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Supplement Article: Function-Promoting Therapies

Maladaptive Immune Activation in Age-Related Decline of Muscle Function

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Abstract

Age-related changes in immune competency and inflammation play a role in the decline of physical function. In this review of the conference on Function-Promoting Therapies held in March 2022, we discuss the biology of aging and geroscience with an emphasis on decline in physical function and the role of age-related changes in immune competence and inflammation. More recent studies in skeletal muscle and aging highlighting a crosstalk between skeletal muscle, neuromuscular feedback, and immune cell subsets are also discussed. The value of strategies targeting specific pathways that affect skeletal muscle and more systems-wide approaches that provide benefits in muscle homeostasis with aging are underscored. Goals in clinical trial design and the need for incorporating differences in life history when interpreting results from these intervention strategies are important. Where applicable, references are made to papers presented at the conference. We conclude by underscoring the need to incorporate age-related immune competency and inflammation when interpreting results from interventions that target specific pathways predicted to promote skeletal muscle function and tissue homeostasis.

Keywords: Functional decline, Immune system, Inflammaging, Sarcopenia, Skeletal muscle

Although aging is a commonly recognized feature of life and living, there is a growing awareness that this process is heterogeneous, influenced by a life history of exposures and experience, from cell to whole person to ecosystem. How these experiences variably shape biological vulnerabilities and reserves, the mechanistic details, and the rate of their effects on health outcomes have become central questions in studies of biological aging.

Over the last decade, multiple molecular tools have been developed to measure the pace of biological aging and have revealed that people with the same chronological age (years from birth) can differ in biological age based on various molecular clocks, including methods measuring a composite immune profile (1), epigenetic clocks based on DNA methylation (2,3), and circulating plasma proteome signatures (4). A central question in the emerging field of geroscience is defining the linkage between molecular clocks and associations with capacities, reserve and resilience, and consequent health-span outcomes (5).

More recently, there has been interest in whether multiple aging conditions (eg, disease conditions, cognitive and physical decline, immune dysfunction) are outcomes of age-related changes in a limited set of molecular pathways, referred to as the hallmarks or pillars of aging (6). These include pathways related to senescence, stem cell function, macromolecular damage, and inflammation. How these pathways change and interact to drive biological aging at the cellular, organ, and whole-body levels, and whether those effects are asynchronous across organ systems to alter the pace of biological aging is unclear but is likely related to the history of stress exposures and host responses over the life course.

As highlighted in the conference focused on Function-Promoting Therapies by Anne Newman (7), mobility disability is among the most common types of age-related disability that can be in part averted through increased physical activity. How biological aging changes the transduction of benefits of physical activity remains a key challenge in the field. Functional independence and mobility are essential features of healthy aging. Loss in functional independence, while having a complex etiology, is often linked to derangements in at least one of the hallmarks of aging: inflammation and immune homeostasis (8,9). Immune derangements (addressed later) generally include changes in

immune cell subsets, for example, lymphoid and myeloid cell subsets, their function in inter-organ crosstalk, and changes in circulating factors that promote inflammation. Immune derangements are also associated with multiple age-related conditions, and indeed, systems-guided approaches have identified associations between immune age biomarkers and multimorbid burden (1).

Skeletal muscle homeostasis is a dynamic process of muscle remodeling that relies on crosstalk with immune factors during muscle regeneration. This immuno-myogenic crosstalk occurs both in response to injury and in skeletal muscle regeneration as part of skeletal muscle maintenance (10,11). Therefore, identifying specific modifiable pathways that drive immune changes with aging, and the role of those changes in altering immune function, by altering tissue maintenance (eg, skeletal muscle tissue), as well as negative (or positive) effects on tissue vulnerability to stressors or resilience to stressors requires further investigation.

Immune Aging

Biological aging affects immune homeostasis, with age-related changes occurring in both the proportion of immune cell subsets and their functionality. Overall, there tends to be a decline in immunocompetence (eg, presentation, signaling, and pathogen clearance) and an increase in inflammation. The decline in immune function that occurs with aging includes thymic involution and loss in lymphopoiesis by hematopoietic stem cells. Broad changes are evident across innate, adaptive, and circulating immune profiles, with declines in naïve T and B lymphocytes and expansion of memory and cell exhaustion phenotypes (Table 1).

