infiltration and activation, senescence, impaired lipid turnover, and secretion of deleterious factors (315). In turn, exercise plays a key role in maintaining a healthy metabolic phenotype in adipose tissue (314).

Subcutaneous adipose tissue specimens can be extracted from the abdomen or gluteal prominence using a punch biopsy, aspiration with a Bergström or Mercedes liposuction needle, or surgical removal (20, 185, 302, 1008). Depending on the technique, approximately 100 mg to several grams of tissue can be obtained. The sample should be washed with ice cold phosphate-buffered saline and then flash-frozen in liquid nitrogen or prepared for histology by embedding in parafilm. A number of histomorphological methods have been developed to image and quantify adipocyte size and number (121, 230, 852). Furthermore, collagenase digestion of the adipose specimen allows the separation of stromal vascular cells (T-regulatory cells, macrophages, smooth muscle cells, and mesenchymal stem cells) from mature adipocytes, which can then be analyzed via flow cytometry or single-cell 'omics approaches (54, 130).

High-throughput 'omics approaches

Transcriptomics—Relatively recent advancements in high-throughput data collection, analysis, and computation have greatly accelerated the discovery of the molecular transducers of biological phenomena in health, disease, and exercise. Prior to the advent of next-generation sequencing tools, studies employed microarray technology to examine transcriptome-wide changes in gene expression as a result of AE (253, 839, 1296, 1308) and RE (253, 1040, 1051, 1299, 1300). Since this time, newer direct sequencing technologies designed to more precisely and deeply define tissue- and cell-level transcriptomes have been applied to the study of exercise (264, 332, 1051, 1053, 1062). RNA-sequencing (RNA-seq) directly sequences cellular RNA and maps reads to a reference genome through bioinformatic analysis to quantify levels of individual transcripts (929). RNA-seq can be applied to measurement of all available forms of RNA or limited to messenger RNA (via pulldown of all polyadenylated RNA species). True to its nature as a discovery tool, RNA-seq can reveal nonprotein coding transcripts (e.g., long noncoding, circular, small, and miRNAs), which are receiving increased attention as regulatory factors in exercise biology (813, 1203).

A comprehensive and powerful approach is to integrate RNA-seq with other 'omics (264, 532), linking gene expression to variation in the genomic architecture, epigenetic regulation, and other molecular phenotypes. For example, chromatin immunoprecipitation sequencing

(ChIP-seq) involves immunoprecipitation of DNA-interacting proteins and subsequent direct sequencing of associated DNA fragments (652). Using antibodies to specific histone modifications, the epigenetic landscape of the sample can be determined. A recent elegant study used epigenetic markers of transcriptional enhancers (demethylation of histone 3 lysine 4 and acetylated histone 3 lysine 27) in combination with RNA-seq in a mouse wheel running model (1088). Integration of the gene expression and epigenetic data revealed activation of transcription factors myocyte enhancer factor 2 (MEF-2) and estrogen-related receptor (ERR) upstream of heightened expression of oxidative metabolism genes (1088). Integrated multi-omics designs such as this, along with ever-evolving molecular mapping technologies (532) may provide mechanistic insight into observed biological relationships (440).

Bulk tissue RNA-seq and related techniques, while powerful, represent composite gene expression in an entire sample. In contrast, recent advancements in cDNA synthesis from single cells allow interrogation of single-cell transcriptomes by RNA-seq (929), providing the ability to profile gene expression in individual cell populations before and after a given intervention. Studies investigating the cellular composition of skeletal muscle tissue samples (319, 461, 1127) have revealed a number of resident cell types (e.g., immune, endothelial, satellite, and fibro-adipogenic progenitor cells), each displaying a unique transcriptomic signature. Due to size limitations of the single-cell isolation, these studies typically filter myofibers out of analysis. Other technologies such as single-nuclei RNA-seq should theoretically enable assessment of all cell types including myofibers (500, 597); however, the multinucleated nature of mature skeletal myofibers may introduce complexity in this approach. The emerging spatial transcriptomic technology, which enables measurement of gene expression on intact histological specimens (913, 1243), may become a viable technique for assessing gene expression in specific regions of muscle tissue.

Proteomics—Our understanding of molecular interactions governing adaptations to exercise is more deeply enriched by evaluation of multiple levels of omics data (899). Similar to high-throughput sequencing technologies, advances in mass spectrometry allow broad and unbiased survey of the proteome (478). Using this approach, several studies have reported training-induced changes in skeletal muscle metabolic proteins encoded by mitochondrial and genetic DNA, a finding consistent with transcriptomic datasets (357, 586, 1109, 1160). The circulating plasma proteome also reflects a positive influence of activity status on mitochondrial proteins, in addition to reductions in inflammatory, immune, and stress response proteins (1149). Single myofiber proteomics has also been developed (948). When applied to humans, this technique reveals differences in glycolytic as well as sarcomere chaperone pathways in slow and fast fibers (950). These approaches will undoubtedly be useful in assessing myofiber type-specific proteomic changes and adaptations to exercise. Furthermore, agnostic bioinformatics pipelines originally developed for gene expression datasets (e.g., Weighted Gene Correlation Network Analysis) can be applied to proteomics and other high-throughput datasets with relative ease (1149).

Measurements of posttranslational modifications such as phosphorylation and acetylation provide an additional layer of information and biological complexity. Phosphorylation is typically reversible and regulates multiple aspects of protein function (e.g., conformational

change, enzyme activation, subcellular localization, degradation, stability). A small but seminal study by Hoffman et al. identified changes in the human skeletal muscle phosphoproteome following a high-intensity exercise bout (576): this work outlined a complex network of phosphorylation events mediated by multiple kinase pathways. A follow-up study combined this dataset with phosphoproteomics in mice and rats to identify exercise responsive adenosine monophosphate-activated protein kinase (AMPK)-dependent regulation of store-operated calcium entry (967). Unlike phosphorylation events catalyzed by kinases, acetylation of lysine residues on nonhistone proteins is thought to be mediated by nonenzymatic mass action (1381). Affinity purification of acetylated lysine residues followed by mass spectrometry allows for an unbiased survey of the acetylome (543). Given the role of acetylation in mitochondrial dynamics and metabolism (338, 1264, 1429), assessment of the acetylome will likely be a valuable tool in exercise biology.

Finally, proteins are susceptible to modification by reactive oxygen species and reactive nitrogen species, collectively termed redox modifications. These processes are known to contribute to age-related muscle loss and atrophy (1139). Mass spectrometry-based techniques utilizing differential labeling of free thiol groups on cysteine residues have now been developed, with studies focusing on redox modifications in aging mouse skeletal muscle (867, 1221). Future application of this and other proteomic techniques to human exercise is likely to reveal transducers of acute responses and long-term adaptation.

Metabolomics—Both acute and chronic exercise-induced flux in energy substrate utilization (584) may be reflected in the metabolite pool of systemic circulation or specific tissues. Like proteomics, advances in mass spectrometry allow for both supervised (targeted) and unsupervised (unbiased) surveys of metabolites influenced by exercise. For instance, Lewis et al. observed acute increases in circulating lactate, adenine nucleotide catabolites, and tricarboxylic acid cycle intermediates (e.g., succinate, pyruvate, malate) following a Vo_2max test, as well as reductions in gluconeogenic amino acids following marathon running (786). Following long-term (~6 month) AE training, changes in circulating metabolites have been associated with changes in cardiorespiratory fitness (147) and insulin sensitivity (604). Thus, the circulating metabolome may represent an accessible method for assessment of the influence of exercise on health and disease. Naturally, metabolomics may also be applied to tissues of interest, such as skeletal muscle (603).

Lipidomics—Mass spectrometry may also be applied to measurement of lipid species (519), including both structural (phospholipids, sphingolipids, etc.) and signaling (prostaglandins, leukotrienes, etc.) molecules. Most commonly, the technique involves an organic extraction followed by a liquid chromatography (LC) step prior to mass spectrometry. This approach has been used to characterize exercise-induced changes in skeletal muscle lipids in both preclinical models and humans (768, 850, 885, 1178, 1239). Prominently, changes in levels of the mitochondrial structural lipid cardiolipin have been shown to relate to mitochondrial capacity following weight loss and moderate AE training (258, 885). Others have shown an acute rise in the signaling lipid 12,13-diHOME following a single bout of AE (1239). Recently, a more comprehensive lipidomics approach has been developed: removal of the LC step has the potential to identify a range of lipid species

missed by traditional methods (520). This method has recently been used to measure lipids in skeletal muscle, including after exercise (1053, 1331).

Section summary

A range of complex approaches to collect, process, and comprehensively profile biospecimens have been developed over the past 50 years (Figure 4). In addition to molecular mapping with transcriptomics, methylomics, proteomics, etc., the influence of internal [e.g., gut microbiome, (1421)] and external environmental factors [e.g., the "exposome" (88)] has yet to be explored as a mediator of inter-individual response to exercise. At this point, our capacity for generating data exceeds our ability to interpret findings. Like genetic data, metabolomic and lipidomic data sets may be limited by the reference against which identified species are matched; thus, continued efforts to expand these resources will be fruitful. As such, continued development of both data and knowledge driven bioinformatics analysis tools will aid in expansion, integration, and interpretation of multi-omics data sets from exercise studies (532).

Skeletal Muscle Adaptations to Exercise

For obvious reasons, skeletal muscle has been a tissue of interest for insight into adaptation to exercise. Early studies led by pioneers such as Bengt Saltin, John Holloszy, David Costill, and others provided insight into key histological and cellular phenotypes affected by long-term training and acute exercise. Since these early works, collective knowledge of the molecular biology of skeletal muscle has been broadly amplified. The plasticity of skeletal muscle to perturbations such as training, overtraining, detraining, bed rest, unloading, and microgravity is astounding. Beyond this, skeletal muscle is no longer seen as merely a machine for movement, but an endocrine organ, an immune reservoir, and an indicator of physiological wellness.

Structure and function of skeletal muscle

Muscle comprises 40% to 50% of total body mass (428). At the system level, muscle is a hierarchically arranged structure divided into fascicles by the presence of connective tissue called perimysium. Fascicles are comprised of myofibers, and myofibers are composed of myofibrils, which house a contractile unit referred to as the sarcomere. At this structure, receipt of an action potential from an innervating neuron is translated into the release of calcium from the sarcoplasmic reticulum, which enables interaction between the primary filaments of the contractile apparatus (24, 484). To summarize an exquisitely described concept introduced by Huxley and Hanson (616), myosin filaments slide over interlocking actin, a process by which the sarcomere is shortened and the muscle "contracts." During a contraction, the physical interaction between actin and myosin is continually broken and renewed in a process known as cross-bridge cycling. This process requires energy, and the energy system by which a given myosin isoform generates the necessary ATP dictates its metabolic profile (753). For instance, myosin heavy chain (MHC) I preferentially utilizes oxidative phosphorylation, whereas MHC II has greater glycolytic ATPase activity.

In addition to a well-engineered mechanism for contraction and movement, skeletal muscle tissue houses a range of other cell types such as satellite cells, macrophages, endothelial cells, pericytes, and others (1127). Muscle itself is considered a syncytium: each myofiber is multinucleated. As such, muscle nuclei may be able to orchestrate a wide-ranging yet integrated response to a given stimulus, such as exercise or loading. The degree to which muscle secretions, such as myokines (1020) and exosome-like vesicles (1423), influence adaptation continues to be elucidated. Finally, muscle's extensive protein content makes it a primary amino acid reservoir for an organism (428, 1438); thus, muscle is a common casualty in conditions requiring a substantial, sustained immune response. While the complexity of muscle has presented unique methodological challenges, its relevance for exercise, performance and health, relative ease of access, and rich history of its study have led the field to an appreciation for its adaptability to AE and RE (Figure 5) and an enthusiasm to continue to explore the unknown.

Skeletal muscle adaptations to aerobic exercise

The molecular and histological adaptations to an AE training stimulus have been classically examined in skeletal muscle. AE performance is contingent on both high oxidative capacity and fuel economy, and muscle-level adaptations contribute to both factors. Importantly, the maximal metabolic capacity (33) and blood flow (756) of skeletal muscle exceed what can be physiologically achieved by cardiac output, indicating that the physiological ceiling exists outside of muscle itself in most environments (the obvious exception being low oxygen tension at altitude). Nevertheless, whole-body oxygen consumption is highly correlated with molecular indices of muscle oxidative capacity, including activity of enzymes such as succinate dehydrogenase (277) and citrate synthase (1368), both involved in oxidative phosphorylation. Despite the directional correlation, the magnitude of plasticity in these outcomes varies considerably: Gollnick et al. found that five months of AE training induced a 25% increase in Vo_2max but a 95% increase in succinate dehydrogenase activity and a 116% increase in phosphofructokinase activity (469). These adaptations are likely to facilitate submaximal activity common in long-duration AE, improving the efficiency of energy production and utilization.

Myofiber adaptations—In addition to being characteristically smaller (~10%–20% vs. type IIa) and less powerful (~5-fold lower power vs. type IIa), type I myofibers are less fatigable than their fast-twitch counterparts (404). In humans, AE training does not usually induce a II-to-I shift (1322), although this has occasionally been reported (708). Also, hybrid (e.g., IIa/IIx or I/IIa) fibers may transition toward a pure type I myofiber phenotype (1322). Cross-sectional studies that report higher type I myofiber distribution in AE-trained individuals (470) cannot definitively rule out that individuals with differential proportions of slow-versus-fast myofibers self-select for a given exercise mode. In fact, genetic predisposition to athletic success has been an area of academic interest (623). It is unlikely that the observed differences are the effects of long-term training, since lifelong AE-trained older adults do not demonstrate a significantly higher proportion of type I myofibers than age-matched counterparts (498). The phenomenon by which type II myofibers undergo preferential age-related atrophy and apoptosis adds an additional complexity to this comparison (979, 1105). While preclinical studies have identified some

of the molecular determinants that lead to an oxidative myofiber phenotype (e.g., MEF-2) (1063, 1452), it is unclear whether these factors play similar roles in adult human muscle adaptations to exercise. Illustrating a potential connection, muscle unloading, a stimulus that induces a slow-to-fast myofiber shift in humans (133, 1324), has been associated with inhibition of MEF-2 (1130).

At the cellular level, AE training induces important adaptations in the structure and function of type I myofibers. Some evidence suggests a reduction in type I myofiber diameter (1322, 1427), which is thought to be beneficial for reducing diffusion distance between oxygen-supplying capillaries and the center of the myofiber. However, this is not a universal finding (469, 522, 1075). Furthermore, the addition of muscle capillaries with AE training is likely to keep pace with or exceed myofiber hypertrophy, such that unavailability of blood supply is unlikely to impose a size limitation (708). Myofiber functions such as shortening velocity (405, 522), power (498), and oxidative capacity (544) are commonly improved or preserved with AE, with the strongest effects usually reported in type I myofibers. The common AE practice of tapering appears to have additional effects in type IIa myofibers that may contribute to athletic performance (523, 824, 1319). Thus, despite the classically overengineered architecture of skeletal muscle (35, 139), long-term training elicits beneficial effects at the level of the muscle cell.

Mitochondrial biogenesis—As the site of ATP production, muscle mitochondria form a dense and active network that supports the bioenergetic needs of skeletal muscle (535). Animal-based research as early as the 1950's demonstrated a relationship between aerobic capacity and respiratory enzyme content (760, 1012), leading to a host of studies examining the influence of AE on mitochondrial biogenesis in a range of tissues and populations (344, 472, 809, 1132). Increased mitochondrial biogenesis in response to AE may be reflected by changes in copy number of mitochondrial DNA (mtDNA) (884, 1431). Similarly, membrane phospholipid cardiolipin may be used as a marker for mitochondrial content (883). Copy number is elevated by >50% in AE-trained versus untrained individuals (1079) and may increase following short-term training in older adults (883). These effects are thought to be a result of acute "bursts" in transcription of mtDNA following exercise (426, 1033).

Mitochondrial proteins are encoded on both the nuclear and mitochondrial genomes (424). Mechanistically, much regarding the transcription and regulation of these factors have been discovered using animal models and later translated to humans in targeted studies. Transcription factor families such as nuclear respiratory factors (NRF) and estrogen-related receptors (ERRs) are key regulators of transcription of nuclear-encoded mitochondrial genes (465, 1154). Both NRF and ERR have been shown to be increased in response to AE (204, 398). Transcription of the mitochondrially encoded genes is largely regulated by Transcription factor A mitochondrial (Tfam) (465, 1373). Tfam is more highly expressed in skeletal muscle of highly AE-trained adults (1323), but acute AE does not consistently lead to upregulation of Tfam at the mRNA (260, 1061) or protein (490) level.

Co-activators such as peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) interact with these transcription factors to promote increased mitochondrial number, size, and protein content in response to AE (62, 273). Both acute (521, 1050) and chronic (490,

1131, 1323) AE stimulate expression of PGC-1α in human skeletal muscle. PGC-1α may be processed via alternative splicing mechanisms into any of four transcripts (PGC-1α1–4) with distinct but overlapping biological roles (856): PGC-1α1 appears most important for adaptations in aerobic metabolism (273, 801), while PGC-1α4 is believed to play a role in muscle hypertrophy (1126). The family of PGC-1α isoforms also partially controls key metabolic processes in skeletal muscle, including lipid oxidation (600), mitochondrial autophagy (1344), and angiogenesis (43, 240) via upregulation of VEGF.

Mitochondrial dynamics—Along with increased mitochondrial biogenesis, dynamic changes in mitochondrial volume and connectivity accompany muscle adaptations to AE (50, 59, 914). In key processes involving inner and outer mitochondrial membrane proteins, mitochondria can either be joined together (fusion) or cleaved apart (fission), based on cellular energy state (45, 366, 410). In a balanced process, fusion and fission maintain overall mitochondrial function as the cellular mechanism of cycling newly formed mitochondria into the mitochondrial pool while damaged/dysfunctional mitochondria undergo autophagy (45).

Fission is promoted through phosphorylation of dynamin-related protein-1 (DRP1), which then binds to an outer membrane receptor such as mitochondrial fission 1 protein (FIS1) or mitochondrial fission factor (MFF) (998). DRP1 activity is increased in response to acute and chronic AE in human muscle (734). Mitochondrial fusion occurs when the outer membrane GTPases mitofusin 1 and 2 (MFN1 and 2) dimerize and pull two mitochondria together (410). The inner membrane compartments are then joined by optic atrophy-1 (OPA1) (836). Markers of both fission and fusion have been shown to be elevated after AE training (721, 1033). Studies in older adults suggest that long-term AE training appears to promote fusion as the ratio of fusion-to-fission proteins increases. These changes are associated with improved metabolic functions including insulin sensitivity and glucose handling (50, 59, 385, 1456). While these and other (1212, 1213, 1273) mechanistic factors underlying improved oxidative capacity have been identified in animal skeletal muscle, continued research is necessary to fully elucidate how mitochondrial biogenesis and dynamics impact exercise training adaptations in health and disease.

Subcellular adaptations—As a regulator of crossbridge formation, calcium plays a key role in skeletal muscle intracellular signaling. During exercise, action potentials travel along the transverse tubules of skeletal muscle to activate dihydropyridine receptors. This promotes opening of the sarcoplasmic reticulum channel ryanodine receptor 1 (RYR1), leading to an increase in cytosolic calcium (24, 484). Naturally, calcium release, muscle contraction, and re-sequestering of calcium are energetically costly. Thus, improved capacity for oxidative phosphorylation is essential for skeletal muscle to support long periods of repetitive contractions during AE (233, 582, 585). The CaMK family plays roles in calcium-sensing, with downstream effects relevant to AE. In mice, CaMK IV activates PGC-1α and associated downstream pathways leading to mitochondrial biogenesis (1451), whereas CaMK II has been associated with structural and contractile adaptations (363). CaMK II is the primary isoform expressed in human muscle (1119, 1120). Basal CaMK II

phosphorylation is elevated following AE training (1061, 1118) in a muscle-specific fashion (1118); acute AE also leads to increased activity of CaMK II (1119).

