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Molecular transducers and the cardiometabolic benefits of exercise

Jonathan Z. Long

Department of Pathology, Stanford University School of Medicine and Stanford ChEM-H, Stanford University, Stanford, CA, USA.

Abstract

Physical activity stimulates tissue crosstalk and provides powerful protection against cardiometabolic disease. This past year, several studies have expanded our knowledge of the secreted molecules regulated by physical activity, uncovered new circuits of cell and tissue crosstalk and provided fundamental insights into the mechanisms that underlie the cardiometabolic benefits of exercise.

Physical activity is a powerful physiological stimulus that induces tissue crosstalk and provides benefits for many organ systems. Some of the metabolic benefits of physical activity include reduced adiposity, improved glucose and lipid metabolism, improved muscle function, and reduced blood pressure¹. The mechanisms by which physical activity stimulates cardiometabolic benefits are not completely understood, but probably extend beyond increases in activity-associated energy expenditure alone². There is great interest in identifying specific exercise-inducible molecules that mediate the cardiometabolic benefits of physical activity. These molecules could enable therapeutic ‘capture’ of the benefits of exercise for the treatment of cardiometabolic diseases.

Of particular interest has been a search for exercise-inducible soluble factors³. These secreted molecules, so called ‘exerkines’ or ‘exercise factors’, are thought to function as paracrine or endocrine effectors of the systemic effects of physical activity⁴. Stimulated by the finding that contracting muscle releases the cytokine IL-6 into blood plasma⁵, much of the work over the past two decades has focused on skeletal muscle as a potential source of such exercise-inducible soluble factors. Several other factors — including proteins, metabolites, lipids and microRNAs — have now been shown to be secreted from muscle in an exercise-inducible manner and mediate pathways of exercise adaptation⁶. With the growing sensitivity and availability of high-resolution multi-omic technologies, many additional exercise-inducible soluble factors could yet be discovered⁷. In the past year, several groups have used candidate ‘bottom-up’ approaches as well as large-scale ‘top-down’ profiling to expand our knowledge of the soluble molecules regulated by physical activity. These complementary approaches have opened exciting new

jzlong@stanford.edu .

Competing interests

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directions for understanding tissue crosstalk in exercise and the mechanisms underlying the cardiometabolic benefits of physical activity.

As one example of a bottom-up approach, in late 2020, Reddy et al.⁸ identified a muscle-derived succinate pathway that regulates exercise capacity and systemic glucose homeostasis. While extracellular levels of succinate had long been recognized to increase after exercise in rodents and humans, the precise biochemical mechanisms by which succinate is exported, and its functional role in exercise, were not entirely understood. Reddy et al.⁸ showed that succinate efflux from muscle is highly selective compared with other citric-acid-cycle intermediates and is regulated by intracellular pH. Surprisingly, succinate secretion is mediated by the lactate transporter MCT1.

Reddy et al.⁸ also demonstrated a non-cell-autonomous paracrine circuit of succinate signalling mediated by the succinate receptor SUCNR1 on non-myofibrillar cells (such as endothelial and stromal cells) within the muscle. SUCNR1-knockout mice exhibited systemic insulin resistance and reduced muscle adaptations after exercise training, establishing that the succinate–SUCNR1 pathway mediates part of the physiological metabolic adaptations to exercise training. This study is important because, while MCT1 had previously been shown to transport short-chain fatty acids in vitro, Reddy et al.⁸ provide the first evidence of MCT1 transport beyond lactate in more-complex cellular and physiological contexts. Furthermore, Reddy et al.⁸ unify disparate observations about exercise-regulated succinate into a complete paracrine pathway that regulates muscle function, exercise capacity and systemic glucose homeostasis.

In 2021, additional muscle-derived proteins were shown to be important mediators of paracrine signalling in response to physical activity. For example, Correia et al.⁹ identified neurturin (a glial-cell-line-derived member of the neurotrophic factor family) as a muscle-derived, exercise-inducible signalling protein that regulates muscle remodelling and systemic glucose metabolism. In the central nervous system, neurturin had been studied as a trophic factor that acts through Ret tyrosine kinase receptors and the GFR α 2 coreceptor to promote neuronal survival. However, the role of neurturin in peripheral metabolism remained more obscure.