Changes in *innate* response include blunted immune responses, with neutrophil and natural killer (NK) cell loss in pattern recognition receptor activation and increases in NK cell number but decline in functional capacity (16–18). There are also increases in myeloid cells; however, there is a functional decline in macrophage phagocytosis. Changes in *adaptive* response include a reduced T-cell receptor mobilization. There is a skewed memory, termed "memory inflation" of T-cell subsets specific for cytomegalovirus that appears to constrict the T-cell repertoire. Autoreactive memory B cells accumulate; B-cell functional antibody responses decline (eg, antibody-dependent cellular cytotoxicity). The relative contribution of these potential drivers of loss in immune homeostasis is likely influenced by antigenic exposures and immune response to environmental stressors (12,19–22).

Changes in *circulating factors* include age-related increases in circulating interleukin-6 and variably other factors including C-reactive protein, interleukin-1beta, fibrinogen, tumor necrosis factor, and others. The drivers that may contribute to age-associated inflammaging include (a) adiposity, (b) microbial translocation, (c) accumulation of T cells reacting to specific antigens, and (d) the senescence-associated secretory phenotype (SASP), a composite of many inflammatory factors. The relative contribution of drivers likely differs based on life history (23,24) and is exacerbated by age (25–28).

The decline of the immune system with aging serves as a catalyst to age-related diseases or conditions by failing to protect older adults against the development of infections and adequate response to vaccines; malignancies, autoimmune diseases, and other conditions; and providing inappropriate or misguided support in tissue regeneration, maintenance, and wound healing (13).

As discussed in the conference proceedings, Denis Mogilenko and colleagues identified a distinct subset of clonal Granzyme K (GZMK)+ CD8+ T cells as a conserved cellular hallmark of inflammaging in mice and humans (27) that accumulate across multiple organs (spleen, lungs, liver, peritoneal cavity) in young and old mice. Further studies of the GZMK+ CD8 T cells showed that expression of GZMK+ is virtually absent in young CD8 T cells and appears as distinct, separate clusters in the "age-associated population" of CD8 T-cell evidence for clonal expansion with age of the CD8 T-cell population. In human cohort studies, single-cell RNA sequencing of the blood of healthy young and old human males revealed that GZMK+ cells were distinctly accumulating with healthy aging. Dissecting healthy aging cross-sectionally (GZMK+ CD8 T cells and lifetime trajectory of human aging) was another approach taken by investigators *to* explore whether a cross-sectional look at multiple points of the lifetime would yield similar types of trajectories and observed 3 major subpopulations accumulated with age—central memory cells, GZMK+ effector memory cells, and Granzyme B (GZMB)+ effector memory cells (27,29).

Interactions between multiple organs (eg, immune compartment and skeletal muscle, neuroendocrine) are essential to ensure physiologic homeostasis and are the basis for exciting new technologies focused on inter-organ crosstalk (30) and disease progression (31). Whether and how mechanistically the accumulation of distinct lymphoid subsets in distinct organs with aging skews inter-organ crosstalk to dysregulate global homeostasis of physiologic function remains to be determined (Figure 1).

Table 1. Inflammation and Immunocompetence in Aging

Decline in Immunocompetence and Increase in Inflammation
General changes in immune function
Thymic involution
Loss in lymphopoiesis by HSCs
Declines in naïve T and B lymphocytes
Expansion of memory and cell exhaustion phenotypes
Changes in innate response
Blunted immune responses
Neutrophil and NK cell loss in PRR activation
Increase in NK cell number but loss in functional capacity
Relative increase in myeloid cells
Decline in macrophage phagocytosis
Changes in adaptive response
Reduced TCR mobilization
"Memory inflation" of T-cell subsets specific to CMV
Autoreactive memory B cells accumulate
B-cell functional antibody response declines
Changes in circulating factors
Aging-related increases in circulating IL-6
Changes in CRP, IL-1b, fibrinogen, TNF, and other factors
Drivers contributing to age-associated inflammaging
Adiposity
Microbial translocation
Accumulation of T cells reacting to specific antigens (eg, CMV)
Senescence and SASP

Notes: The table summarizes consensus observations from reviews on immune aging (12–15). CMV = cytomegalovirus; CRP = C-reactive protein; HSCs = hematopoietic stem cells; IL = interleukin; NK = natural killer; PRR = pattern recognition receptor; SASP = senescence-associated secretory phenotype; TCR = T-cell receptor; TNF = tumor necrosis factor.