In 1982, Davies et al. reported a molecular signature associated with tissue-damaging exercise (308). Since this time, reactive oxidative species (ROS) and reactive nitrogen species have received attention for their roles in communication and signal transduction in response to exercise (1067, 1068). For instance, superoxide (O_2^-) is produced in a variety of skeletal muscle structures such as the sarcoplasmic reticulum, transverse tubules, sarcolemma, and (most often) complexes I and III of the mitochondrial electron transport chain (85). Active superoxide can undergo dismutation into hydrogen peroxide (H_2O_2) either spontaneously or via enzymatic reaction. In animals, mechanisms that facilitate dismutation are more abundant in type II myofibers (36). Notably, H_2O_2 is a weak oxidant and may react with many signaling pathways to promote mitochondrial health (383, 628, 629, 1067, 1364). In humans, emission of H_2O_2 is elevated during inactivity and reduced by AE training (487). Another key signaling molecule is NO, which is converted from the amino acid L-arginine by one of four nitric oxide synthase (NOS) isoforms; NOS1 and NOS3 are the most prevalent isoforms produced in skeletal muscle (457, 938). When NO is increased in skeletal muscle in response to aerobic exercise, it may promote mitochondrial biogenesis through PGC-1α (807). Alternatively, NO may react with molecular oxygen to form the oxidizing agent peroxynitrite, which may result in inflammatory (1272) or cytotoxic (938) stress.

While these factors are known to contribute to mitochondrial turnover and exercise adaptation (1067), the full range of their function in skeletal muscle adaptation is a complex and hotly debated research area (200). Some evidence suggests that skeletal muscle increases endogenous ROS scavenging in response to the heightened oxidative stress of training, indicated by increased expression of superoxide dismutase (SOD), glutathione peroxidase (GPX), and markers of mitochondrial biogenesis (1102). However, it remains incompletely clear whether supplementation with exogenous antioxidants (e.g., vitamins C & E) is detrimental during this early adaptation window. Ristow et al. found that, while four weeks of AE training-induced improvements in glucose and fatty acid metabolism, insulin sensitivity, and antioxidant defense in both trained and untrained men, vitamins C and E blocked these favorable metabolic adaptations (1102). Although several of these factors appear to be more highly expressed at baseline in muscle of trained individuals (Vo_2max ~20% higher vs. untrained), this was not statistically evaluated. In conflict, Bente Pedersen and colleagues have performed a series of studies that collectively demonstrate that vitamin C & E supplementation has no effect on training-induced increases in aerobic capacity, mitochondrial adaptations, superoxide dismutase activity, and insulin sensitivity in healthy young men (1460, 1462), although it does alter muscle inflammatory signaling (400, 401, 1461). More recently, it was shown that antioxidants blunt long-term increases in several other cellular adaptations, independently of any negative effects on whole-body or mitochondrial aerobic capacity (927, 1013). Notably, however, many of these studies assess performance based only on Vo_2max, whereas metabolic efficiency (i.e., running economy) is an equally important determinant of AE performance (96). Given the unique metabolic stress associated with longer-duration AE (529, 975, 1357), the subcellular effects of exogenous antioxidant supplementation may be differentially manifested in longer events. This area

clearly warrants further investigation, particularly given the apparent influence of sex, age, and/or training status (141, 329).

Myokines—The role of skeletal muscle in intracellular communication is illustrated by a class of factors known as myokines, a muscle-specific subcategory of signaling molecules called cytokines (1023). These factors were originally characterized for their roles in coordinating immune cell motility, activation, and function (1385), but knowledge of their wide-ranging behavior has increased exponentially. Furthermore, the cytokine nomenclature has been amended as necessary for application to signaling molecules exchanged by other tissue types (e.g., adipokines, hepatokines), while myokine has since been expanded to include all factors produced and released by muscle, including lipid-derived molecules and other metabolites. IL-6 was the first signaling factor identified as a myokine (997): it is now known to serve a range of functions relevant to skeletal muscle, including promotion and resolution of exercise-induced inflammation (1019), protein balance (508, 1348), and energy metabolism (549, 1440). Acute AE activates skeletal muscle transcription and secretion of IL-6, along with other myokines, including (but certainly not limited to) IL-10, IL-4, and IL-8 (220, 820, 977, 978, 1241).

The time point at which peak myokine activity occurs postexercise appears to vary widely based on the intensity and duration of the stimulus. For example, using a time course series of muscle biopsies, Louis et al. found that muscle IL-6 gene expression was elevated up to 24 h after a 30-min AE bout but peaked at the 8 h time point (820). Steensberg et al. demonstrated that muscle IL-6 increased 30 min into a 3 h knee extension exercise bout and remained significantly elevated at the cessation of exercise (1248). It is also likely that training status plays a role in the myokine response to acute exercise (402). As little as one previous exposure to an identical exercise bout may influence myokine production (330, 602) and release (571, 881), even when spaced up to 4 weeks apart. At the other extreme, males with a lifelong history of AE exhibit a less robust inflammatory response to an unaccustomed loading stimulus than age-matched nonexercisers (757). Continued research is necessary to elucidate what impact this effect has on immune health and/or muscle adaptation.

Research using ‘omics approaches has expanded knowledge of the full range of myokines produced and secreted by skeletal muscle. For example, Pourteymour et al. applied RNA-sequencing to the discovery of the muscle “secretome” (1064) and revealed an important role for macrophage colony-stimulating factor-1 in response to combined AE+RE training. This and other molecules that elicit communication with immune cells (904, 1259) are likely to play a role in muscle adaptations to exercise, given the role of macrophage biology in resolution of inflammation and skeletal muscle regeneration (228, 691). The complex interplay of myokine dynamics, biology of target cells, and phenotypic influences (e.g., age, training status) clearly warrants continued investigation via integrated application of ‘omics platforms.

Skeletal muscle adaptations to resistance exercise

The inherently high degree of plasticity in skeletal muscle tissue is perhaps most apparent in its adaptation to RE, in which muscle contracts against a load. Classically, RE involves progressive overload of the muscle to challenge homeostasis and trigger numerous molecular pathways resulting in structural and physiological adaptations (76, 647, 758, 1107). One of the hallmark adaptations to RE is increased skeletal muscle mass, or hypertrophy (76, 531, 647, 758, 1107). Provided that the amount of skeletal muscle mass is associated with increased healthspan, protection against various diseases (97, 758, 1309), and better survival outcomes following infection, hospitalization, and surgery (274, 666, 773, 1353), research focus has been directed toward identifying and understanding mechanisms of RE-induced muscle hypertrophy. However, other dimensions of skeletal muscle health (e.g., strength, fatigability, fuel economy) are also common RE outcomes.

Histological and cellular adaptations—In addition to increased whole muscle size, myofiber cross-sectional area commonly increases with RE training (1016). Some studies report that this is most notable in type IIa myofibers (1244, 1246). Application of the size principle for motor neuron firing would dictate that higher RE loads necessitate the recruitment of myofibers with a higher firing threshold, that is, type II myofibers (880). Indeed, most studies support that higher loads elicit a higher contribution of energy from type II myofibers (471, 496), yielding a more pronounced molecular response (1091). Emerging research is investigating whether similar effects can be achieved at lower intensities performed to failure (933) or with blood flow restriction (1167, 1201). While a complete slow-to-fast shift is uncommon, RE training induces an increase in type IIa myofiber distribution, often at the expense of hybrid or type IIx myofibers (1244, 1246). Beyond this, RE training enables myofibers to contract in synchronicity due to underlying neural adaptations to improve efficiency of movement (1, 1140). Within the myofiber, physiological parameters such as unloaded shortening velocity and power are increased following RE training in both fiber types (1325, 1328), although these patterns are not well-sustained into the ninth decade of life (1090, 1216), suggesting a potential age-related impairment in muscle plasticity. Thus, while RE training is important for maintenance of muscle mass and function throughout aging (758), there is evidence to suggest that an RE regimen must be initiated at least in middle-age and continued through later life. Future investigation of muscle and other health phenotypes in lifelong RE-trained individuals may shed light on the optimal strategy to preserve lifetime peak muscle mass throughout aging.

Muscle protein balance—Skeletal muscle mass is regulated by the equilibrium between muscle protein synthesis and breakdown. Naturally, a positive muscle protein balance, in which synthesis rates exceed breakdown, yields increased overall muscle protein accretion (297, 309, 872, 1043, 1256). In healthy, disease-free, normal conditions, RE has a more pronounced effect on muscle protein synthesis than on protein breakdown (56, 467, 741). In fact, an acute bout of RE is a potent enough stimulus to increase protein synthesis for up to 48 h (297), favoring a positive net protein balance. Transiently elevated muscle protein synthesis eventually returns to basal levels after acute RE. Thus, to facilitate long-term hypertrophy, it is necessary to perform repeated bouts (i.e., training). Previous studies have corroborated that the magnitude of the hypertrophic response is predicted by

changes in acute muscle protein synthesis (157, 296), but others have found otherwise (905). These discrepancies may be related to the method used to quantify protein synthesis (infusion protocols vs. deuterium-enriched water), selected sampling time frame, participant demographics (age, sex, training status) (296), and a mixture of other intrinsic factors (e.g., individual genotype, epigenetic effects, etc.). Despite the wide range of hypertrophic responses to RE, there is a consensus that markers of protein synthesis are at least qualitatively predictive of long-term muscle hypertrophy (157, 296, 297, 905). Therefore, complementing measurement of muscle protein balance with abundance of molecular factors known to influence synthesis and/or breakdown may provide the clearest picture of the effects of RE.

Protein translational efficiency—In addition to contractile proteins actin and myosin, skeletal muscle hypertrophy is dependent on increased availability of proteins that serve a range of muscle functions. To produce functional proteins, muscle must be equipped to translate nascent transcripts (mRNAs) upregulated in response to RE in an efficient manner. So-called “translational efficiency” can be defined as the rate of mRNA translation by skeletal muscle cell (868). The current understanding is that changes in translation efficiency are mainly mediated by a variety of molecular pathways including phosphatidylinositol 3-kinase (PI3K), protein kinase B (Akt), and mammalian target of rapamycin (mTOR). In particular, mTOR targets p70S6 kinase (p70s6k) as well as eukaryotic translation initiation factor binding protein-1 (4E-BP1). Activity of these factors is upregulated following acute (607, 905, 1297) and chronic (530) RE.

Protein translational capacity—In addition to an increased abundance of enzymes and other factors in the translation pipeline, overall capacity to translate mRNAs is a rate-limiting step in protein synthesis. The highly conserved organelle responsible for translation is the ribosome, an amalgamation of ribosomal proteins and single-stranded rRNA into distinct subunits that position mRNAs while facilitating binding of specific tRNAs to yield an amino acid sequence. While the overall muscle RNA pool is composed of rRNA, mRNA, tRNA, and other noncoding RNA species (395), rRNA constitutes almost approximately 80% of the total pool. Thus, assessment of overall RNA content may be used as a proxy for ribosomal content and, indirectly, a reflection of the capacity for regulation of muscle protein synthesis (155, 217, 395).

Increases in the ribosome pool (i.e., ribosome biogenesis) demand a fine and coordinated process of several pathways. Briefly, this involves transcription of ribosomal DNA (rDNA), followed by processing, maturation, and assembly of rRNA and its ribosomal proteins (155, 395). It has been demonstrated that acute bouts of RE can upregulate some of these pathways, facilitating the molecular environment to promote ribosome biogenesis (396, 397). For instance, Figueiredo et al. (397) demonstrated increases in the phosphorylation of rDNA transcription factors such as upstream binding factor (UBF) and c-Myc, as well as the total protein levels of UBF and transcription initiation factor (TIF)-IA; these changes were accompanied by increases in pre-rRNA-45S. With chronic RE exposure, these acute elevations in factors related to ribosome biogenesis yield augmented total RNA concentration and rRNA density within skeletal muscle (157, 396, 517, 1094,

1244), increasing the overall capacity to support hypertrophy. Muscle cell culture models corroborate the importance of ribosomes in muscle hypertrophy in the absence of systemic influences: myotube growth in vitro may be completely blunted by administration of mTORC1 inhibitor rapamycin (956) or inhibition of polymerase I, the DNA polymerase responsible for transcription of rRNA (1244).

Studies in humans have demonstrated a relationship between ribosomal density and the magnitude of RE-induced hypertrophy (396, 517, 908, 1244). For example, using total muscle RNA as a surrogate for ribosomal density, Stec et al. found that individuals that experienced the most robust hypertrophic response ("extreme responders") presented not only a higher ribosomal density at baseline but also heightened posttraining ribosomal density, indicating ribosome biogenesis, in comparison to individuals that responded poorly to RE (1244). In concert with these results, Mobley et al. (908) demonstrated that only individuals that demonstrated moderate to large gains in muscle mass exhibited increased total RNA concentration in response to an RE intervention. Ribosome biogenesis, or at least translational capacity, is thought to be a contributor to the observed differences in hypertrophic response to RE between young and old individuals: data support that older individuals may present an attenuated hypertrophic response in comparison to younger adults. An underlying reason may be impaired activation of molecular pathways related to ribosome biogenesis (e.g., c-Myc gene expression and total protein levels of c-Myc and TIF-IA) in older individuals (156). Similarly, others have found that only middle-aged adults exhibit increased expression of 45S-preRNA after a single acute bout of resistance exercise, whereas older adults do not (1245). Many other potential mechanisms are thought to be at play in the attenuated age-related response to RE training, including (but not limited to) changes in the hormonal milieu (638), oxidative stress (656), and chronic basal muscle inflammation (757, 886).

Satellite cells and the myogenic program—There is limited evidence in humans that muscle fibers increase in number (hyperplasia) in response to RE. However, progressive overload contributes to a stress that eventually necessitates a key structural change: the addition of nuclei to the mature muscle syncytium. Each myonucleus is thought to be responsible for (and only capable of) coordinating homeostatic processes within a limited volume of cytoplasm, a region known as its "myonuclear domain" (533, 663, 1039). Accordingly, the preexisting number of myonuclei may eventually become a limiting factor as myofiber size increases in response to RE. The addition of new myonuclei into skeletal muscle is reliant on specialized, mononuclear, stem-like cells known as satellite cells (SCs), found between the sarcolemma and the basal lamina (862). In resting conditions, SCs are quiescent but are activated in response to an exercise stimulus, such as mechanical stress imposed by RE. Activated SCs may then proliferate and either fuse with an existing myofiber, donating its nucleus, or return to a quiescent state, rejoining the SC pool (225, 349, 533, 534, 1014, 1227, 1463).

RE promotes an orchestrated increase in the expression of several factors thought to be crucial in regulating the SC cycle, such as mechano-growth factor (MGF), hepatocyte growth factor, and myogenic regulatory factors: for example, increased MyoD, myogenin, myogenic factors (Myf)-5 and -6, decreased myostatin (75, 871, 993, 1227, 1463). In

addition to these molecular factors, studies typically examine SC content in histological muscle preparations using immuonostaining for their characteristic markers CD56 or paired-box protein 7 (Pax7) (390). Several studies have demonstrated an expansion of the SC pool in response to both acute (345, 964, 1228) and chronic RE (295, 908, 1039, 1229, 1360). Furthermore, several have shown that long-term hypertrophy is related to expansion of the SC pool (104, 1038, 1039, 1361, 1362), while others have demonstrated that the basal SC pool size is of equal importance (1039). However, still others have not observed significant relationships between SC number and magnitude of RT-related hypertrophic response (908).

Notwithstanding the apparent effects of acute and chronic RE on SC dynamics, the exact threshold at which addition of myonuclei becomes necessary is still not clearly understood (946). While the standing estimate had been that an approximately 25% increase in myofiber size would necessitate myonuclear addition (664), a recent meta-analysis indicated that increases above 10% were sufficient (263). Even within this meta-analysis, the myonuclear addition response appears to track with the cellular demand such that more myonuclei are added at approximately 20% than at 10% myofiber hypertrophy. Furthermore, myofiber type may play a role in this process: some studies have observed that type I myofibers are more likely than type II myofibers to increase the number of myonuclei (104, 924, 1229). This could be explained by a higher myonuclear domain ceiling in type II myofibers or characteristically different architecture between myofiber types; for example, type I myofibers tend to be situated near more muscle capillaries, which may deliver factors to activate SCs more efficiently (648, 963). While the threshold for addition of myonuclei to existing myofibers is not presently clear, skeletal muscle is capable of managing RE-induced perturbations to homeostasis without the immediate addition of myonuclei, indicating that SC fusion is a more stable change or that their heightened activity after RE may serve a different biological purpose (946).

Importantly, the role of SCs in hypertrophic response to RE training has been under increased scrutiny. Animal models provide an avenue for mechanistic manipulation of SCs, such as the use of a tamoxifen-inducible muscle-specific Pax7 knockout mouse. Using this design, McCarthy et al. (866) found that depleting approximately 90% of the muscle SC pool in mature mice does not impair hypertrophic capacity, at least in response to short-term (i.e., 2 week) mechanical overload stimulus. In contrast, Fry et al. (429) demonstrated that longer-term hypertrophy (i.e., 8 week) was attenuated in animals with SC depletion. Thus, perhaps the muscle hypertrophy attained in the former study was not sufficient to surpass the threshold at which addition of new myonuclei via SC fusion was necessary. In addition to continued research into the concept of the myonuclear domain, discovery of other factors that play a role in the myogenic program may prove useful, particularly as potential targets for individuals that are poor responders to RE.

Section summary

Skeletal muscle mass and function are clearly important for movement, but available evidence supports that the molecular environment within the tissue is equally critical for healthy function. While decades of research in human exercise studies have elaborated on the molecular transducers of skeletal muscle adaptations to both AE and RE, there

is a rapidly growing understanding of muscle's roles in physiology that extend beyond movement and contraction. For example, mechanisms by which muscle communicates with other organ systems are still being elucidated. Given the ease of access to skeletal muscle tissue and the insight it may provide into overall health, continued investigation of its molecular profile in response to acute and chronic exercise is likely to provide guidance toward therapeutic targets to improve exercise tolerance and responsiveness across individuals, particularly in the context of morbidity and disease.

Cardiovascular System Adaptations to Exercise

The cardiovascular system is often acknowledged as the primary limitation to exercise performance (35) and is a key determinant of overall aerobic capacity, an indicator of whole-body health (954). Exercise (particularly AE) necessitates sustained, elevated cardiac output, reduces peripheral vascular resistance, and increases venous return of blood to the heart, stressing the cardiovascular system to adapt to heightened mechanical and metabolic demands. Beyond this, assessment of cardiovascular function using electrocardiography, blood pressure, and circulating metabolic markers is relatively well-developed and highly accessible. As such, the cardiovascular system is a frequently investigated and well-understood system in the context of exercise.

Cardiovascular adaptations to aerobic exercise

Ventricular morphology—Adaptations to chronic AE are highly studied and include physiological cardiac hypertrophy (551, 1114), increased myocardial oxygen supply, blood flow, and transport capacity, increased vessel size, and improved endothelial function (551). In particular, the left ventricle (LV), whose action is responsible for pumping oxygen-rich blood into the aorta for delivery to the periphery, is often increased in both size (volumetric hypertrophy) and wall thickness (structural hypertrophy) (1412), driven by increased cardiomyocyte size (545). This process, referred to as cardiac remodeling, is brought about to meet the heightened physiological demands associated with higher tissue oxygen consumption rates during exercise (840, 1359).

Cardiac remodeling is traditionally categorized as either concentric or eccentric (1179, 1359). Under physiological conditions, concentric growth is typically defined by greater increase in LV wall thickness compared to internal diameter, whereas physiological eccentric growth is characterized by increases in both LV internal diameter and wall thickness (1359). The time course of these adaptations is not uniformly linear. For instance, one year of intensive AE marathon training in young, sedentary men and women progressively increases both left and right ventricular mass; however, LV volume does not demonstrate a significant increase until after six months of training (44). Furthermore, adaptations are easily reversed: although sometimes accrued within two to three months of training, they may diminish as early as a few weeks into detraining (360, 686, 851).