Correia et al.⁹ demonstrated that *Nrtm* mRNA expression in muscle is induced by voluntary wheel running in mice and is downstream of classic transcriptional proteins involved in exercise adaptations in muscle, including the PGC1 coactivators and ERR γ . Functionally, muscle-specific overexpression of neurturin promotes the development of oxidative, slow-twitch skeletal muscle in mice. Activity-based kinase profiling of muscles from these mice suggested that neurturin signalling in muscle was associated with phosphorylation and activation of the same Ret receptor pathway as had been described in neurons. Finally, the authors demonstrated that systemic delivery of neurturin was not only sufficient to mimic the effects of muscle-derived neurturin on motor coordination but also resulted in improved systemic glucose homeostasis. These gain-of-function data therefore uncover a neurotrophic pathway that controls local muscle remodelling and systemic glucose homeostasis. That a trophic factor for neurons is co-opted by muscle in physical activity suggests a potentially broad shared landscape of growth control pathways in both development and exercise.



Large-scale, multi-omic top-down profiling has also been used in 2021 to profile and correlate exercise-regulated molecular changes with parameters of cardiometabolic health in humans. Robbins et al.¹⁰ used an aptamer-based proteomic method to understand the relationship between approximately 5,000 plasma proteins and VO₂max in a cohort of over 600 individuals from the HERITAGE Family Study. VO₂max is widely considered to be a direct measurement of cardiorespiratory fitness and an independent prognostic marker for both cardiometabolic disease risk and all-cause mortality. This study was much larger than similar past studies, both in terms of the number of proteins analysed and the size of the study cohort. Plasma proteins positively associated with baseline VO₂max included those related to striated muscle structure and function (such as ACTN2, TNNI2 and MYL3) as well as secreted signalling molecules with broader tissue expression (such as SMOC1 and BMP8B). Conversely, a distinct set of plasma proteins — including IL22RA2, FMOD and NT5E — were positively associated with changes in VO₂max in response to exercise. Lastly, many of the plasma proteins associated with either baseline or change in VO₂max were independently found to be associated with incident all-cause mortality in approximately 1,900 individuals from a separate population-based cohort, the Framingham Heart Study. Robbins et al.¹⁰ provide one of the most comprehensive analyses of the human plasma proteome and its association with VO₂max following exercise training, and identify specific plasma proteins not previously known to be increased by exercise training.

These three studies have established new frontiers in our understanding of both the molecules of exercise-induced tissue crosstalk and the signalling pathways that they engage to promote cardiometabolic health. These studies also underscore the exciting and unanswered questions in exercise metabolism in 2022 and beyond. First, it will become increasingly important to organize newly identified exercise-regulated molecules into a holistic molecular and physiological framework and to understand their comparative importance in humans. Second, the potential benefits of pharmacologically targeting these pathways for cardiometabolic health will need to be balanced with the potentially adverse effects associated with activation of these pathways on other cell types and organs. Finally, the proteomic identification of exercise-regulated molecules that are not exclusively expressed in muscle provocatively suggests that many additional cell types and tissues might participate in the production of exercise-inducible soluble factors. The full scope of the cell-specific and tissue-specific exercise response is only beginning to be systematically mapped.

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Key advances

- An exercise-inducible paracrine signalling circuit in muscle, mediated by the citric-acid-cycle intermediate succinate and its receptor SUCNR1, controls exercise capacity and systemic glucose homeostasis in mice⁸.
- Exercise induces the expression of the secreted trophic factor neurturin in muscle, which acts to promote the development of slow-twitch fibres and to improve mouse motor coordination and running performance⁹.
- Aptamer-based plasma proteomics of a large and deeply phenotyped human exercise cohort identifies new circulating biomarkers of baseline and exercise-inducible VO₂max; these markers are found to be associated with all-cause mortality¹⁰.