Skeletal Muscle—Immune Interactions

Age-related loss in muscle mass (atrophy), although initially conceived as an imbalance in protein synthesis versus protein degradation, is now understood to be driven by multiple interrelated conditions as discussed by Sue Bodine and others (7). These interrelated conditions

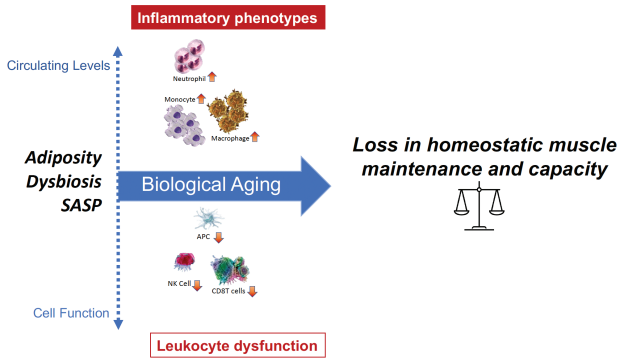

Figure 1. Drivers of loss in homeostatic muscle maintenance of capacity. The accumulation of dysfunctional lymphoid subsets with aging skews inter-organ crosstalk. Shown are upstream effectors (eg, adiposity, microbial translocation, SASP) that potentially influence immuno-muscle crosstalk and homeostatic maintenance. SASP = senescence-associated secretory phenotype.

include disuse atrophy and denervation, and metabolic states such as chronic inflammation associated with multiple disease states both noncommunicable (8) chronic infection (31), hypoxia (32), altered autophagy and proteostasis (33), loss in bioenergetic capacity (34), and loss in optimal signaling through mechano-transduction and inter-organ crosstalk between muscle and nerve cells (35). It is likely that immune mechanisms interact with all of these atrophy pathways and stem cell–mediated remodeling of skeletal muscle to exacerbate muscle maintenance (36) and reflect a concomitant burden of poor muscle quality (37). Although outside the scope of this review, there is an emerging literature on the role for inflammasome activity, in response to pathogen or endogenous stressors, in reducing muscle function and increasing sarcopenic risk, as well as in the design of targeted interventions (38,39).

Immune interactions driving skeletal muscle regeneration and repair are well described (36). Upon muscle injury, muscle tissue with resident muscle stem cells (ie, satellite cells) produces a chemotactic cytokine, monocyte chemoattractant protein 1, that recruits macrophages to the muscle tissue site of injury, whereupon the macrophage polarizes into an M1 type of macrophage that mediates removal of damaged muscle, followed by a transition into an M2 type of macrophage that stimulates muscle stem cell proliferation, differentiation, and fusion, that in effect replace damaged muscle (10,11). Age- and disease-related changes in circulating immune factors, as well as age-related changes in immune cell subsets and their function, might then be predicted to perturb muscle homeostasis. Indeed, with aging, the composition of muscle tissue shifts toward an increased presence of fibrotic cells and an altered and stiffer extracellular matrix that collectively impair muscle remodeling and reduce functional capacity (40–42). Recent studies highlight a role for optimal compression and sensory neuron mechano-transduction as essential for skeletal muscle adaptation during exercise and aging (43,44).

Notably, neural input into muscle maintenance undergoes age-related changes, as noted by Brian Clark (7), limiting anabolic improvements in muscle strength and physical function. Loss in neural activation in part due to structural and functional changes in motor units resulting in the loss of motor units innervating muscle, reduced firing rates, and neuromuscular junction derangements (45). Additionally, sensory neurons through neuroimmune crosstalk and nociceptor signaling may contribute to and modulate inflammatory response affecting tissue homeostasis (46). The rate of loss in neural input is likely affected by multiple factors that can include both intrinsic changes in motor unit number with biological aging as well as extrinsic environmental factors such as hormones, nutrition, inflammation, physical activity, and psychosocial factors (47,48).

Therapeutic Strategies and Immune Considerations

Targeted Strategies Focused on Modulating Skeletal Muscle Intrinsic Mechanisms (Eg, Testosterone, Selective Androgen Receptor Modulators, Myostatin)

Testosterone levels have been inversely associated with age-related circulating markers of inflammation (49), and sex steroids more generally have been linked to immunocompetence (50). Testosterone treatment increases skeletal muscle mass and strength in young and older men and can be augmented by exercise and growth hormone. Testosterone promotes increase by inducing type 1 and 2 muscle fibers and increasing satellite cell number but has more modest effects on physical performance measures such as gait speed, as discussed by Shalender Bhasin (7). The advent of selective androgen receptor modulators (SARMs) may provide anabolic benefits while minimizing the androgenic risk of prostate hyperplasmia and erythrocytosis, as discussed by Adrian Dobs (7). Combined modalities that include testosterone, SARMs, and other nutritional supplements with exercise need to be explored in future studies.