Cardiac remodeling is influenced by mechanical stimuli known as hemodynamic forces such as flow, pressure, stretch, strain, and compression (166, 492). The combination and/or contribution of these hemodynamic forces upon the cardiovascular system establish the appropriate parameters for adaptation (1359). Thus, exercise type and modality influence

physiological cardiovascular adaptations. During a purely aerobic activity, heart rate, venous return, and contractility are all elevated above resting levels; still, even within this broad category, important distinctions exist. For example, although running and rowing are both AE activities requiring a substantial cardiovascular component, downstream outcomes on cardiac remodeling can vary considerably (Figure 6). Rowing is associated with both volume (isotonic) and pressure (isometric) stress, while running involves primarily isotonic forces on the heart (1399). As such, highly trained individuals in both modalities exhibit larger LV volumes (341), but rowers exhibit greater LV mass (1399).

Cardiac cell adaptations—Increases in cardiomyocyte size drive LV hypertrophy (1179, 1359) and are considered a hallmark feature of AE training (420, 678, 1066). Like skeletal muscle, cardiomyocytes are terminally differentiated and primarily increase in size rather than number after exercise training. However, AE training in animals has been shown to lead to increases in newly formed cardiomyocytes, angiogenesis, and other parameters of myocardial remodeling through a range of cardiomyocyte growth factors including neuregulin (NRG)-1, bone morphogenic protein-10, and periostin (1398). Examination of cardiomyocyte physiology is naturally limited to preclinical models but provides important insight into potential mechanisms of adaptation. For example, in rats, AE enhances contractility and calcium handling (961, 1393, 1437). Molecular cues that propagate these effects in addition to cardiomyocyte hypertrophy are wide-ranging and likely vary by exercise type (AE vs. RE), hemodynamic stress-induced hypertrophic outcome (concentric vs. eccentric), and other phenotypic variables (840).

Although cardiomyocytes are the primary cause of cardiac hypertrophy in adults (784), there is evidence that other cardiac cell types also adapt to exercise training and may be the basis of other beneficial training effects. For instance, fibroblasts are responsible for production and release of angiogenic factors including VEGF and matrix metalloproteinases (MMPs) (1074). Furthermore, adult endothelial cardiac stem cells can be activated to differentiate toward the cardiomyocyte lineage by increased cardiac workload for smooth muscle cells and endothelial cells (1341). In the periphery, endothelial progenitor cells (EPCs) are affected by both AE and RE (431, 1086) in a manner influenced by exercise duration and intensity (431, 755). Derived from bone marrow stem cells (782), EPCs are involved in the regulation of large vessels and microvasculature expansion. EPCs are involved in vascular repair and vessel formation and have the ability to differentiate into mature endothelial cells when prompted by exercise training (51). In peripheral blood, EPC concentration increases with AE (1086), indicated by heightened presence of the common surface marker CD34 (51). Moreover, EPCs may secrete VEGF and granulocyte-colony factors, leading to neoangiogenesis (51).

Arterial adaptations—Arteries constitute the first branch of peripheral circulation and are responsible for transportation of blood from the heart to other organs. In addition to an approximately five-fold increase from basal cardiac output, exercise necessitates a highly regulated redistribution of blood flow to contracting muscle in lieu of visceral organs, the brain, and so on (431, 1124). To facilitate this redistribution, both conduit and resistance arteries play roles in regulating blood flow (551). Conduit arteries are

highly elastic and handle the highest pressure loads from the aorta; thus, exercise-induced adaptation in major conduits has been an area of clinical interest. A hallmark study by Hambrecht et al. investigated the role of hemodynamic forces on vascular function of the coronary artery (514), which supplies blood to the myocardium. They demonstrated that four weeks of exercise in individuals with stable coronary artery disease led to improved endothelium-dependent vasodilatory capacity (514). Others have illustrated that exercise improves coronary artery diameter and blood flow (343, 492).

Additionally, Dinenno et al. (334) found that AE increases femoral arterial remodeling, and Miyachi et al. reported that AE-induced increases in femoral artery size were associated with regional increases in blood flow (907). Furthermore, exercise training may promote increased flow within the carotid artery in healthy populations (810) and women with sarcopenic obesity (1007). These training-induced improvements may facilitate efficient delivery of energy substrates, heightened capacity for clearance of metabolic by-products, and reduced endothelial shear stress, the latter of which is thought to contribute to impaired endothelial cell function (494).

Resistance arteries are largely responsible for directing blood flow (244) and can be assessed in humans using plethysmography (659) or flow-mediated dilation (1310). Hemodynamic forces are critical for vascular adaptation: during acute AE, increased heart rate and blood pressure impose cyclic circumferential stress on the cardiovascular system. In a complex pathway, endothelial cells respond via upregulation of genes including endothelial nitric oxide synthase (eNOS), leading to heightened abundance of ROS such as NO (492). Training may also increase superoxide dismutases 1 and 3 (430, 570, 1069), enzymes that play a role in antioxidant defense (1466). Thus, while exercise acutely increases oxidative and shear stress, adaptive mechanisms are in place to handle repeated bouts (492), concurrently improving the basal health of the system.

Chronic exercise training-induced acute shear stress may prompt arterial remodeling, structurally preparing the vasculature to handle increases in shear stress or other hemodynamic perturbations (493). The mechanisms behind this effect continue to receive attention but appear to involve increased arterial diameter partly mediated by NO (551), which is primarily produced in vasculature through the actions of eNOS (1310). Further supporting that intermittent high shear stress is an adaptive trigger, complete removal of shear stress in rats increases expression of pro-inflammatory genes such as ICAM-1, VCAM-1, E-selectin, and monocyte chemoattractant protein-1 (MCP-1) (643).

Microcirculation—Broadly, the microcirculation is a network of arterioles, capillaries, and venules which distribute, perfuse, and collect blood from tissues. Several clinical trials have investigated adaptations in microcirculation in response to exercise training. Capillaries are in direct contact with skeletal myofibers and can be easily visualized and counted in skeletal muscle biopsy samples. Via angiogenesis, AE commonly leads to proliferation of the capillary network in human skeletal muscle (34, 930). Increased muscle capillarization is one of the later adaptations to AE (35), and newly added capillaries are fairly stable, lasting a few weeks into detraining (708, 943) or even throughout aging if training is continued (499, 1326). Angiogenesis is largely an adaptation to low oxygen stress, as a

hypoxia-based training paradigm (four weeks single-leg cycling with ischemia) increases capillary-to-myofiber ratio (376). Increased capillarization, induced by shear and passive stress, is mediated through angiogenic factors such as VEGF (579, 842, 990, 1284). In animals, removal of VEGF blunts exercise-induced increases in muscle capillary density and capillary-to-myofiber ratio (317).

Cardiovascular adaptations to resistance exercise

Although the vast majority of literature focuses on cardiorespiratory adaptations to AE, research into RE adaptations has increased, exposing a knowledge gap related to cellular, molecular, and regulatory mechanisms that may be specific to RE. Generally, RE has been shown to lead to increased ventricular mass, ventricular wall thickness, septum thickness, and peripheral vascular resistance (431, 1257). Short, intense bouts characteristic of RE are associated with increased blood pressure (1359). Thus, this physiological stimulus is more often associated with a pressure than volume load, leading to concentric hypertrophy (1057). Indeed, LV adaptations to RE are uncommon when accounting for LV wall thickness (1233). Others have shown that six months of RE training leads to decreased carotid wall thickness; however, the authors suggest that these changes may be driven by general exercise-induced increments in blood flow and shear stress, rather than a feature unique to RE (1234). It is well-established that RE training elicits pressure overload response in cardiac cells, which leads to intracellular signaling through endocrine cascades (113). Specifically, the renin-angiotensin system (RAS) responds to overload eliciting a mechanical stretch, and angiotensin II type I receptor (AT1) expression is associated with physiological cardiac hypertrophy after RE in a rat model (83). In the periphery, moderate RE can lead to increases in circulating EPCs and angiogenic factors such as MMP-2, MMP-3, and MMP-9 (1122); MMP-9 is a key regulator of vascularization, as its absence in a mouse knockout model reduces the capacity to recruit EPCs and develop blood vessels (598). Studies in humans have demonstrated increased skeletal muscle capillarization following short-term RE in young (587) and older men (1363), and additional evidence supports that capillarization may be highly important in muscle hypertrophy, a fundamental RE outcome (923, 1226). Together, the paucity of literature examining cardiovascular adaptations to RE represents an area ripe for continued study, particularly in the context of mechanistic factors that facilitate adaptation.

Molecular transducers of cardiovascular adaptations

Growth factors—Ligands including IGF-1, VEGF, and thyroid hormones modulate cellular growth, survival, and metabolism necessary for angiogenesis. Released from liver in response to growth hormone, circulating IGF-1 increases in response to both AE (1467) and RE (1482). Both insulin and IGF-1 are necessary for growth and development through intracellular signaling cascades (526). The IGF-1 receptor is a regulator of physiological cardiac hypertrophy (697, 875). In clinical models, VEGF interacts with NO in response to hemodynamic force such as shear stress. Known for regulating both vasculogenesis in development and angiogenesis in a mature organism, VEGF stimulates the production of NO in endothelial cells (551, 1005).

Thyroid hormones—Thyroid hormones can have significant cardioprotective effects on the cardiomyocytes and the vasculature (631). Furthermore, thyroid hormone increases venous return, cardiac output, and systemic vascular resistance (476). Thyroid hormone signaling occurs through the thyroid gland, which secretes thyroxine (T4) and triiodothyronine (T3), the active form of the thyroid hormone; both are associated with physiological cardiac hypertrophy (665). Conflicting findings exist in regard to the effects of a single bout of aerobic treadmill exercise on thyroid hormones (250, 601). Some evidence demonstrates decreased thyroid hormone after acute AE (695), whereas others report an increase (714); these discrepancies may be the result of duration, intensity, or exercise mode. In support, Simsch et al. found a differential effect of AE versus RE on levels of thyroid stimulating hormone (thyrotropin) (1208), a pituitary hormone upstream of the thyroid gland (1004). In this study, well-trained rowers performed three weeks of RE training followed by one week of rest and subsequent three weeks of AE training. Thyroid stimulating hormone decreased after RE training and increased after AE training, an effect that the authors attribute to energy demand associated with high intensity.

Key pathways—PGC-1α plays an important role in physiological cardiac hypertrophy. Exercise training increases circulating catecholamine (e.g., β-adrenergic signaling) which, in turn, upregulates PGC-1α (431, 1359). PGC-1α is mediated via peroxisome proliferator-activated receptor α (PPARα) and appears to play a role in exercise adaptations related to energy metabolism and mitochondrial biogenesis. Downstream targets of PGC-1α include NRFs 1 and 2, as well as the transcription factor ERR, a regulator of mitochondria and fatty acid oxidation. Akt is a central regulator of cell growth and survival (553) and is activated downstream of kinase cascades such as phosphatidylinositol 3-kinase (PI3K). In preclinical models, it is well established that exercise training alters IGF-1 and insulin-induced signaling through PI3K cascade (1179, 1181, 1410). Briefly, binding of ligands to receptor tyrosine kinases (780) leads to activation of the 110 kDa lipid kinase subunit α of PI3K and internal stimulation of adaptor proteins insulin receptor substrate (IRS)-1 and 2 (553, 875). The PI3K pathway has been associated with cell growth, survival, differentiation, and proliferation (188, 224).

Downstream, acute increases in activity of Akt can promote growth, whereas chronic increases may lead to pathological hypertrophy (840). These differential effects appear to depend on the active isoform of Akt and the activity/abundance of downstream targets. For instance, the Akt1 isoform appears to be involved in physiological rather than pathological cardiac hypertrophy (313). Akt can also inhibit glycogen synthase kinase-3 β (GSK3β), which can lead to pathological hypertrophy (40). Another notable target of Akt is mammalian target of rapamycin (mTOR) (188, 1078), a key regulator of protein translation through atypical serine/threonine protein kinases composed of two adaptor proteins. Moreover, mTOR complex 1 (mTORC1) regulates protein synthesis, cell growth, and proliferation (1454), while complex 2 (mTORC2) is involved in cell survival and polarity (1454). Combined, these complexes are necessary for adaptive physiological hypertrophy (1172). In addition, mTORC1 is responsive to growth factors including IGF-1 induction of the P13K/Akt pathway (875).

Akt is also capable of exerting a cardioprotective effect through a pathway involving the growth factor NRG1, ErbB4, and the CCAAT enhancer-binding protein β (C/EBPβ) pathway. In a preclinical model, the activity of this pathway is associated with increased myocardial regeneration (117). Briefly, Akt blocks the activity of C/EBPβ, serine (Ser473)/threonine (Thr308) kinase (847, 1286), an inhibitor of the positive effects of Creb binding protein (CBP)/p300-interacting transactivator with ED-rich carboxyl-terminal domain-4 (CITED4) (840). In animals, downregulation of transcription factor C/EBPβ may drive cardiomyocyte proliferation and increase CITED4 expression in mice after aerobic exercise (135). Continued research into this pathway and its relationship to exercise adaptation (135) could have implications for cardiac remodeling and resistance to HF.

Emerging research into regulators of gene expression has revealed a role for miRNAs in exercise-induced adaptations in the cardiovascular system (1286). Briefly, miRNAs are small, noncoding RNA molecules that influence translation of target messenger RNAs. Found throughout the genome, miRNAs are involved in various cardiac functions, including adaptive processes, contractile force generation, and inflammation (65). Conveniently, miRNA may be sampled from circulation to gain insight into cardiovascular function, adaptation, and remodeling. Several species of miRNA are thought to be either cardiac-specific or to have a particularly high degree of relevance to cardiovascular function. Of note, miRNAs regulating the vascular endothelium (miR-208a and miR-126), cardiac remodeling (miR-222), and inflammatory pathways (miR-146a) have been associated with the heart (65). MiR-126 is acutely increased in circulation following AE in humans (65), and some research proposes an intensity-dependent effect (1382). This endothelial-specific miRNA may be related to exercise-induced cardiac angiogenesis through pathways such as MAPK and PI3K/Akt/eNOS (1204). Targets of miRNA-126 include Sprouty-related protein 1 (Spred-1) and PI3K regulatory subunit 2, negative regulators of angiogenesis through inhibition of the VEGF pathway (918). Moreover, EPC-derived exosomes may promote vascular repair and angiogenesis through miR-126. This regulatory network including Spred-1 and VEGF may represent a mechanism by which exercise protects endothelial cells (830).

A noteworthy mediator of cardiac hypertrophy influenced by exercise is miR-222, which inhibits adverse cardiac remodeling through targets including cyclin-dependent kinase inhibitor 1B (p27), homeobox-containing 1, and homeodomain-interacting protein kinases 1 and 2 (814). In humans, circulating miR-222 is increased after both acute (1165) and chronic HIIT (590). Additionally, free circulating miRNAs (c-miRNAs) may be released by cardiac cells after acute stress such as exercise (65). Preclinical and cell culture-based studies are useful in discovery of c-miRNAs and elucidation of their mechanisms of action; these approaches can then be complemented clinically with targeted assessment in human exercise studies. There appear to be a range of possible effects of acute and chronic exercise on c-miRNAs (64, 976), and it is likely that mode- and intensity-dependent effects also exist.

Section summary

The central role of the cardiovascular system in blood and oxygen supply makes it an extremely adaptive system in response to exercise. Highly responsive to metabolic (energy

stress, hypoxia), and mechanical (hemodynamic forces) stressors, the heart and associated vascular increase in size and function to meet peripheral demands of heightened training loads. On the molecular level, signaling cascades initiated by hormones, growth factors, and other regulatory molecules are critical for these adaptations to occur. Certainly, continued investigation in areas of sparse knowledge would be advantageous for the field, for example, a focus on cardiac outcomes in response to RE or combined training.

Adipose Tissue Adaptations to Exercise

Now recognized as highly metabolically active, adipose tissue (AT) actively engages in cross talk with skeletal muscle in response to exercise to positively modulate hormones, energy metabolism, and the resolution of exercise-induced inflammation. In addition, AT secretes regulatory factors that influence multiple physiological systems beyond skeletal muscle. While a significant body of research has traditionally examined the influence of exercise on the quantity of adipose, emerging research supports that adipose quality is of utmost importance for health.

Structure and function of adipose tissue

AT is considered a connective tissue and is found throughout the body in specific sites called depots that derive from different origins. These depots thus play distinct functional roles under the overarching role of AT in metabolism and endocrine signaling. At the cellular level, adipose cells (adipocytes) are classified as white, brown, and beige adipocytes. Beyond the primary adipocyte populations (762), AT is a heterogeneous and complex tissue comprised of fibroblasts, endothelial cells, immune cells, and innervating sympathetic nerves, activation of which is required to mediate breakdown or lipolysis (66, 93).

White adipocytes are well-characterized for their role in storage of excess energy as triglycerides and the release of hormones and adipokines (762). They are often distinguishable by their single large lipid droplet and sparse mitochondrial population (1198). White adipocytes constitute white adipose tissue (WAT), the most abundant and ubiquitous adipose depot, which forms the basis of both subcutaneous and visceral AT (742). Subcutaneous adipose can be easily sampled, whereas visceral adipose is situated within the abdominal cavity, presenting a challenge for direct analysis. Thus, there is generally a better understanding of the mechanistic role of subcutaneous WAT in adaptation to exercise. Given that WAT is found in various specific depots, acts in different metabolic and endocrine capacities, and has been shown to arise in certain patterns during embryogenesis and growth, it has been generally accepted that the origins of WAT vary based on developmental patterning.

During embryogenesis, brown adipose tissue (BAT) develops before WAT (774) and arises from progenitor cells expressing Myf5 (774). In humans, BAT is primarily localized to the intrascapular region (1198) but also exists in select depots in the neck, supraclavicular, axillary, paravertebral, and a few vascular regions in adult humans (778). Originally, BAT was thought to be metabolically active during only embryogenesis and infancy; however, in 2009, Virtanen et al. (1374) reported its measurable metabolic function in adults. Biopsy samples taken from supraclavicular BAT exhibit three-fold higher oxygen

consumption versus WAT (1369). BAT is primarily responsible for generation of heat through nonshivering thermogenesis, a process mediated by the actions of uncoupling protein 1 (UCP-1). Briefly, UCP-1 partially alleviates the hydrogen ion gradient established across the mitochondrial membrane during aerobic respiration, reducing its potential to be harvested for energy in favor of heat production (66). Fittingly, brown adipocytes have an extensive mitochondrial network and are comprised of multiple small lipid droplets (1198). While many studies examine BAT via 18F-fluorodeoxyglucose positron emission tomography-computed tomography imaging, molecular studies using biopsies are rare due to the difficulty of access, complicating its examination in the context of human exercise (241).

Recently, it was discovered that mature white adipocytes exhibited considerable plasticity and could transition toward a brown adipocyte phenotype via a process known as "browning" (774). These apparently white adipocytes are referred to as "beige adipocytes," which are thought to be derived from the vascular smooth muscle niche (21, 114, 818) and thus distinct from fully brown adipocytes. Characteristically, beige adipocytes have a unique dendritic morphology and typically express the markers CD34, PDGF Receptor α, spinocerebellar ataxia type 1, and UCP-1; morphologically, they are similar to brown adipocytes with a large number of mitochondria and multiple lipid droplets (762, 774, 1339). Beige adipocytes tend to be interspersed throughout WAT and are thought to play a role in response to injury and cold stress (1199, 1338). Currently, the process of WAT browning has not been elucidated in humans (1338), perhaps a consequence of small biopsy size. Nevertheless, the study of factors that promote browning or beiging of WAT is targeted at harnessing potential mechanisms of obesity treatment, based on the premise that conversion of energy-rich WAT to the essentially energy-inefficient BAT might represent an intervention to increase basal metabolic rate (1355).

In disuse, disease, and energy surplus, adipose tissue can be mobilized from depots, redistribute throughout the body, and infiltrate other tissues such as skeletal muscle. Intermuscular adipose tissue (IMAT) is considered an ectopic deposition of subcutaneous AT induced by factors such as age, overall adiposity, chronic disease, and inactivity (10, 219, 320, 846). A high degree of IMAT is disruptive to normal muscle function and has been linked to impaired strength and mobility, chronic inflammation, insulin resistance, T2D, CVD, and other chronic conditions (10, 174).

While not a proper AT depot, skeletal muscle stores fat molecules as intramuscular triglyceride molecules (IMTG) that have a high degree of relevance for exercise. IMTG are found in lipid droplets in all fiber types, with higher density in oxidative, type I myofibers (292, 693). Spatially, IMTG lipid droplets are conveniently located in proximity to the endoplasmic reticulum and mitochondria (292). IMTGs, composed of three fatty acids linked to a glycerol backbone, can be catabolized for energy production to support muscle contraction in both AE (614) and RE (377). Free fatty acids released from other adipose depots can also be transported to skeletal muscle via circulating albumin and trafficked into these lipid droplets until oxidation (669). Before ultimately undergoing oxidation, fatty acids are bound to a carnitine molecule and shuttled into muscle mitochondria via the enzyme carnitine palmitoyl acyl-transferase (827). However, supplementation with carnitine

has failed to yield ergogenic benefits (87, 983, 1327), indicating that this substrate is not a rate-limiting factor.

Role of adipose tissue in acute exercise

In AT, exercise initiates a cascade of events that leads to lipolysis and recruitment of fatty acids to skeletal muscle. Skeletal muscle further promotes this through release of myokines, key mediators of lipid oxidation (621, 762, 1238). Through the exercise-induced exchange of myokines and adipokines, the two systems interact to influence metabolic function of immune, cardiac, and endocrine systems (1238). This requires a molecular cascade that stimulates lipolysis to respond adequately to heightened energy consumption and metabolic demand during exercise. As such, it is necessary to consider the role of AT in exercise in its context downstream of endocrine events signaling its activation.

Initially, exercise stimulates the hypothalamus (1384) to produce corticotropin-releasing hormone (CRH), which in turn stimulates the anterior pituitary gland to secrete ACTH. ACTH acts upon the adrenal cortex in the kidney to release cortisol, a catabolic glucocorticoid hormone, into the blood-stream (170): cortisol helps maintain blood pressure during exercise and plays a central role in fat metabolism. During exercise, circulating levels of cortisol are monitored by the hypothalamus and anterior pituitary to determine the amount of ACTH that is released (568). Glucocorticoids such as cortisol promote AT lipolysis through increased expression of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) (342) and glucocorticoid receptor-α (GRα) (649). As demonstrated by animal models, both factors are important in the appropriate response to exercise-induced increases in cortisol (184): 11β-HSD1 is capable of activating inactive glucocorticoids, and GRα is a necessary component in lipolysis and lipid secretion. Interestingly, upregulation of GRα has been correlated to the reduction of AT mass (649), leading some to pursue it as a treatment for obesity (649).

White adipose tissue signaling in exercise—Exercise-induced lipolysis in WAT is relatively well-understood due to the size and ease of access of subcutaneous WAT depots. Given the important endocrine role of AT, a great deal about its health can be ascertained by the secretory phenotype (315) at rest or in response to a challenge, such as exercise. While aging negatively influences these parameters, training promotes an oxidative phenotype and increases mitochondria in WAT (1052). WAT is primarily stimulated through sympathetic innervation of WAT or the action of circulating endocrine factors (e.g., norepinephrine, epinephrine, cortisol, and cardiac-derived natriuretic peptides) (21, 93). Following stimulation of a primary receptor on the surface of an adipocyte, such as β-adrenergic receptor, a cAMP/PKA cascade is activated (920), resulting in downstream phosphorylation of various lipase enzymes to initiate lipolysis at the surface of the lipid droplet. These include hormone-sensitive lipase (HSL), adipose triglyceride lipase, and monoacylglycerol lipase, acting in turn until the glycerol backbone is separated from the fatty acids. The resulting single fatty acids are released into circulation, bound to serum albumin, and directed to various tissues, including working muscle, to generate ATP for energy (920).

To further support lipolytic metabolism, exercising muscle releases an array of myokines such as IL-6, a prominent factor in glucose sensing. Often considered a pleiotropic cytokine, IL-6 has numerous beneficial effects on AT when stimulated by exercise. In addition to promoting AT lipolysis through the activation of the AMPK pathway (762), exercise-induced IL-6 has been associated with reduced visceral AT mass in humans (1409) and reduced inflammatory cell infiltration into AT in an animal model (835). Furthermore, myokine β-aminoisobutyric acid (BAIBA) is produced and released by skeletal muscle downstream of PGC-1α activation. BAIBA can lead to the upregulation of UCP-1 and other markers of browning in pluripotent stem cells (1106). BAIBA has been linked to obesity treatment through stimulation of fatty acid oxidation, attenuation of lipogenesis in WAT, and reduction of inflammation and insulin resistance (460, 662). Muscle-derived irisin has also been associated with lower levels of visceral AT and browning of WAT (762, 774), although the extent of its direct effects on browning is still a subject of debate.

An important class of myokine mediators of AT is the peroxisome proliferator-activated receptor (PPAR) isoform family (762, 778). These receptors bind fatty acids to initiate a range of pertinent effects on processes including lipolysis, adipogenesis, and lipid storage (649). Together, PPARs play complementary roles in AT, acting as the “master regulators” of lipolysis and lipid storage balance. For instance, PPARγ is involved in adipogenesis and lipid storage, leading to its study as a target of obesity research (649). On the other hand, PPARα plays a prominent role in lipolysis and has been linked to the role of BAIBA in browning (1106) and increased fatty acid uptake and oxidation in skeletal muscle (177, 591). Similarly, PPARδ also functions to increase fatty acid uptake and oxidation in muscle (177) and can be activated in response to exercise-induced increases in myokine IL-15, a factor inversely correlated to AT mass (762). PPARs initiate downstream effects in both AT and skeletal muscle. For example, angiopoietin-like 4 (ANGPTL4) is both a myokine and an adipokine with roles in multiple processes related to energy metabolism (762) including promoting lipolysis (624), raising insulin sensitivity (251), and increasing circulating fatty acids (1089).

Immediately after exercise, cardiac-derived natriuretic peptides, such as atrial (ANP) and B-type (BNP), are released from the heart (423). These have widespread effects on several tissues within the body, including AT (744). In AT, natriuretic peptides promote lipolysis through a cAMP-independent pathway induced by natriuretic peptide guanylyl cyclase receptor A (NPR-A) (744). In addition, evidence suggests that natriuretic peptides can cause the browning of WAT by inducing a browning program in gene expression (132). However, the magnitude of contribution that natriuretic peptides have in inducing lipolysis is unknown and likely small when compared to the typical induction of lipolysis. Overall, exercise induces a wide variety of molecular responses in WAT beyond those covered here, and continued investigation using ‘omics is likely to reveal important signaling factors beyond the currently understood adipokine-myokine cross talk.

Role of other adipose depots in exercise

Brown adipose tissue—In contrast to WAT, there is a less-developed body of knowledge surrounding molecular effects of exercise on BAT, as BAT depots are difficult to access

and study. As such, our understanding of the molecular mechanisms of exercise cross talk with BAT is limited and primarily based on animal models and in vitro human cell studies. Unfortunately, existing evidence in human exercise is not only sparse but contradictory: while some evidence suggests that overall BAT mass decreases and becomes less active in response to exercise (778, 1379), others have demonstrated that BAT activity is higher in young, lean humans and associated with better glucose tolerance in obesity (1422). In an effort to clarify the role of BAT in humans, several animal models of BAT have identified BAT-derived chemokines (so-called “batokines”) that play major roles in metabolism, glucose and lipid homeostasis, and overall have similar endocrine, paracrine and autocrine effects similar to WAT (1422). Theoretically, batokines could be used as biomarkers of BAT activity in human exercise. In reality, detection of batokines in humans has been difficult, likely due to the predominant outpouring of WAT signaling factors induced by exercise. Identification of a circulating factor specific to BAT or BAT metabolism is needed to further explore BAT’s role in acute and chronic exercise.

Intermuscular AT—Despite the physical proximity of the two, the molecular cross talk between skeletal muscle and IMAT has not been well defined to date. It can be hypothesized that due to the secretory nature of AT, IMAT is also a source of regulatory molecules that directly impact skeletal muscle. A recent study found that, at rest, IMAT secretes factors that decrease skeletal muscle insulin sensitivity and increase free fatty acid concentration, potentially promoting muscle insulin resistance (1135). Additionally, myostatin, an inhibitor of myogenesis, has been positively correlated with IMAT mass, suggesting that IMAT may negatively regulate muscle growth (722). However, AE can reduce (722) or prevent (219) the accumulation of IMAT, suggesting that this may be an easily accessible energy reservoir for working muscle. In further support, exercise-induced changes in the quantity of IMAT appear to be site-specific, as a recent study by Chambers et al. found lower age-related IMAT accumulation in the thigh but not the calf muscles of lifelong-trained men and women performing primarily cycling (219). Furthermore, higher intensity training was associated with attenuated deposition of IMAT. Thus, continued research is needed to understand whether the overall abundance of IMAT is a primary determinant of muscle quality or if exercise training positively modulates the composition of IMAT (e.g., via browning or other indices of adipocyte health).

Intramuscular triglycerides—While IMTG content is negatively related to insulin sensitivity in untrained individuals, training reverses this relationship, a phenomenon known as the “athlete’s paradox” (111, 729). IMTG are a substantial source of energy during (693, 1350, 1403) and after (694) moderate-intensity long-duration exercise and chronic AE training increases reliance on IMTG at an absolute workload (110, 614). Interestingly, a sex-specific pattern may exist such that females typically store more IMTG than males (618) and may preferentially utilize IMTG during exercise (1251). During exercise, IMTG are acted upon by HSL and subsequently by perilipin 5 (PLIN5), which is thought to mediate shuttling of liberated fatty acids into the mitochondrion for efficient oxidation (134, 693). Interestingly, HSL can be differentially regulated in skeletal muscle and AT by selective phosphorylation of distinct serine residues, allowing the source of energy substrates for lipolysis to be controlled (1404).

Section summary

While the majority of studies related to exercise training effects on adipose focus on changes in total fat mass, the field is shifting toward a more intricate understanding of adipose tissue health. In the context of human exercise, examining molecular communication between AT and skeletal muscle may reveal factors with key bioenergetic, inflammatory, and endocrine roles that can be leveraged for therapeutic benefits. For instance, exercise-induced adipokines or myokines that promote browning or beiging have potential for treatment of chronic metabolic diseases. Regardless, AT is clearly required for proper endocrine function, response to exercise, and energetic support of the skeletal muscle system; benefits of long-term exercise on adipose health are likely to further promote these critical functions.

Liver Adaptations to Exercise

Metabolic support for exercise is largely regulated by the liver. Through its roles in managing glycogen, lactate, lipids, and other metabolites, the liver is critical to support continued muscle contraction during exercise. In addition, the liver is a filtration system; thus, good insight into overall health, liver function, and inter-organ communication can be assessed from circulating factors, including lipoproteins (e.g., LDL, HDL) and cholesterol. While much is known about the liver in acute exercise (particularly AE), the specific molecular benefits of long-term exercise on liver health are less understood outside of preclinical models. Nevertheless, an understanding of the liver's actions in supporting acute exercise provides important perspective into overall health and the adaptive effects that support improved exercise performance and metabolic homeostasis.

Structure and function of liver

The liver is the largest gland in the body (~2.5% of total body weight) (951) and its energy expenditure accounts for approximately 20% of basal metabolic rate (432, 1394). This is related to various homeostatic roles, including synthesis of proteins and hormones, extraction and processing of nutrients (e.g., lipids), removal of waste products, antigens, and microbes, and storage of glucose and bile (84, 951, 1189). Briefly, oxygen-rich blood enters the liver through the hepatic artery. Peripheral blood from the gastrointestinal system gathers nutrients, metabolites, and other molecules that may be carried to liver via the portal vein. Within the liver, blood is processed in the liver acini and various substances are synthesized, either for export through the hepatic vein to remain in circulation or conversion into bile for excretion. At the cellular level, liver is comprised of hepatocytes, cholangiocytes, liver sinusoidal endothelial cells, natural killer cells, Kupffer cells, and hepatic stellate cells. Together, these structures orchestrate the functions of liver as the molecular milieu and metabolite flux change.

Role of liver in acute exercise

As a digestive organ, the liver is affected by reduced blood flow to the splanchnic bed at the onset of exercise: while it receives approximately 25% of cardiac output at rest, redistribution of blood flow substantially reduces this (548, 1031) in favor of skeletal muscle (359, 432). However, while working muscle metabolic demand increases, liver is capable of maintaining its functioning to support the metabolite flux of exercise (432, 932), including

mobilization of lipids (160) and glucose output (1383). Rodent models demonstrate that acute exercise markedly affects liver expression of genes related to cellular stress (575), perhaps a reflection of the liver's importance in bearing the metabolic burden of exercise.

Carbohydrate metabolism—Glycogen is the major storage form of carbohydrate (644), a highly branched structure arranged that is easily dismantled to constituent glucose molecules. Liver glycogen stores are highly concentrated but, given the small mass of the liver (~1.5–2 kg), quite limited in comparison to those in skeletal muscle (644), particularly in well-trained individuals (477). In fact, it is estimated that hepatic glycogen utilization alone could not support exercise for longer than ~20 min (865). Thus, muscle glycogen reservoirs are critical to provide carbohydrate during exercise (477), and further advantages are conferred by carbohydrate-sparing adaptations within muscle or exogenous carbohydrate supplementation (477).

Despite its inadequate glycogen storage capacity, the liver plays a major role in coordinating carbohydrate flux to support exercise (11, 300). This role was first illustrated by Carl and Gerty Cori in a sophisticated mechanism for which they were awarded the 1947 Nobel Prize in Physiology or Medicine (1128). Since this time, it has become well appreciated that liver is the central hub of carbohydrate traffic during exercise. For instance, lactate and pyruvate, byproducts of glycolysis, can leave working muscle and travel to the liver to be converted into glucose (11, 456, 477) and resynthesized into glycogen (270), or simply shuttled to inactive tissues (e.g., other muscles) for immediate use as energy substrates (16). During exercise, skeletal muscle preferentially uses its own stored glycogen as a carbohydrate source, especially at higher intensities (1115), but may draw from plasma glucose as resident stores are depleted. As plasma glucose drops, glucagon is released from the pancreas (1103) and stimulates liver glycogenolysis, by which liver glycogen is broken down to fortify circulating glucose (1103) and support continued muscle contraction (1383). Glucose production may also be stimulated in response to exercise-induced increases in skeletal muscle IL-6 (1018) and circulating epinephrine (348, 1103), although the latter effects may only be seen at very high concentrations (707).

The process by which circulating glucose enters skeletal muscle has been of great research interest, particularly in the context of metabolic diseases (e.g., T2D). This occurs in both an insulin-dependent (644, 1285) and insulin-independent fashion (28, 1073). The former is reliant on the upregulation of the membrane-bound insulin-mediated GLUT4 transporter (644). Within the myofiber, insulin may activate glycogen synthase, which is necessary for glycogen production and eventual storage in skeletal muscle (644). Due to high metabolic demands, the actions of insulin in promoting resynthesis and storage of glycogen are limited during exercise but prominent after cessation of an acute bout (645, 1073). Throughout and after exercise, muscle-derived IL-6 may function as a carbohydrate sensor, promoting insulin-mediated glucose uptake through communication with the liver (549, 1018). Preclinical evidence from John Holloszy's laboratory demonstrated that skeletal muscle glycogen was resynthesized more quickly than liver glycogen 24 h following exhaustive exercise in rats (388), supporting that skeletal muscle is preferentially replenished and equipped for future metabolically demanding activity.

Lipid metabolism—In addition to storing small depots of lipids, liver coordinates overall lipid metabolism (Figure 7) through its interactions with adipose (source) and muscle (sink) (1035, 1189). Under resting conditions, liver metabolizes approximately 40% of free fatty acids (FFAs) circulating throughout the body for disposal or storage. During exercise, however, FFAs are redirected to support muscle energetics (1189). In fact, hepatic lipid metabolism is largely unchanged during exercise (1189), but hepatic lipid concentrations are increased after acute AE (653). In regulating hepatic lipid metabolism during exercise, pancreatic glucagon serves a dual purpose, stimulating fatty acid breakdown in the liver while simultaneously inhibiting lipogenesis (1103). These actions are thought to be primarily driven through activation of AMPK, which is known to affect both glucose and lipid metabolism in the liver (897).

The liver acts as the central mediator of lipolysis and lipogenesis, feeding fatty acids to the body tissues such as skeletal muscle and adipose tissue (999). Glycerol byproducts of lipolysis in AT can be shuttled to the liver, where they are then used as a noncarbohydrate substrate for conversion to glucose via gluconeogenesis (1123). Alternatively, glycerol may also be processed into a triglyceride via reesterification with free fatty acids (958, 1439). This process occurs both in adipocytes and skeletal muscle (354, 917). Throughout the body, the degree of fatty acid cycling that occurs at rest and after exercise is remarkable (1439), and flexibility in the process appears important to transition from resting metabolism to the heightened demands of a perturbation such as exercise.

Molecular transducers of liver roles in exercise

Key pathways—The mechanisms mediating the range of liver functions are incompletely characterized but include several key factors. For instance, 5′-AMPK acts as a central metabolic switch that is particularly sensitive to exercise in both the liver and skeletal muscle (640). In the liver, AMPK activation is involved in glucose and lipid metabolism (348, 897, 1103), along with other processes including catabolism, cell cycle arrest, mitochondrial biogenesis, fatty acid oxidation, glucose uptake, and insulin signaling (942). Specifically, AMPK phosphorylation leads to suppression of fatty acid synthesis and favors fatty acid uptake and oxidation (640). The specific downstream effects of AMPK activation in energy sensing and metabolism appear to depend on differential activities of its subunits. For example, phosphorylation of the α subunit of AMPK facilitates hepatic glucose secretion (640), while the β2 subunit has been described to bind to glycogen and promote in an increase of skeletal muscle glucose uptake (640). Additionally, angiopoietin-like protein-4 (ANGPTL4) is a plasma protein secreted by adipose and liver (688, 696) that reduces the activity of lipoprotein lipase to regulate plasma triglyceride levels (624). In response to exercise, the liver increases ANGPTL4 production through glucagon-induced stimulation of the cAMP/PKA pathway (624). ANGPTL4 also plays roles in lipolysis in adipose and skeletal muscle, angiogenesis, and vascular permeability (577). Continued investigation of the impact of these factors in response to differential energy stress is warranted in the context of human exercise.

Exosomes—The role of exosomes in exercise-mediated tissue cross talk is a developing area of study (1136), but the liver may be particularly relevant to these research efforts,

since exosomes released from skeletal muscle have an apparent tendency to localize in the liver (1423). This may represent a mechanism for muscle-liver cross talk or a central role for the liver in filtering and/or redistributing muscle-derived exosomes to other tissues. Whitham et al. recently demonstrated that the vesicular adhesion protein integrin beta 5 (ITGB5) was both released by exercising muscle and taken up by animal liver cells in vitro, indicating its potential importance in directing exosomes to liver (1423). These findings provide direction toward identification of mechanisms underlying exosome and extracellular vesicle trafficking through the liver. Given the wide range of possible downstream effects, continued investigation is necessary.

Liver adaptations to chronic exercise

The effects of chronic exercise training on the liver are poorly understood in healthy human populations. The present understanding of molecular pathways driving liver adaptations to exercise is obtained through a combination of preclinical models and histological observations in human disease (e.g., fatty liver disease, diabetes). Chronic AE leads to lower hepatic fat deposition (432, 1330), and studies in animals have associated these changes with improved coupling of mitochondrial oxidation to the tricarboxylic acid cycle and decreased oxidation of palmitate (1330). As most of these utilize a treadmill running paradigm, is unclear whether other modes of exercise (e.g., RE, HIIT) elicit the same metabolic impact that contributes to these effects. Nevertheless, exercise-induced reductions in liver lipid droplet distribution have potential relevance for nonalcoholic fatty liver disease (84). Impaired PPAR signaling is thought to play a role in the development of characteristic features of this condition, including liver steatosis, dysregulated lipid profile, and inflammation (177, 808).