A key repressor of skeletal muscle hypertrophy is the secreted factor myostatin (a.k.a. growth differentiation factor 8, GDF-8), achieved in part through inhibition of the mTOR signaling pathway (51). Overexpression or knockout of myostatin expression can cause significant atrophy (52) or hypertrophy (53), respectively. Daniel Rooks (7) discusses progress in clinical trial manipulating myostatin levels. Interestingly, myostatin inhibition has been linked to a reduction in systemic inflammation (54,55), further linking anabolic processes with immune homeostasis.

Systems Strategies Targeting Skeletal Muscle Extrinsic Modulators

The geroscience hypothesis (ie, that multiple age-related conditions result from a finite set of evolutionarily conserved molecular processes) implies a dynamic balance between gerodrivers and geroprotectors over the life course (5,31). Research presented by Joseph Baur (7) describes nicotinamide adenine dinucleotide (NAD) decline with aging adding to a growing appreciation for the linkage between decline in NAD levels and various age-related disease states (56–59). Age-related declines in NAD in blood and tissues in multiple models have been linked to deficits in mitochondrial function and metabolic capacity (60–63). In humans, data are more limited with evidence for age-associated declines in NAD in skin (62), brain (63), and adipose tissue (64). In mouse skeletal muscle, genetic knockout of NAD biosynthesis results in elevated centrally located nuclei and reduced PGC-1a activity (65), followed by a decline in mitochondrial function and exercise capacity (65). Cellular inflammatory responses require bioenergetic adaptations to mediate effector functions. Knockdown of the energy sensor adenosine monophosphate–activated protein kinase (AMPK) increases pro-inflammatory cytokines; conversely, activation of AMPK increases anti-inflammatory expression (66,67), in part through activation of the NAD-dependent SIRT1 deacetylation of the p65 subunit of NF-kB (68,69). The interplay between the AMPK->NAD->SIRT pathway and NF-kB-driven inflammation with aging requires further study.

Physical activity can act as a geroprotector by promoting resilience and reserve and providing a buffer against fatigue and fatigability (70,71), age-related multimorbidity (72), and inflammation (73). As discussed by Roger Fielding, Marco Pahor, Tom Storer, and others (7), exercise is an effective intervention to avert mobility loss (74). However, the exact molecular pathways that explain the beneficial effects of exercise and physical activity require further study—a major goal of the Molecular Transducers of Physical Activity Consortium, MoTrPAC (75). Physical reserves are geroprotectors that promote resilience and provide a buffer against fatigue and fatigability, thereby increasing capacity for physical activity beyond rest (70,71). Physical activity, in turn, may provide positive feedback, amplifying reserves that in effect decrease the risk for age-related multimorbidity and inflammation (72). Indeed, exercise improves mitochondrial health, which is linked to age-related inflammation (76).

Perspective on Function-Promoting Trials

Inhibiting or activating signaling molecules of the numerous known pathways underlying immunosenescence may offer an opportunity to pharmacologically prevent, reduce, or reverse age-related loss of muscle mass, strength, and function. In papers presented by Shalender Bhasin and Bill Evans (7), framing indications and standardizing outcomes and trial endpoints targeting skeletal muscle mass, function, and performance are needed. As a new flourishing therapeutic target, investigating the aging immune system may help us determine the impact of various lifestyle (nutrition, physical exercise) and pharmacological interventions. New biomarkers and indexes may be identified or better understood in their relation to the immune cells and cytokines that can eventually benefit the assessment and treatment of age-related skeletal muscle dysfunctions.

The arsenal of therapeutic strategies based on geroscience that may be useful in this context continues to grow; however, defining the molecular transducers is currently an active area of research. For example, senolytic approaches appear to promote the clearance of senescent cells through apoptosis by B-cell lymphoma 2 (Bcl-2) inhibitors/Bcl-2 Homology 3 (BH3) mimetics, signaling pathway inhibitors (such as heat shock proteins, p53, histone deacetylase, and kinases), and mitochondria targeting (tamoxifen). For example, quercetin (a plant flavanol with senolytic activity that inhibits the Bcl-2 pro-survival pathway) when combined with dasatinib (a tyrosine kinase inhibitor) can improve the physical function in the context of some disease states (77). Senomorphic approaches do not clear senescent cells but block their proliferation of a senescence phenotype (ie, SASP) (78), which as discussed earlier, is a significant contributor to age-related inflammation.

In summary, the conference on Function-Promoting Therapies raised many important questions regarding the role of immune–muscle interactions and potential therapeutic opportunities, This adds to a growing awareness of the need to include aging effects on immunocompetence and inflammation when evaluating declines in physical function and when designing age-adjusted therapeutic strategies.

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Conflict of Interest

None declared.

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