While the mechanisms are not completely clear, exercise training often leads to changes in levels of circulating lipoproteins produced in the liver, for example, cholesterol, HDL, LDL (1358). However, reductions in cholesterol are not a universal outcome of exercise training studies (725). Some evidence suggests that an intensity threshold exists to modify blood lipid profile (1129); this may be a result of metabolic stress associated with increased carbohydrate utilization at higher intensity. Nevertheless, exercise-induced increases in HDL may contribute to reduced overall systemic burden, promoting hydrolysis of cholesteryl esters in the liver through the actions of sterol carrier protein 2 and fatty acid binding protein 1 (27). Furthermore, HDL facilitates removal of cholesterol released by arterial macrophages (1081), a process upregulated with regular exercise (1129).

As the body’s toxin filtration system, the liver sees inflammatory and oxidizing factors originating from a variety of sources, including free radicals and ammonia derived from active skeletal muscle (1134, 1330). Acute inflammation following exercise is associated with increased production of ROS in liver mitochondria, which may result in liver injury in animal models (84, 403). Some evidence supports that IL-6, a key factor in carbohydrate metabolism during/after exercise, can contribute to liver pathology when chronically elevated (1162). However, chronic exercise training has both anti-inflammatory and antioxidant effects, which may bolster resistance to these acute stresses (84, 1084). In support, moderate- and high-intensity exercise reduces inflammatory cytokines and injury-

related markers in the liver (84), including superoxide dismutase, catalase, and reduced glutathione. In consideration of these results, it is important to recognize that combination of exercise with antioxidant supplementation may obscure the natural antioxidant effects of exercise.

Another prime liver-derived indicator of overall health is C-reactive protein (CRP). Liver produces CRP in response to inflammatory signals such as IL-6 and IL-1 (441, 1162). CRP serves as a nonspecific diagnostic marker for the progression of a variety of conditions characterized by an inflammatory component (42), which, incidentally, is a feature of many chronic diseases (433). At the cellular level, CRP is involved with activation of immune functions including phagocytosis (5) and complement activation (1236). While more highly fit, higher-functioning individuals often demonstrate lower circulating CRP than their counterparts (450, 462, 1096, 1280), short-term exercise does not consistently induce changes in circulating CRP (518, 716, 974). It is therefore unclear whether the etiology of an exercise training effect is based in the liver or another tissue, for example, adipose (186, 1367). Nevertheless, exercise likely lessens the overall systemic inflammatory burden, reducing the load on the liver and enabling its optimal functioning.

Section summary

The capacity to maintain normal liver function is important both for resting and exercising metabolism. Continued investigation into the role of the liver in managing metabolites affected by exercise may be supplemented by exercise studies employing metabolomics, lipidomics, and other unsupervised ‘omics platforms. Finally, the health of other splanchnic organs, including the gastrointestinal system, is likely to be important in overall metabolism. Attention to this area via improved understanding of the gut microbiome will be fruitful in our understanding of the integration of physiological systems to maintain homeostasis during acute and chronic exercise.

Nervous System Adaptations to Exercise

A.V. Hill once postulated that exercise performance was likely controlled by a physiological ceiling in work output imposed by the heart or the nervous system (566). Nearly a century later, Timothy Noakes introduced what is known as the Central Governor Theory, maintaining that the brain enforces necessary limitations to exercise performance to protect the organism as a whole (458, 981). While the theory’s underlying mechanisms (1054, 1148) and shortcomings (627, 1188) continue to captivate the field, it is clear that the nervous system is both an integral player in adaptation to exercise and a beneficiary of regular structured exercise.

The central nervous system

Until very recently (374), it was believed that the central nervous system (CNS) was not plastic in adult humans; that is, neurogenesis did not occur in a fully formed adult brain. We now appreciate that exercise training may exert a powerful influence on the architecture and thus the function of the CNS, typically defined as the brain itself and the spinal cord. In an elegant series of animal studies, van Praag et al. have established a direct effect of treadmill

running on neurogenesis (1351, 1376). In humans, compelling evidence exists to suggest that elite exercise performance may be attributable to neural plasticity (541, 542, 826). Cross-sectional studies suggest structural differences in the CNS of highly trained athletes (1290) that may confer performance-related advantages (599). Evidence in young (79) and older (80) adults suggests that baseline neural architecture may determine the degree of adaptability to training: individuals with increased separation between neural networks (termed “modularity”) exhibit more favorable changes in learning and cognition with exercise training. Thus, as with many physiological systems, it is likely that a combination of baseline phenotype and extrinsic factors (e.g., exercise mode, frequency, and intensity) combine to influence exercise adaptations in the CNS.

Central nervous system adaptations to aerobic exercise

Research into the effects of exercise on the CNS has largely focused on the hippocampus (267), the learning and memory center of the brain that appears very plastic to exercise training. In adult humans, the left hemisphere of the hippocampus is generally more responsive, although some studies demonstrate additional benefits for the right hippocampus (399). These structures are involved in episodic and spatial memory, respectively (379). These effects are thought to be mediated by induction of long-term potentiation and upregulation of receptors for the neurotransmitters excitatory glutamate (1138) and inhibitory GABA (267). Animal research demonstrates that voluntary wheel running (AE) promotes the proliferation, development, and survival of hippocampal neurons, which are then guided toward the nearby entorhinal cortex, a structure involved in spatiotemporal processing and memory (1375). In adult humans, the entorhinal cortex is activated by walking (371) and combined exercise (819, 1195), including AE, RE, walking, and stretching. Interestingly, animal data also suggest a positive correlation between the magnitude of cardiovascular adaptability to AE and degree of hippocampal neurogenesis (982), suggesting a strong influence of genetics on these connections.

Many studies link neural plasticity (1171), hippocampal volume (215, 372), and cognitive function (1101) to aerobic capacity at various stages of life. However, in mid-life (i.e., outside periods of brain growth or atrophy), fitness correlates best with viscoelasticity, a measure of brain structural organization (1171). This raises the important distinction that exercise does not necessarily increase hippocampal volume during periods of maintenance (e.g., mid-life) but is most effective during development and age-related atrophy (373, 399). During childhood brain development, exercise appears to have a beneficial role in hippocampal volume (215, 562, 1029), translating to better learning (562), memory (215), and academic performance (449). In older adults, AE interventions may slow or reverse age-related hippocampal atrophy in a year or less (373). Evidence in Master’s athletes supports that high-intensity AE may protect structural integrity. This population exhibits increased cortical thickness (1443), preserved integrity of white matter composed primarily of myelinated axons (1337), and attenuated loss of grey matter in brain regions associated with memory and motor control (1336). These patterns are complemented by an 83% reduction in white matter hyperintensities, hotspots that indicate loss of myelination and are correlated with risk of dementia and death (311, 1337).

In addition to promoting improvements in size and function of these brain regions, regular exercise prepares the brain for subsequent bouts of exercise. Anticipatory increases in heart rate and respiration, as well as appropriate redistribution of blood flow, are components of this adaptation mediated by the cortical autonomic network (23). CNS regions including the insular, medial prefrontal, and anterior cingular cortices communicate with peripheral mediators to reduce parasympathetic input, aiding in preparing the body for the onset of exercise. Whereas impaired activity of the cortical autonomic network in aging (1443) and disease (31) may contribute to increased perceived effort during exercise, long-term training enhances the system's efficiency, improving exercise tolerance. This is supported by examining the alpha:beta ratio, a comprehensive measure of brain efficiency in multiple regions monitored through electroencephalogram (826). During cycling, highly trained cyclists with higher Vo_2max demonstrate greater alpha:beta activity ratio, indicating less active cognitive processing during an accustomed exercise bout (826).

Central nervous system adaptations to resistance exercise

Functional domains of neural health are also improved after short-term RE in older adults (209, 560). Progressive RE outperforms computer-based cognition training in older women with MCI (1271), improving both cognitive performance and white matter lesion frequency. In a randomized controlled trial of 100 community-dwelling adults, RE-induced improvements in cognition were better associated with gains in strength than with change in aerobic capacity (863). This may be due to greater absolute dynamic range in skeletal muscle strength gains than in aerobic capacity, which others have shown to be associated with neurocognitive outcomes and structural integrity in the pretrained state (215, 372, 1101, 1171). Data regarding structural adaptations to RE are less conclusive. It has been shown that a year of RE training in older women reduces the rate of total white matter atrophy (118), with benefits persisting up to a year after cessation of supervised training. Hippocampal neurogenesis in animals subjected to weighted ladder climbing, a model of RE, is not consistently elevated (474, 982), but simply the act of learning a motor-based task may improve synapse formation in the rat motor cortex (709). Additional research is needed to understand the impact of RE on prevention of hippocampal atrophy throughout aging.

RE generally receives less attention than AE in studies designed to examine neural adaptations to exercise. This discrepancy might be due to the vast preponderance of mechanistic information from animal research using treadmill running, difficulty in discerning the tissue origin of systemic responses to AE, the lack of a universally accepted RE-based analog to cardiovascular fitness (e.g., muscle size, strength, or power), and/or some other methodological consideration. Further evidence exists to suggest that cardiovascular stress, presumably reflective of greater systemic burden, is necessary to elicit beneficial effects of exercise on memory (1378) and functional connectivity (869). In support, some authors have suggested using blood flow-restricted RE to increase the metabolic load above that of more traditional RE, theoretically enhancing the production of neuroactive substances that impact cognitive outcomes (1318). Clearly, further work using a wider range of intensities and alternative modes of exercise is needed to elaborate on these findings (559).

Molecular transducers of central nervous system adaptations

Growth factors—Several factors believed to influence neural adaptability to exercise have been identified, and it is thought that muscle either directly secretes them or indirectly promotes their secretion (318, 1021). In distinguishing whether a muscle-derived signaling molecule may act in the CNS, it is critical to establish whether the factor has the capacity to cross the blood-brain barrier (BBB). This physical barricade between peripheral circulation and cerebrospinal fluid is selectively permeable and regulates leakage of potentially toxic materials into proximity with the brain. Some evidence suggests that BBB integrity is generally fortified by exercise training (246, 864), whereas its permeability is increased in aging (370, 909) and disease (799, 841).

Studies in humans have linked exercise-induced increases in hippocampal volume to a rise in circulating brain-derived neurotrophic factor, BDNF (373). Binding to tropomyosin receptor kinase (Trk)B receptor (812, 1041), BDNF acts centrally by promoting long-term potentiation and survival of neurons (737). BDNF may also exert peripheral effects through other receptors, such as muscle regeneration in myocytes via neurotrophin receptor $p75^{NTR}$ (262). Numerous studies demonstrate increased concentrations of circulating BDNF during and after exercise (812, 1277). However, it remains unclear whether muscle is the direct source of this increase, with studies showing varying results (860, 1389). Circulating megakaryocytes are likely to produce a substantial fraction of BDNF in humans (214, 860), suggesting an integration of body systems is involved in this response to exercise. Furthermore, successive exercise bouts are believed to have a synergistic effect on circulating BDNF (1277), although conflicting data exist as to the impact of long-term AE on basal BDNF (63, 105, 1435, 1481). The role of BDNF in neural adaptations to RE is also unclear. Animal models often demonstrate hippocampal neurogenesis independent of an increase in BDNF (474, 982). Similarly, BDNF is unchanged after 12-week RE in humans (617), though some data suggest responsiveness to RE may be contingent on variables such as sex (411, 412), intensity (870), or training status (247, 1459).

VEGF is intricately involved in cardiovascular adaptations to exercise (579) but may also be a major player in neural adaptations (671, 1098). In animals, exercise-induced VEGF promotes neurogenesis after injury (1476) and cerebral angiogenesis via hydroxycarboxylic acid receptor (HCAR1) (921). While upregulation of VEGF mRNA is commonly detectable in human skeletal muscle following both AE and RE (128, 285, 1292), there is a broad range of potential sources of exercise-induced VEGF. Concerningly, however, an age-dependent decrease in acute AE-induced muscle VEGF expression is apparent in women (285), and long-term AE may not be fully protective against this (1150). Nevertheless, cerebrospinal fluid concentrations of VEGF are increased after RE in individuals with chronic hydrocephalus (1458), a neural condition contributing to dementia and cognitive impairment. Thus, improved blood flow promoted by VEGF signaling may represent a potential therapeutic mechanism for restoring delivery of blood and oxygen to the brain (1194).

PGC-1α plays a central role in coordinating production/secretion of VEGF (779) and other neuroactive molecules following exercise (318). For example, irisin and kynurenine

aminotransferase (KAT) enzymes are upregulated through the transcriptional co-factor activity of PGC-1α. Irisin represents the secreted form of fibronectin III domain-containing protein 5 (FNDC5), which is upregulated postexercise in mouse hippocampal and cortical neurons upstream of an increase in BDNF (1448). In humans, acute exercise increases circulating irisin approximately 15% to 20% (414), although long-term training does not appear to influence basal irisin levels (120). Skeletal muscle FNDC5 shows no increase with acute exercise or chronic training (1024) but is increased in young men following 20 days of twice-daily high volume HIIT (352), suggesting a potential intensity- or frequency-mediated effect. The precise implications of the PGC1α-FNDC5-irisin axis for neural adaptations to exercise in humans are not yet clear, but this pathway is receiving increasing attention as a target for neurodegenerative (1465) and neurological conditions (151).

Neuroactive peptides—KAT facilitates the breakdown of kynurenine (KYN), a byproduct of tryptophan metabolism. Under normal physiological conditions, tryptophan is metabolized into neurotoxic and BBB-transient KYN; however, exercise promotes the breakdown of this substance into kynurenic acid (KYNA). The BBB is impenetrable to KYNA (1021), and this has been associated with neuroprotective, antidepressive, and anxiolytic effects (13, 912). KAT expression in healthy adult skeletal muscle is increased by acute exercise and long-term AE (1161), and acute increases in KYNA are seen after marathon running (786). Furthermore, skeletal muscle expression of genes in the KYN pathway are upregulated following RE training (25), and dysregulated urine concentrations of KYN in chemotherapy patients are normalized by RE (1480). However, depressed individuals undergoing moderate AE or combined AE/RE training do not exhibit changes in circulating KYN or KYNA, despite improvements in depression score and fitness (903). As with BDNF (1277, 1459, 1481) and VEGF (1292), a higher training status may predict a stronger signaling response; thus, longer-term studies may be necessary to elucidate the dynamics of tryptophan metabolite processing in exercise and mood disorders.

Exercise promotes the release of other neuroactive factors that may improve mood and pain tolerance (18, 452). For instance, endorphins interact with opioid receptors (1133), and endocannabinoids such as anandamide bind to cannabinoid receptors (436). Heightened endorphin activity is detectable in the human brain after HIIT (1133) and AE lasting approximately 2 h (124). Increases in circulating endocannabinoids are thought to result from cortisol signaling (569) and may be involved with BDNF (563). Circulating anandamide is increased following 30 min of moderate-intensity AE, but not after high- or low-intensity (1085). Further, anandamide is increased in healthy adults regardless of whether exercise is prescribed or self-selected (144), whereas only the former elicits increases in depressed individuals (896). Given these mechanisms of action, it is enticing to consider that exercise training might help reduce dependence on recreational drugs (145, 829, 1110). However, clinical trials investigating this connection have produced equivocal results (1153, 1332, 1478). More human-based research is clearly needed to expand on the mechanisms of exercise-induced improvements in mood disorders and addiction, including whether long-term exercise reduces lifetime risk.

Furthermore, while regular exercise has numerous benefits for cognitive health throughout the lifespan, it is worth noting that dependence on exercise remains a risk to mental health

(266, 906), especially in young individuals and those involved in physique-oriented sports (e.g., gymnastics, bodybuilding, wrestling). Thus, mindfulness of exercise dose, as well as purpose (e.g., competition, wellness, weight loss), is encouraged. On the other hand, abstinence from exercise in an exercise-dependent individual may bring about disordered mood and affect, apparently mediated by dysregulated endorphin and anandamide signaling (41). This fragile balance between wellness and illness further highlights the range of physical activity thresholds that exist across body systems. The field is encouraged to consider this when designing integrated exercise trials to target the health of multiple organ systems.

The peripheral nervous system

The peripheral nervous system (PNS) includes the somatic and autonomic systems, which are under voluntary and involuntary control, respectively. Skeletal muscle is innervated by both systems through physical connections with both motor (169, 1311) and sympathetic (86, 223, 1261) neurons (Figure 8). The neuromuscular junction (NMJ) represents the direct physical interface between the somatic nervous system and skeletal muscle. Sympathetic input typically exists in close proximity to an NMJ (690) and, through the adrenergic receptors (690), may influence a range of skeletal muscle functions and processes (1104) including ion transport, calcium sequestering, and even gene expression (1112). These neural inputs are critical for muscle survival in addition to contraction, locomotion, and exercise.

Somatic nervous system—A given motor neuron and all fibers that it innervates are considered one motor unit. According to Henneman's "size principle" (554), the motor units associated with the smallest neuron bodies (and, usually, the least fatigable myofibers) fire at the lowest threshold. Thus, exercise intensity dictates the demand on the motor unit pool of a given muscle and is likely to explain adaptations to different types of training. For example, regular AE reduces the firing threshold, allowing maintenance of rhythmic muscle contractions with lesser neural current. Rats subjected to treadmill training exhibit hyperpolarized resting potential, specifically in the slow motor neurons most impacted by continuous AE (98). It is suspected that this finding may be driven by trophic factors such as BDNF (98) or adaptative changes in abundance of receptors for neurotransmitters (e.g., GABA and serotonin) and other signals whose integration determines muscular contraction (831).

Motor units can be indirectly assessed in humans using motor unit number estimate (MUNE), calculated by dividing the summed muscle action potential of all motor units by the average motor unit potential measured throughout the muscle (316). While not sensitive to a large range in motor unit potentials across the muscle, this approach is well-correlated with the number of motor units and enables the detection of general dynamic changes in neuromuscular remodeling (557). A salient finding in humans is that primary aging tends to reduce MUNE (876, 1044) while increasing estimates of motor unit size. This observation is most commonly understood as the result of myofiber denervation followed by collateral reinnervation by a neighboring motor neuron's axon (787, 877). The functional consequences of this are only beginning to be elucidated, but it is generally thought to

be preferable to denervation without reinnervation, in which myofibers undergo death and contribute to overall atrophy and impairments in function (1045, 1105).

In older adults, habitual exercise appears to promote reinnervation in a mode-specific manner, as supported by higher MUNE values (1065) in muscles that are regularly activated by the activity of choice (1044). On the other hand, neither AE nor RE has an effect on motor unit potential in young adults (1044), although power training may increase the overall number of motor units. In highly AE-trained older adults, reinnervation may occur to such an extent that type I motor units are remodeled into a “grouped” configuration (934, 935, 1065), due to shifts in myosin heavy chain composition caused by collateral innervation with a type I motor neuron. The underlying molecular mechanisms are not completely clear but may involve signaling to promote cell adhesion, NMJ stability, and myofiber survival (683, 684, 759).

Evidence from animals supports that age-related changes in NMJ structure are mitigated by exercise (1345). In humans, improvements in muscle innervation are reported to occur with short-term training (683, 889), and histological evidence supports that long-term AE may protect against denervation and/or failed reinnervation in old age (934). Denervated skeletal muscle undergoes predictable changes in membrane composition, including disassembly of the Ach receptor (505), and recapitulated expression of factors such as neonatal myosin, neural cell adhesion molecule (340), and developmental ion channels. Presently, insight as to the effects of muscle contraction on these factors comes from diseased populations such as individuals with PD (683) or spinal cord injury (195). The mechanistic effects of long-term training on NMJ stability in healthy populations constitute a considerable knowledge gap. Nevertheless, that a considerable degree of plasticity still exists in chronic disease may suggest that adaptation is possible in healthy older muscle, given the appropriate type and degree of exercise stress.

Animal models have provided considerable insight into mechanisms underlying exercise-induced alterations in neuromuscular junction integrity. For instance, in an animal model of denervation, exercise facilitates more extensive dendrite branching (237), axonal sprouting, and NMJ stability (980). In mice bred for high versus low running performance, factors related to NMJ integrity are differentially responsive to AE initiated in later life (165), suggesting an influence of genetic composition, as is thought to exist in the CNS (79, 80, 982). While the ability to discern whether a given genotype predetermines response to exercise in humans is an attractive area of current research, it is not currently known whether responder status is associated with improvements in NMJ dynamics such as reduced denervation or heightened success of reinnervation throughout aging.

Autonomic nervous system—Downstream of the cortical autonomic network, the other primary PNS pathway includes both the sympathetic and parasympathetic nervous systems. Sympathetic output orchestrates the endocrine responses that accompany exercise, including upregulations in the hormone norepinephrine. Norepinephrine consequently interacts directly with NMJs, the site of chemical exchange underlying muscle contraction (1104), augmenting the effect of Ach exchange. In animals, removal of sympathetic innervation obliterates the catecholamine response, alters neurotransmitter release, reduces

membrane Ach receptor density, and contributes to an array of muscle gene expression changes that mirror motor denervation [e.g., upregulated expression of Ach receptor subunit γ and histone deacetylase 4 (HDAC4), upstream of an increase in atrophy signal muscle ring-finger 1 (MuRF-1) (1112)]. Individuals with spinal cord injury impacting autonomic function display a blunted sympathetic response to AE (e.g., wheelchair cycling over a half-marathon distance) (574, 987), but it is presently unclear what the ramifications are for long-term adaptability or recovery. In healthy populations, regular training does not notably impact the sympathetic response to exercise (22, 201), likely due to its importance as a highly conserved integrated response. At rest, parasympathetic tone is elevated in highly trained athletes (201), just as resting sympathetic output may be curtailed in individuals with metabolically stressful conditions such as hypertension (201) or during periods of altered hormonal flux, such as menopause (992). Notably, extremely high training doses are thought to partially reverse these beneficial effects (254, 1278), an area warranting continued investigation.

Additional knowledge gaps facing the field include molecular examination of PNS structures such as muscle spindle fibers and the Golgi tendon organ (832). These proprioceptive mechanisms enable continual awareness of body position (1076) and muscle forces to protect against damage from excessive stretch or ill-timed contraction (1077). Methodological difficulties are likely contributors to the lack of molecular knowledge related to these structures in humans, but researchers are encouraged to consider their roles in exercise adaptations, fatigue, and performance. For example, function of the muscle spindle appears to be linked to skeletal muscle satellite cell abundance (369, 632), with clear implications for adaptability to a training regimen.

Section summary

The nervous system is a master regulator of physiological function and performance, and the full range of its plasticity with exercise training is continuing to unfold. Across the lifespan, exercise confers benefits for neural functions such as learning, memory, and spatial awareness, while facilitating neural adaptations underlying exercise tolerance. Presently, a range of mechanistic factors have been identified, and continued pursuit of their roles in human exercise will be fruitful. Eventually, this knowledge could be applied to the use of exercise as a preventative or adjuvant therapy for neurodegenerative disease, cognitive impairment and dementia, neuromuscular conditions, mental health disorders, and substance dependence.

Skeletal System and Associated Structures in Adaptation to Exercise

Critical to locomotion and load-bearing, the skeletal system (e.g., bone) provides structural support and protection for many organs. Skeletal muscles, directly attached to bones through tendons, contract to create bone movement that forms the basis of exercise. Like most physiological systems, bone is adaptive to structured exercise training. Though most mechanistic work is limited to preclinical studies, system-level exercise-induced improvements in bone, joint, and tendon (Figure 9) illustrate that these structures are active and responsive to acute and chronic exercise.

Structure and function of bone

Bone is an osseous tissue comprised of four primary cell types: osteocytes, osteoclasts, osteoblasts, and bone lining cells known as the basic multicellular unit (BMU) (407, 501, 1406). BMU cells are responsible for sensing changes occurring within their niche and respond accordingly by reabsorbing or laying down new bone (407). Normally, osteoblasts secrete bone matrix and osteoclasts reabsorb matrix in a coupled fashion to maintain relative homeostasis. However, when this equilibrium is dysregulated (e.g., as in osteoporosis), osteoclasts promote greater demineralization than the osteoblasts restore, resulting in decreased bone mineral density (BMD) (58). Exercise also affects this balance, most typically in a positive manner to promote bone health outcomes (1147), such as increased BMD and strength (1407).

BMD is the most common measure of bone health and is commonly taken at the femoral head, hip, and lumbar spine with the use of dual-energy X-ray absorptiometry (DEXA) (588, 635, 1279). While common, use of DEXA alone provides information on only one facet of bone health and may not capture the intricacy of other important outcomes related to bone strength, such as cortical and trabecular volume (127, 236, 443, 642). Attempts to provide more comprehensive measurements include geometric analysis by peripheral quantitative computer tomography (pQCT) (365, 630, 1334). Use of DEXA in conjunction with pQCT may provide complementary approaches for assessment of exercise-induced adaptations in bone health (815).

Adaptive responses in bone are brought about by metabolic and mechanotransductive forces that initiate signaling cascades specific to a given microenvironment (1147). Briefly, mechanical sheer signals through ion-gated channels and propagates through cell-to-cell contact via integrins and gap junctions (480). These forces upon bone promote anabolism by blunting osteocyte release of receptor activator of nuclear factor- ligand (RANKL) and activating the Wnt/β-catenin pathway (1000). Through the latter mechanism, β-catenin is stabilized and can translocate to the nucleus to promote expression of encoding RUNT-related transcription factor 2 (RUNX2), aiding in progression toward the osteogenic lineage (205).

Bone adaptations to aerobic exercise

Under load or high muscle force typical of exercise, bone is formed (480). The greater the load, the more immense the skeletal strain, and, likewise, the larger the increase in BMD (216). Thus, when considering aerobic exercise prescription for bone health and increased BMD, modalities with greater concussive forces may lead to a more dramatic outcome (715). Specifically, AE such as walking may produce forces from 2.2 to 2.5 times body weight, while descending stairs increases the force absorbed to 2.8 times body weight (1294). Moreover, activities such as sprinting or downhill running increase the load on the tibia up to three-fold that of walking (176). Thus, athletes that participate in sports involving high forces due to ground contact have higher BMD than their counterparts (715). However, increases in BMD appear site-specific and dependent on activity (634).

Acutely, markers of bone turnover in humans do not differ between weight-bearing (running) or weight-assisted (cycling) AE modalities (727). However, in chronically trained female athletes across high-, medium-, and low-impact sports, all three groups exhibit similar markers of resorption, but only the high- and medium-impact groups exhibit greater BMD bone formation (284). This suggests that there is a differential response to chronic loading on BMD and bone formation markers. Sclerostin, a negative regulator of bone formation via attenuation of the Wnt/β-catenin pathway, increases in serum following AE in both males and females (382, 727, 1046). However, the effect of this in humans is not yet clear, as there are no long-term changes in bone turnover markers such as procollagen type I amino-terminal propeptide (PINP) and cross-linked telopeptide of type I collagen (CXTI) (727, 728). In contrast, chronic AE training consisting of walking, running, step-ups, and mobility exercises led to decreased sclerostin levels and higher levels of bone anabolism (46). Thus, multiple exercise bouts may be necessary to propagate intracellular signaling that leads to meaningful changes in BMD.

Bone adaptations to resistance exercise

There appear to be many benefits of RE in relation to bone health (588). Presently, a large fraction of human research into bone adaptations to RE examines postmenopausal women, an at-risk group for osteoporosis and osteopenia (675). These interventions are based on the premise that RE may be leveraged to mitigate the progression of bone health decline (368, 596, 635, 674, 680, 1059, 1253, 1402, 1468, 1474), which may start as early as three years after the onset of menopause (675). Strong evidence in a recent meta-analysis by Zhao et al. suggests that RE is an effective strategy for increasing BMD in these cohorts (1474). Likewise, males exhibit similar increases in BMD following resistance training (126, 738). Less is known about the influence of RE training on bone compartments such as the trabeculae. However, in diseases such as type II diabetes, bone quality is more affected than BMD, suggesting a need to examine this phenotype. Some evidence in literature reviews and meta-analyses describes the ability of exercise to prolong trabecular volume, but discrepancies in study design limit the statistical power to completely investigate this (588, 1059). In a rat model of type II diabetes, RE in the form of percutaneous muscle stimulation promotes BMD and bone quality (622), and human exercise trials are ongoing (73).

Recent studies have provided valuable insight into molecular communication of bone with surrounding tissues beyond the currently understood mechanisms of mechanotransduction. In particular, signaling between bone and the closely associated skeletal muscle has been of research interest (159, 190) with an emphasis on myokine, osteokine, and growth factor cross talk, as reviewed in detail (761). Muscle-bone cross talk has the capacity to regulate each tissue in an anabolic or catabolic fashion, depending upon the stimulus (701, 702). Harry et al. reported that open tibial fractures in mice recovered significantly faster when a flap of skeletal muscle was placed over the wound in comparison to a fasciocutaneous tissue, resulting in 50% greater cortical bone content (525). Thus, muscle secretions may promote regeneration and repair when bone is compromised. Even healthy bone allows molecular penetrants through the periosteum in a size-dependent fashion in mice (745), and a number of myokines and other muscle-derived species (such as IGF-1, IL-15, PGE_2, and FGF-2) fall within the size constraint predicted to be able to penetrate through the periosteum (745).

Given that muscle has a well-established role as a secretory organ (1017) and myokines are augmented during exercise (767), it appears that exercise-induced adaptations in bone are at least partially mediated by myokine production and cross talk with bone (761).

Despite the benefits of exercise for BMD and other parameters of bone health on earth, there is limited knowledge of the optimal exercise intervention to support the skeletal system without a gravitational vector: that is, in space. While exercise countermeasures are protective for the skeletal muscle and cardiovascular systems in surprisingly small doses, loss of bone integrity in microgravity poses a major barrier to long-duration spaceflight missions (282, 1222, 1224). Furthermore, bone formation upon return to gravity does not appear to fully recover (1366), potentially heightening long-term fracture risk. Existing exercise devices aboard the International Space Station appear unable in isolation to apply sufficient loads to stimulate bone formation over resorption, prompting investigation into nutritional supplementation approaches to promote bone health (764, 1037, 1197, 1222, 1223). Animal models taken aboard space-faring vessels have provided insight into the time course of bone integrity loss and molecular signatures associated with this process (1291, 1450), and earth-based analogs such as bedrest can provide an avenue to conduct microgravity research in a controlled setting (719, 763). Certainly, continuation of this line of research is essential to support long-duration space travel and protect long-term astronaut bone health.

Structure and function of joints

Joints are loosely defined as the point of connection between two bones and are classified into three types in humans (661). Fibrous joints are fixed, and collagen is the primary connective tissue holding these joints in place (661). Cartilaginous joints are subcategorized based on the type of cartilage separating bone as either primary (hyaline cartilage) or secondary (fibrocartilage) (1471). Synovial joints are capable of large movements and are made up of a fibrous capsule, which is coated in synovial fluid to permit movement of the articulating bone with minimal friction (661). Joints are formed through a complex network of molecular signaling that occurs throughout development. The main pathways regulating joint development were recently reviewed in detail by Salva and Merrill (1142) and include Wnt, Hedgehog, Notch, and bone morphogenetic protein.

Joint adaptations to aerobic exercise

In relation to the effect of exercise on joint adaptations, the vast majority of mechanistic research is based on individuals with RA and osteoarthritis OA, both degenerative joint diseases. The primary proinflammatory cytokines believed to drive RA progression [e.g., tumor necrosis factor (TNF)-α, IL-1β)] have been demonstrated to destroy joint integrity (434) and induce pain (1390). Conversely, chronic AE elicits a systemic anti-inflammatory effect (757, 1477), which may be able to mitigate inflammatory pathology characteristic of disease progression. In support, a meta-analysis by Baillet et al. showed AE activities in the range of 50% to 90% maximum heart rate decreased pain and increased radiographically assessed bone sparing and quality of life in patients with RA (1155). Continued investigation into mechanisms underlying this effect may reveal both inflammatory and other molecules that could provide therapeutic benefit in RA.

In addition to cartilage and periarticular degradation, OA is characterized by a robust inflammatory pathology in the affected joint and surrounding tissues, compounding the joint damage via molecular tissue cross talk promoting further inflammation and impaired proteostasis (817). As introduced above, exercise prehabilitation may alleviate long-term pain in individuals with OA (1343) through its effects on hypoalgesia (1058). Though potential mechanisms of diminished pain response are wide-ranging, they may include increased release of endorphins, inhibition of the *N*-methyl-d-aspartate receptor (NMDA) subunit NR1, and decreased serotonin transporter activity (1218).

Joint adaptations to resistance exercise

Molecular-level joint adaptations to RE in the context of humans are poorly understood: most of the present knowledge is derived from animal models but could point toward future directions for human research. Rat models of OA have shown favorable responses to agents that reduce oxidative stress, as exercise training might accomplish (234). For instance, hydrogen-rich water inhibits cyclooxygenase activity and MMP-3 and -13 (234). Pathologically expressed MMPs have been shown to play a noteworthy role in OA pathogenesis by degrading cartilage ECM within a joint (879). MMP production is driven by inflammatory mediators such as TNF-α (879). The effects of RE on the inflammatory response are context-dependent. For instance, while long-term RE may alleviate low-grade inflammation in humans, reductions in circulating TNF-α are not a universal finding (99, 181, 1042, 1072). However, mechanotransductive forces have been shown to positively alter joint integrity by diminishing inflammatory mediators and MMPs responsible for cartilage breakdown in animal models (783). Specifically, tissue loading decreases IL-1-induced MMP activation and mitigates collagen loss (1316). Thus, available evidence supports that RE may be beneficial for joint health in inflammatory degradative conditions and highlights the need for further study in human trials to investigate mechanistic underpinnings.

Structure and function of tendon

Tendons are composed of a complex array of bundled molecules making up the functional unit that transmits forces from muscle to bone. The tendon is primarily made of the collagen I molecule, but other collagens (III and IV) and proteoglycans contribute to their structure (1391). Tendons exhibit a hierarchical structure beginning with the collagen molecule (1392): these molecules constitute fibrils, many fibrils form the fiber, fibers form the fascicle, and many fascicles comprise the tendon unit (1391). The tendon attaches to the bone at a point known as the enthesis and allows the contraction of muscle to pull on the bone for locomotion (1391). Tendons have received attention in the context of human exercise due to their obvious role in movement as well as reasonably easy sampling access via microbiopsy needle (900, 937, 1329). For these reasons, the effects of acute and chronic exercise on molecular transducers of tendon adaptation are relatively well-characterized in comparison to bone and joint adaptation.

Tendon adaptations to aerobic exercise

In response to exercise, tendons generally adapt through increased collagen turnover, stiffness, and size (cross-sectional area) (427). Based on a recent meta-analysis, exercise that elicits loading of greater magnitude appears to be most beneficial, and chronic (>12

week) loading is preferable to acute (125). Nevertheless, acute AE has been shown to induce collagen I synthesis in humans (546, 748). Moreover, chronic long-distance runners have approximately 23% greater cross-sectional area at the Achilles tendon than their counterparts (1117). This appears to be partially driven by an acute inflammatory cascade involving IL-6 and PGE_2 (32, 243), which are detectable in serum after high-intensity AE (996, 1015). Attenuation of PGE_2 with nonsteroidal anti-inflammatory drugs has a negative effect on collagen synthesis in young men after acute AE (243). Notably, PGE_2 has been linked to IL-6 in skeletal muscle tissue in vitro (1237), and findings suggest that a regulatory relationship between these factors may exist in tendon (503). In response to IL-6, collagen synthesis markers such as procollagen type I NH_2-terminal propeptide (PINP) are increased (32), but the effects of AE on this marker are dose- and time-dependent (546, 747, 748). Growth factors such as IGF-1, transforming growth factor-beta (TGF-β), and platelet-derived growth factor BB have been shown to positively influence dynamics of tendon remodeling in vitro (710, 994, 1305). Many of these factors are modulated by exercise. However, data in humans is far more equivocal than results from animal studies. It has been suggested that this is due to clinical studies sampling tendon outside of a period of active growth; conversely, many animals are tested during growth, allowing detection of trends in tendon biology that may be masked in mature human tendon (838).

Tendon adaptations to resistance exercise

RE has been shown to lead to tendon adaptations in a load-dependent fashion (125). The primary adaptation observed following RE training in humans is increased tendon stiffness, or Young's modulus (736, 1092). Interestingly, hypertrophy has also been observed in the human patellar tendon, although it is not uniform throughout the length of the tendon: cross-sectional area tends to increase at the proximal and distal ends (720). Investigations have examined the response to acute RE in tendinous tissue, revealing a basis for molecular transducers of these adaptations. Following RE (3 sets of 10 repetitions of knee extension exercise), tendon expression of collagen I, III, and MMP-3 were decreased 4 h postexercise but returned to baseline at 24 h (1269). Others have found that acute RE increases connective tissue growth factor (CTGF) and type I collagen; however, this increase was not matched by fractional synthetic rate of collagen I or other regulatory markers such as TGF-β (333). In preclinical models, TGF-β interacts with CTGF and plays a vital role in tendon remodeling (710, 1335). Like AE, the discrepancy of the effect of RE on tendons may be due to the adult human tendon being more stable than actively remodeling or growing animal tendons (547, 838). Even chronic (10 year) RE training in young adults does not lead to appreciable differences in tendon structure or size (781). Given the effects of age on tendon health (198, 1274), it is possible that meaningful exercise-induced changes in tendon physiology might be best captured using longitudinal studies extending into older age or examining lifelong-trained older adults.

Section summary

Health of the skeletal system and associated structures such as joints and tendons is of utmost importance for exercise. It is important to expand our knowledge of exercise-induced molecular transducers underlying promotion of healthy bones, joints, and tendons in children and adolescents and maintain their health into old age or during periods of

high-volume training. Given sampling limitations of some of these structures in humans, much remains to be learned with regard to molecular drivers of adaptation in the context of performance, health, and disease.

Conclusions and Future Directions

While available evidence supports that exercise may forestall, alter, or even partially reverse the course of many diseases and disorders (Figure 10), a number of knowledge gaps and practical challenges limit its utility as a formal prescription or a tool for leveraging toward development of novel drug targets. First, individual variability in responsiveness (as exists with pharmaceutical interventions) to exercise presents a potential issue (1231). It is not yet completely understood why individuals respond differently to the same exercise regimen, but it is likely that large molecular-level cohort studies, such as MoTrPAC, will shed light on important factors whose variability impacts exercise responsiveness. In examination of these potential influences, it is critical to strive for inclusivity in study cohorts, including racial/ethnic diversity, sex balance, age, and consideration of other important demographics that may introduce variability into a data set (e.g., socioeconomic status, education level). Continued development of bioinformatics platforms [e.g., surrogate variable analysis, svaSeq (775)] to identify confounding artifacts in data and to integrate ‘omics data from multiple phenotypic levels (532) may aid in discriminating molecular associations that are the result of biological relationships or simply individual heterogeneity (i.e., noise).

Secondly, human behavior presents a major challenge to prescription of exercise. While researchers may facilitate a robust, supervised exercise intervention, commitment to long-term exercise is a lifestyle choice. Cross-sectional studies examining the benefits of the exercise lifestyle have provided insight into long-term effects of exercise, but these tend to focus primarily on AE. Attention in this area has revealed which physiological systems are completely, partially, and poorly protected by exercise throughout normal human aging (196, 219, 498, 499, 757, 1030, 1193, 1323). It is likely that examination of lifelong engagement in practices such as RE will reveal differential effects and guide us toward optimization of exercise as an antiaging strategy. Nevertheless, not all individuals may be persuaded to exercise by the promise of a healthier and/or longer life; thus, the challenge is to encourage individuals to discover a preferred modality that is maintainable and enjoyable for its own sake while simultaneously accruing functional benefits. Collaboration with behavioral scientists may guide exercise biologists toward encouraging individuals to build a sustainable habit of physical activity (677, 1141).

Third, the landscape of human health and disease is continually changing. For example, at the time of preparation of this article, the novel coronavirus (COVID-19) pandemic is taking foothold in the United States and much of the world (232, 1210), presenting challenges to both physical (925, 960) and psychological resilience (1315). While it may be impossible to predict such events, strong evidence supports that regular exercise fortifies physiological reserves that may be critical in protection and/or recovery from threats to human health and life. Presently, the impact of regular exercise on strengthening the immune system is of enormous public health relevance (183, 989, 1207). It is probable that the full range of these effects extends beyond our present understanding of skeletal muscle as

the primary amino acid reservoir (1080, 1365, 1438). Furthermore, the protective effects of exercise on physiological reserves other than physical [e.g., cognitive, emotional (235, 988)] are likely of importance. While much research focuses on molecular mechanisms underlying physical benefits of exercise, consideration of exercise as a holistically favorable activity will yield insight into important factors influencing mood, affect, and quality of life. Activities blending physical exercise with mindfulness practices (e.g., yoga, Tai Chi) may be of particular interest.

Despite the challenges ahead and a somewhat incomplete picture of its mechanisms of action, exercise is an accessible, affordable, and effective strategy for prolonging healthspan through a range of physiological benefits. A more complete mechanistic knowledge of exercise adaptations may enable greater specificity in prescribing exercise across demographics (e.g., age, sex, race, health status) and heterogeneous molecular profiles (e.g., transcriptomic, epigenetic). Furthermore, it may enable flexibility of physical activity recommendations in response to changes in population structure and public health status.

In closing, we recognize the rich history of the field of exercise research. Although (to our knowledge) this article will be the most comprehensive ever constructed on the molecular adaptations to exercise (Table 2), we recognize that not all pertinent literature may have been addressed, and this is an inherent limitation. Still, despite the wealth of literature in the area, much remains to be elucidated regarding the molecular adaptations that underlie the beneficial health effects of exercise, and we are hopeful that this article will have illustrated such knowledge gaps. Undoubtedly, the anticipated MoTrPAC dataset will provide substantial opportunity in this area, including evaluation of the molecular map of exercise in healthy individuals, investigation of biological interactions across ‘omics, and direction toward understanding variance in human biology. Even with this promise, many questions remain; as such, continued interdisciplinary collaboration is encouraged to expand our collective understanding of the role of exercise as an ultimate protector of human health.

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Didactic Synopsis

Major teaching points

- Regular, structured exercise promotes prevention of disease, as well as a variety of benefits for general health.
- Throughout its history, the study of exercise has been a multidisciplinary pursuit.
- Basic methodological considerations, analysis techniques, and emerging advancements continue to facilitate collaboration, discovery, and progress.
- Key mechanisms underlying exercise-induced adaptations are driven by cellular and molecular cues throughout the body's physiological systems.
- Aerobic and resistance exercises stimulate distinct but overlapping adaptive mechanisms that improve health, human performance, and system functioning. With the Molecular Transducers of Physical Activity Consortium (MoTrPAC) as important infrastructure, critical knowledge gaps present opportunities for future investigation.

Figure 1.

Marie-Ann Pierrette Lavoisier's sketch depicting her husband Antoine Lavoisier conducting the first exercise physiology experiment and herself taking notes in the right corner. Note the use of the bell-jar calorimeter and the subject pressing a foot pedal below the table. Reused, with permission, from West JB, 2013 (1416).

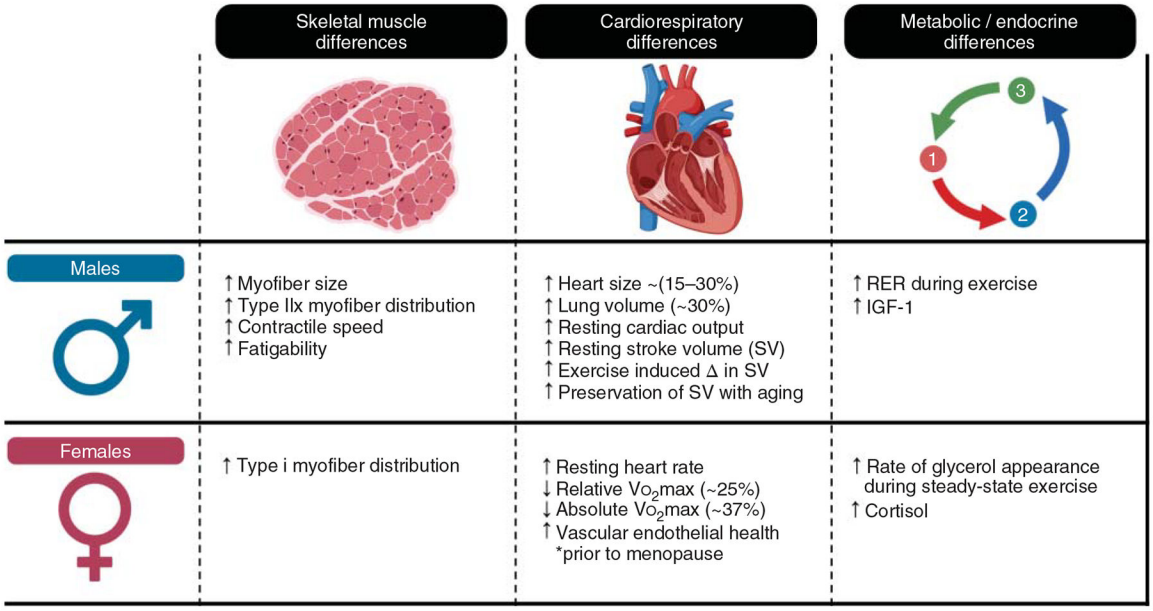

Figure 2.

This figure illustrates an overview of sex-specific differences in skeletal muscle, the cardiovascular system, and energy metabolism that may be important considerations relevant to human exercise.

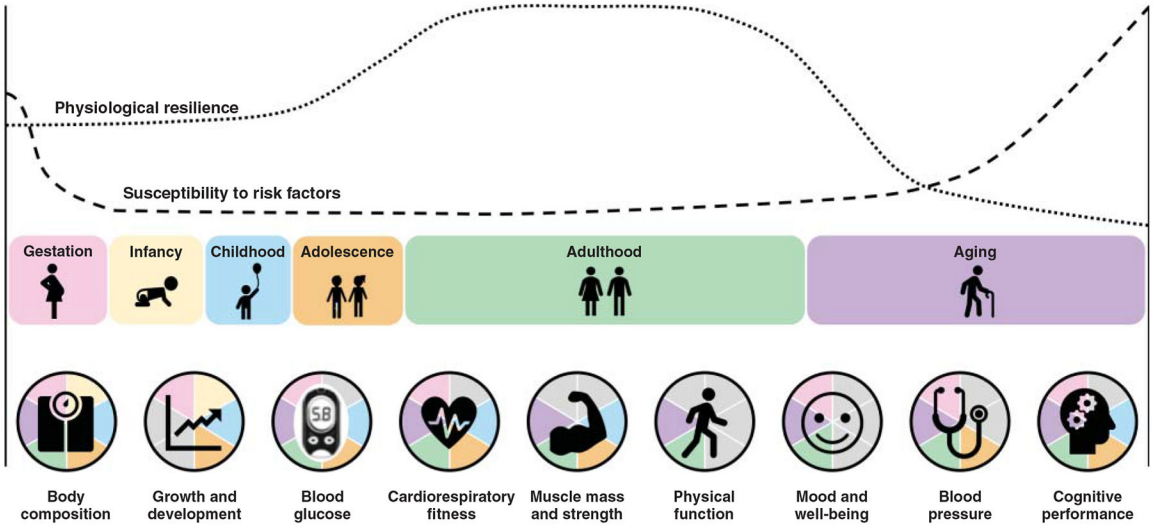

Figure 3.

This figure illustrates exercise benefits across the lifespan. Normal age-related changes affect physiological resilience to environmental or genetic stressors, while the susceptibility to metabolic, cardiovascular, and other risk factors increases. Exercise improves multiple functions and physiological indices of wellness. Pie chart slices are greyed out when (i) the physiological index shown is not relevant for a given age (either no longer growing/developing or process has not yet begun to decline) or (ii) the physiological index has not been sufficiently studied in a population at that life stage.

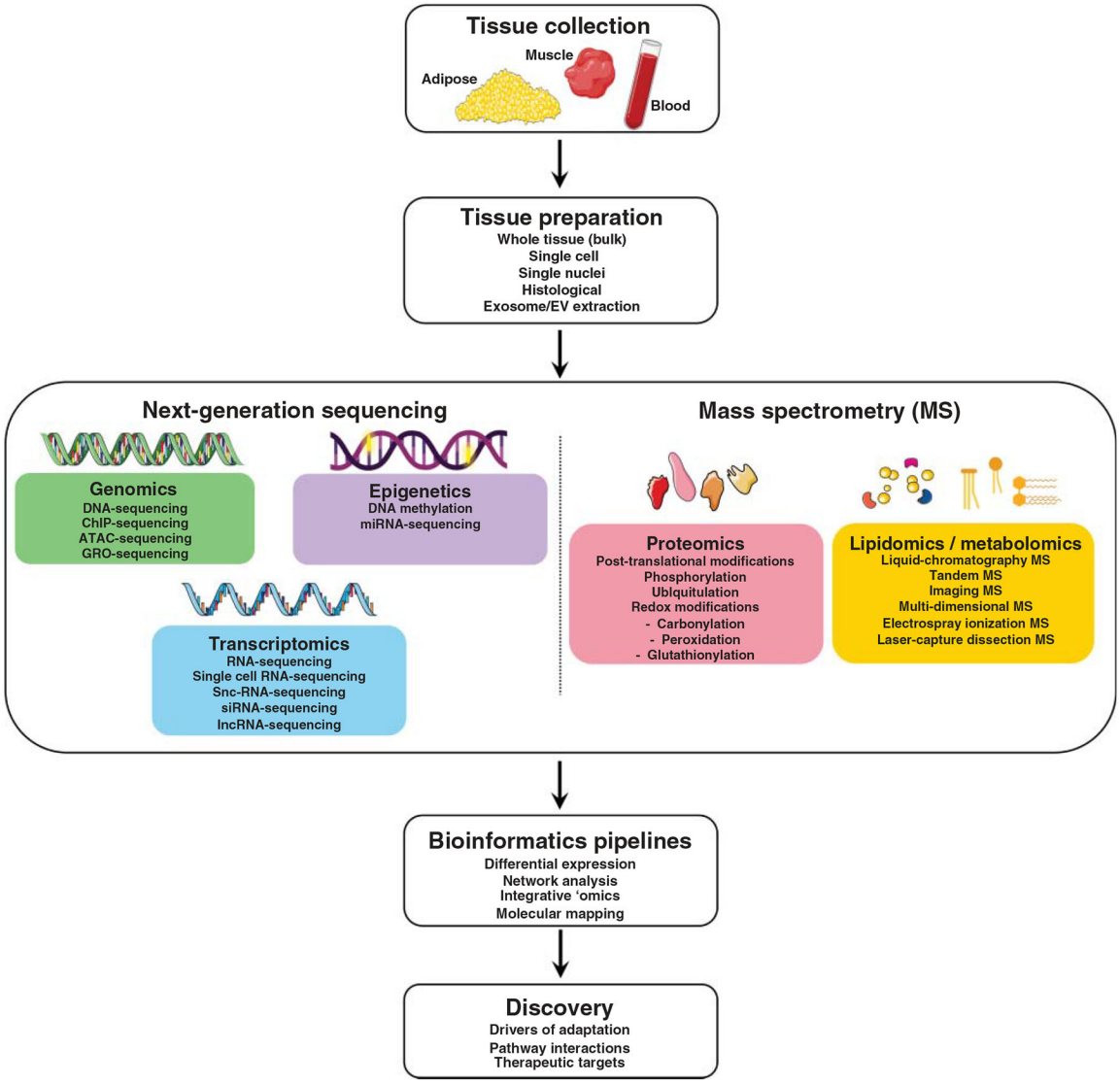

Figure 4.

This figure illustrates the range of current and emerging tools in analysis of human tissue for exercise research, with a focus on preparation of blood, skeletal muscle, and adipose tissues (most easily accessed in humans) for downstream high-throughput 'omics analyses.

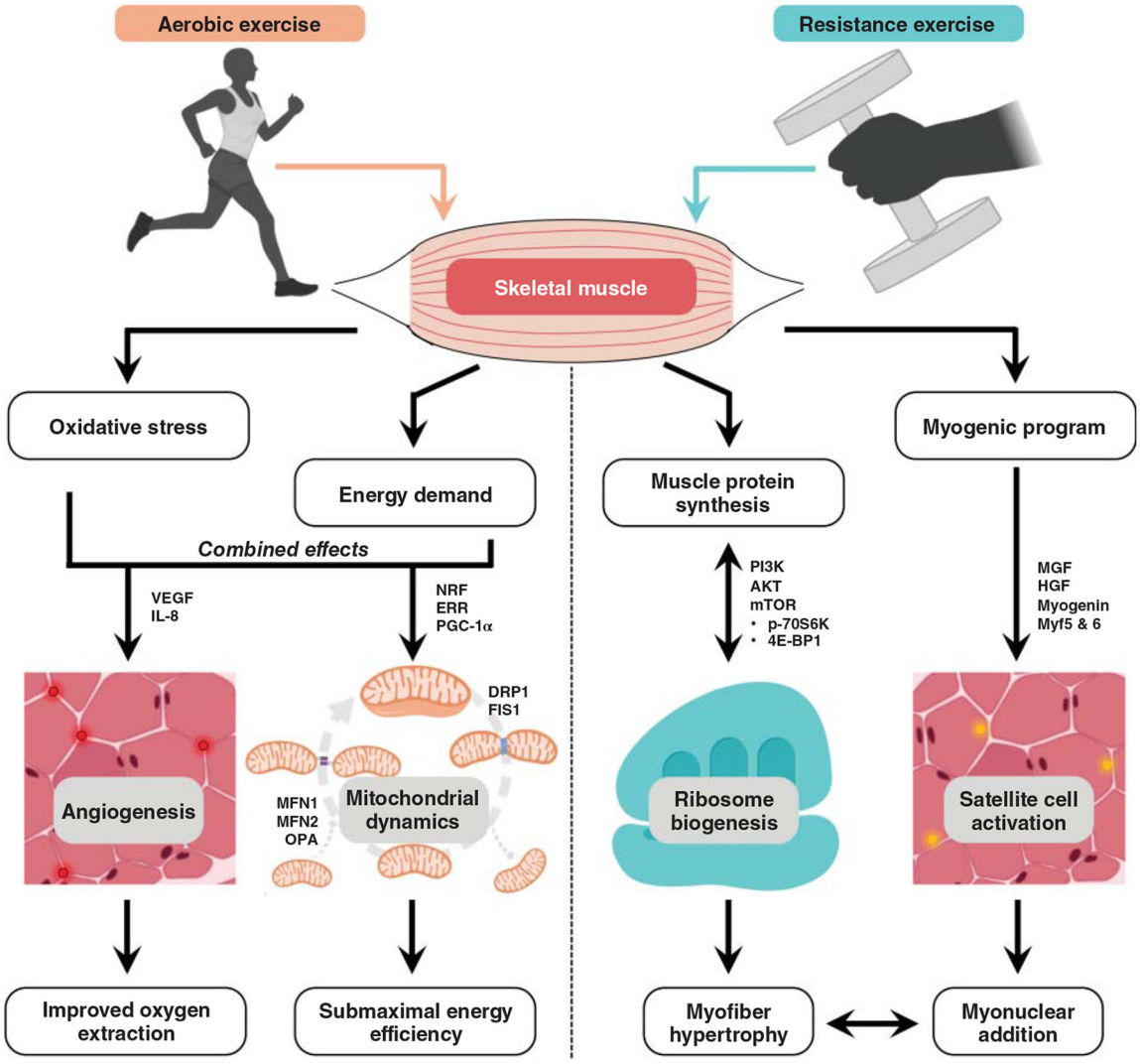

Figure 5.

This figure illustrates key skeletal muscle adaptations to aerobic and resistance exercise, highlighting the role of molecular transducers of these effects that are described in the text.

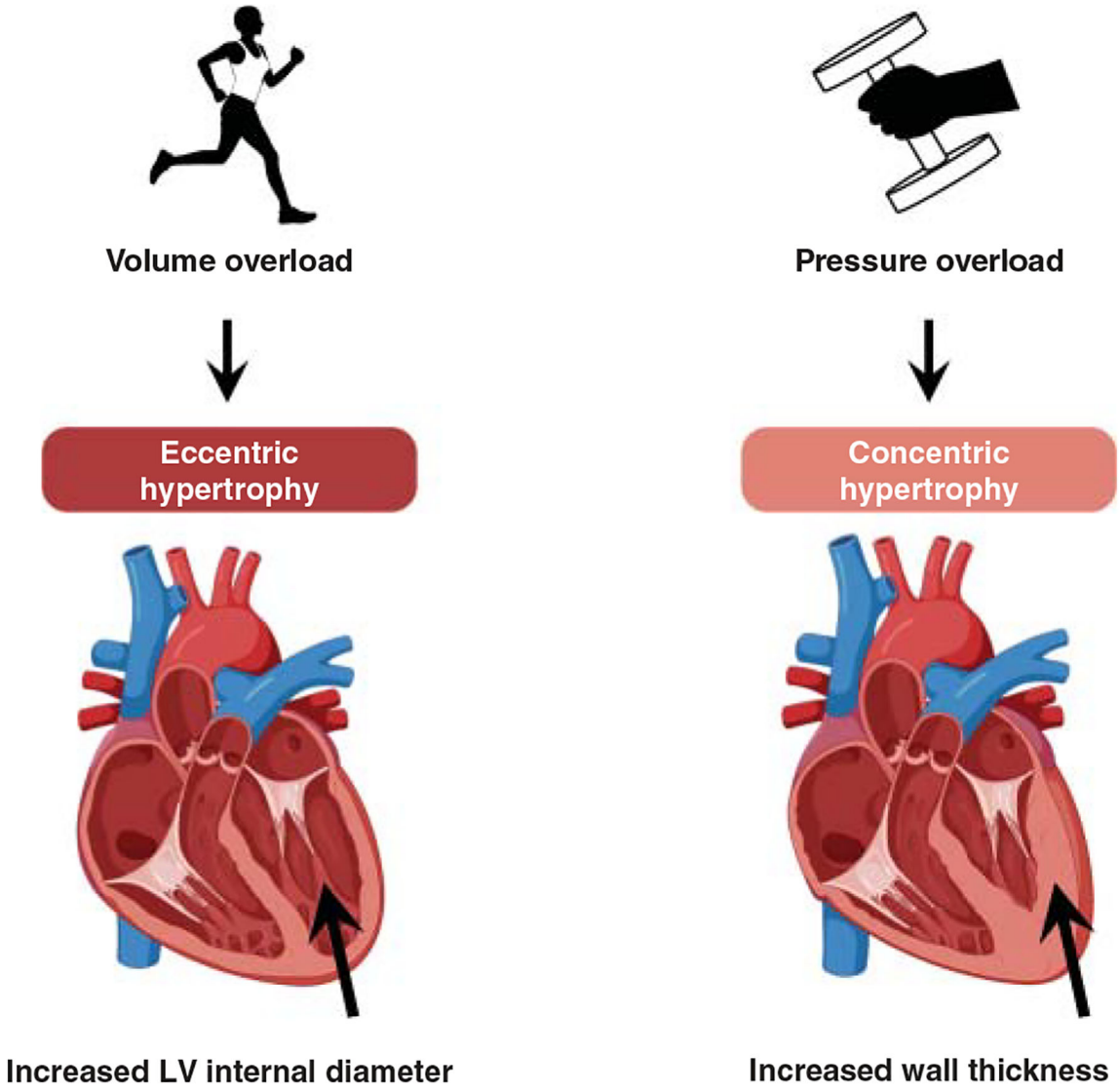

Figure 6.

This figure illustrates physiological hypertrophy resulting from exercise training. The long-term cardiovascular adaptive response depends on the type of hemodynamic stress resulting from the modality of exercise training. Most commonly, aerobic exercise imposes volume overload, leading to eccentric hypertrophy, whereas resistance exercise elicits concentric hypertrophy through pressure overload. Relevant molecular and cellular transducers are explored in the text.

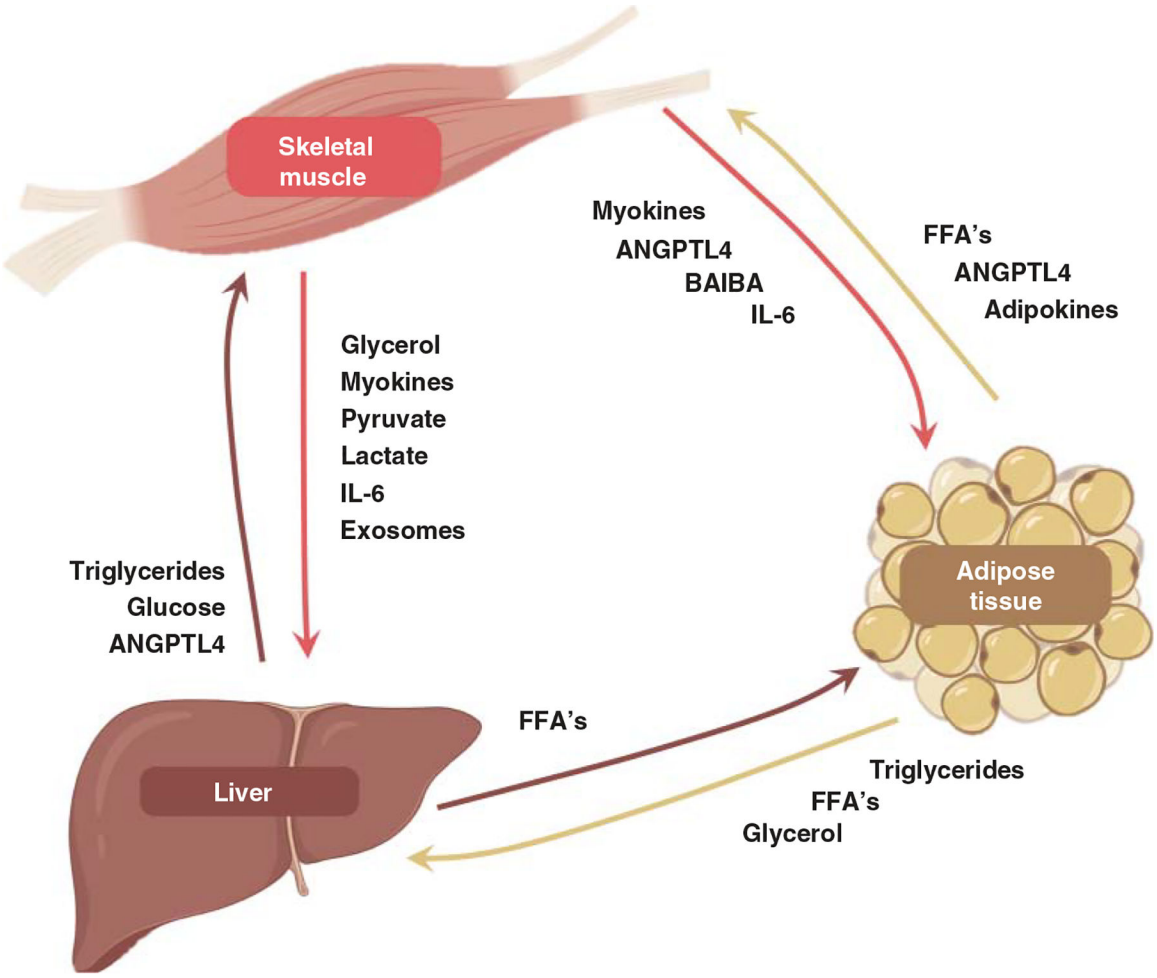

Figure 7.

This figure illustrates molecular-level cross talk between skeletal muscle, adipose tissue, and liver to facilitate energetics during exercise. Key myokines, adipokines, and hepatokines are highlighted.

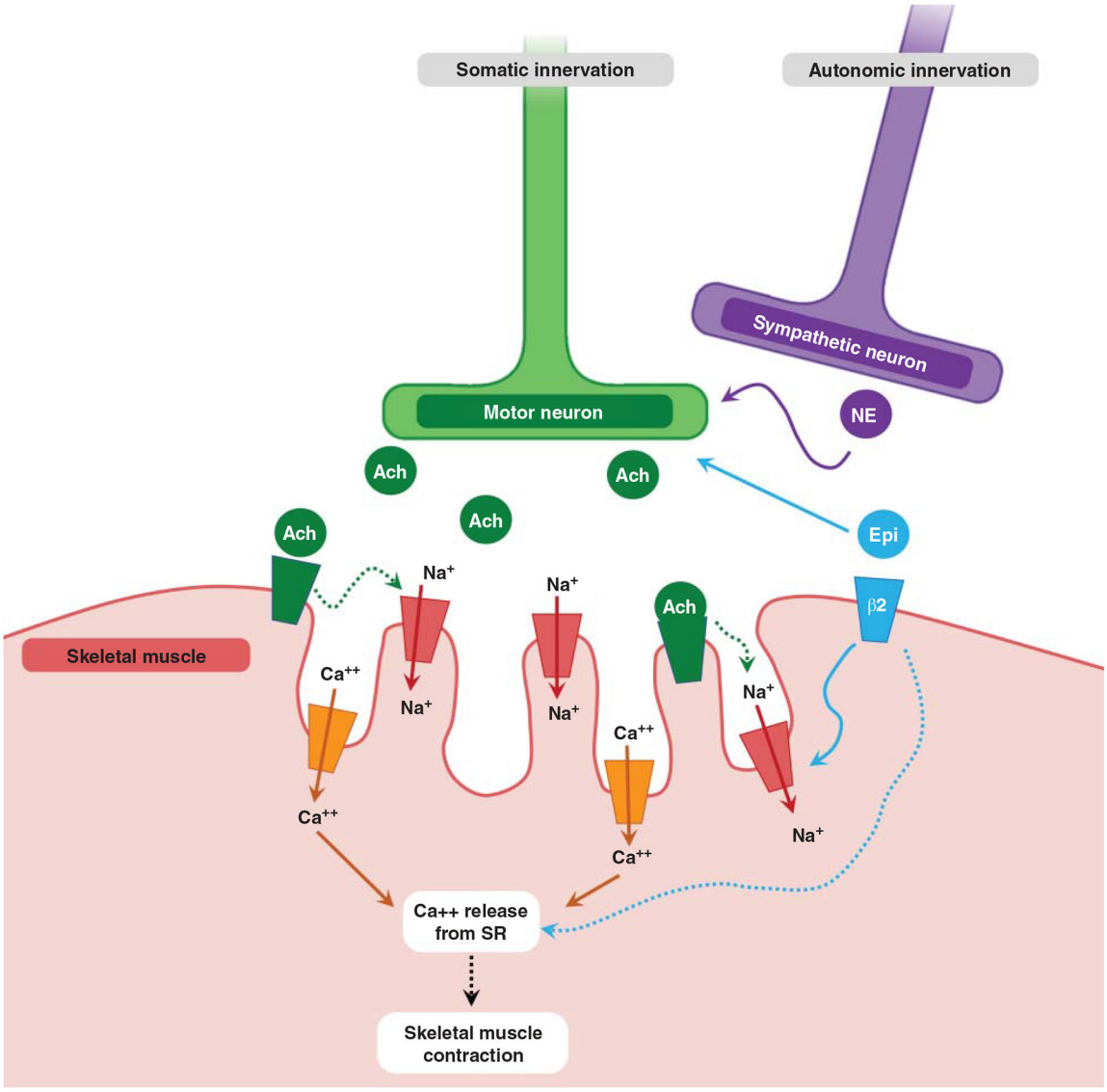

Figure 8.

This figure illustrates simultaneous innervation in skeletal muscle by the somatic and the autonomic nervous systems. Briefly (1104), motor neuron release of acetylcholine (Ach) promotes influx of sodium (Na+) and calcium (Ca++) into skeletal muscle cell. This promotes release of calcium from sarcoplasmic reticulum (SR), leading to contraction. The sympathetic neuron innervates muscle in close proximity and may release norepinephrine (NE) to augment Ach release. Circulating epinephrine from the endocrine system supports sympathetic activation by augmenting Ach release in addition to enhancing Na+ influx and calcium-induced calcium release and re-sequestering.

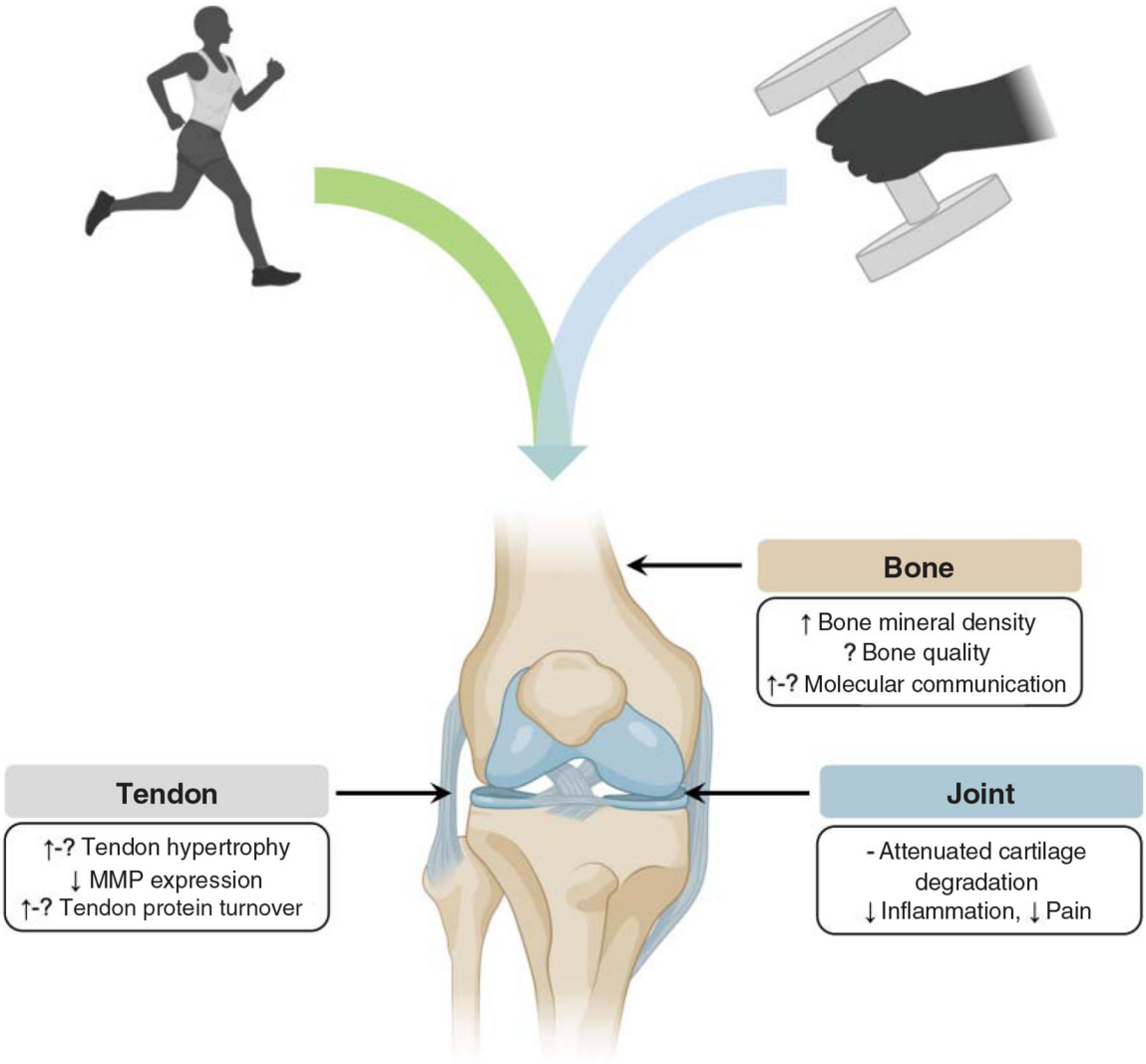

Figure 9.

This figure illustrates summary of exercise-induced adaptations in bone, joint, and tendon; existing knowledge gaps in humans are indicated by question marks (?).

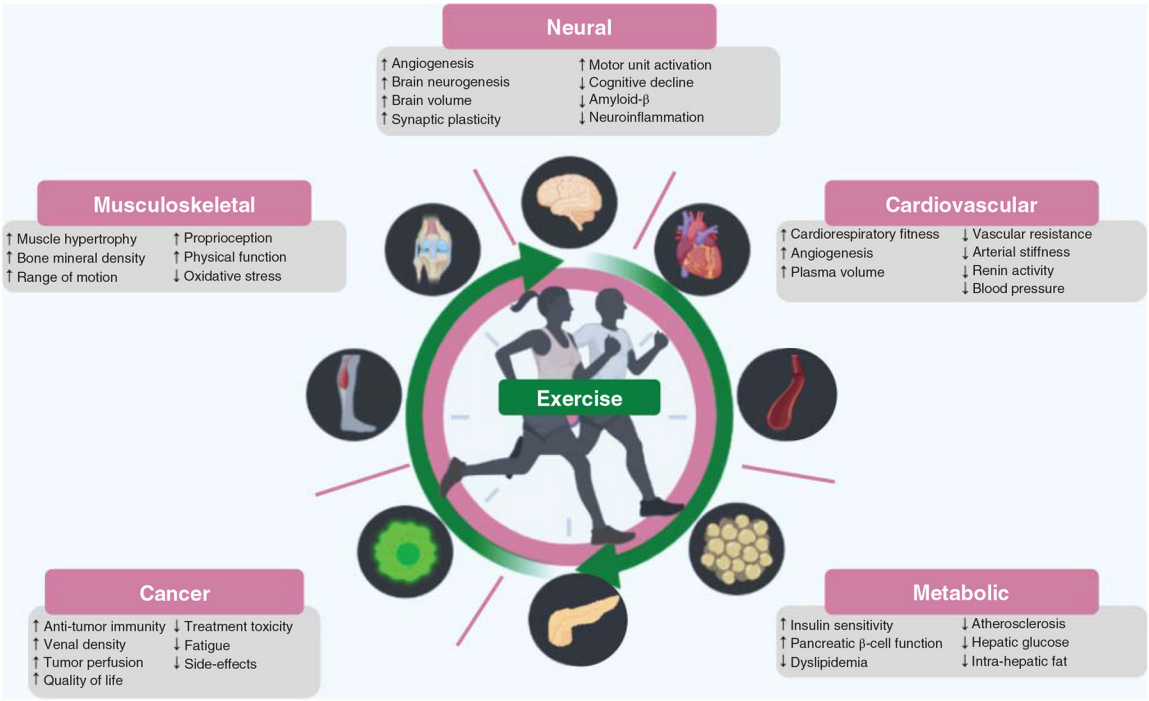

Figure 10.

This figure illustrates the range of the impact of exercise on risk factors and pathologies associated with chronic diseases. Exercise is associated with reduced morbidity, lower hospitalization rates, and decreased risk of all-cause mortality and premature death from disease. Overall, higher cardiorespiratory fitness and a regular exercise training decrease the economic burden of multiple diseases. ↑ indicates increase; ↓ indicates decrease.

Table 1

Commonly Used Intensity Ranges

Intensity classification	Aerobic exercise: %heart rate reserve	Resistance exercise: %1 repetition max
Low	40–50	<50
Moderate	50–70	50–70
High	70–85	70–85
Very high/vigorous	85–100	85–100

Table 2

List of Abbreviations

Abbreviation	Term	Abbreviation	Term
11β-HSD1	11β-Hydroxysteroid dehydrogenase 2	HDAC4	Histone deacetylase 4
12,13-diHOME	12,13-Dihydroxy-9Z-octadecenoic acid	HF	Heart failure
1RM	One-repetition maximum	HFL	Harvard Fatigue Laboratory
4E-BP1	Eukaryotic translation initiation factor binding protein 1	HIIT	High-intensity interval training
AD	Alzheimer's disease	HR	Heart rate
ADHD	Attention deficity/Hyperactivity disorder	HRR	Heart rate reserve
AE	Aerobic exercise	HSL	Hormone-sensitive lipase
AICAR	5-Aminoimidazole-4-carboxaminde-1-β-D-ribofuranoside	IMAT	Intermuscular adipose tissue
Akt	Protein kinase B	IMTG	Intramuscular triglycerides
ANGPTL4	Angiopoietin-like protein-4	KAT	Kynurenine aminotransferase
ANP	Atrial natriuretic peptide	KYNA	Kynurenic acid
ApoE4	Apolipoprotein E4	LBD	Lewy body dementia
ASD	Autism spectrum disorder	LC	Liquid chromatography
AT	Adipose tissue	LV	Left ventricle
BAIBA	β-Aminoisobutyric acid	MCI	Mild cognitive impairment
BAT	Brown adipose tissue	MEF-2	Myocyte enhancer factor 2
BBB	Blood-brain barrier	MetS	Metabolic Syndrome
BMD	Bone mineral density	MFF	Mitochondrial fission factor
BMU	Basic multicellular unit	MFN	Mitofusin
BNDF	Brain-derived neurotrophic factor	MHC	Myosin heavy chain
BNP	Brain natriuretic peptide	miRNA	microRNA
C/EBPβ	CCAAT enhancer-binding protein β	MMP	Matrix metalloproteases
CD	Cluster of differentiation	MoTrPAC	Molecular Transducers of Physical Activity Consortium
CHD	Coronary heart disease	mtDNA	Mitochondrial DNA
CITED4	Creb binding protein (CBP)/p300-interacting transactivator with ED-rich carboxyl-terminal domain-4	mTOR	Mammalian target of rapamycin; C denotes complex 1 vs. 2
CMRC	Copenhagen muscle research center	MUNE	Motor unit number estimate
CNS	Central nervous system	MuRF-1	Muscle ring finger 1
CRH	Corticotropin-releasing hormone	Myf	Myogenic factor

Abbreviation	Term	Abbreviation	Term
CRF	Cardiorespiratory fitness	NCAM	Neural cell adhesion molecule
CRP	C-reactive protein	NMDA	*N*-methyl-D-aspartate receptor
CTGF	Connective tissue growth factor	NMJ	Neuromuscular junction
CVD	Cardiovascular disease	NO	Nitric oxide
CXTI	Cross-linked telopeptide of type I collagen	NOS	Nitric oxide synthase
DEXA	Dual-energy X-ray absorptiometry	NPR-A	Natriuretic peptide guanylyl cyclase receptor A
DRP1	Dynamin-related protein 1	NRF	Nuclear respiratory factors
EPC	Endothelial progenitor cells	NRG	Neuregulin
EPS	Electrical pulse stimulation	OA	Osteoarthritis
ERR	Estrogen-related receptor	p70s6k	p70s6 kinase
EV	Extracellular vesicle	$p75^{NTR}$	Neurotrophin receptor
FFA	Free fatty acid	PA	Physical activity
FIB-SEM	Focused ion beam scanning electron microscopy	PD	Parkinson's disease
FIS1	Mitochondrial fission 1 protein	PGC-1α	Peroxisome proliferator-activated receptor-γ coactivator 1α
FNDC5	Fibronectin III domain-containing protein 5	PINP	Procollagen type I amino-terminal propeptide
GRα	Glucocorticoid receptor-α	PNS	Peripheral nervous system
GSK3β	Glycogen synthase kinase-3 β	PPAR	Peroxisome proliferator-activated receptor
H_2O_2	Hydrogen peroxide	pQCT	Peripheral quantitative computer tomography
HCAR1	Hydroxycarboxylic acid receptor 1	RA	Rheumatoid arthritis
RANKL	Receptor activator of nuclear factor-κ ligand	TGF-β	Transforming growth factor-β
RE	Resistance exercise	TIF	Transcription initiation factor
ROS	Reactive oxygen species	TNF-α	Tumor necrosis factor α
RUNX2	RUNT-related transcription factor 2	TrkB	Tropomyosin receptor kinase B
RYR1	Ryanodine receptor 1	UBF	Upstream binding factor
SC	Satellite cell	UCP-1	Uncoupling protein 1
Spred-1	Sprouty-related protein 1	Vo_2	Oxygen consumption
T1D/T2D	Type 1 diabetes	Vo_2max	Maximal oxygen consumption
T2D	Type 2 diabetes	Vo_2peak	Peak oxygen consumption
TEM	Transmission electron microscopy	WAT	White adipose tissue
Tfam	Transcription factor A mitochondrial		

Please see full list of other APS-approved common abbreviations: https://journals.physiology.org/pb-assets/PDFs/abbreviations-1510761719900.pdf.