Cell Metabolism
Perspective

Looking Ahead Perspective: Where Will the Future of Exercise Biology Take Us?

Juleen R. Zierath[1,2,3,*] and Harriet Wallberg-Henriksson[1,2]
[1]Department of Molecular Medicine and Surgery, Section of Integrative Physiology, Karolinska Institute, von Eulers väg 4a, 4 Tr. SE 171 77, Stockholm, Sweden
[2]Department of Physiology and Pharmacology, Section of Integrative Physiology, Karolinska Institute, von Eulers väg 4a, 4 Tr. SE 171 77, Stockholm, Sweden
[3]Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health Sciences, University of Copenhagen, Blegdamsvej 3B, DK 2200 Copenhagen N, Denmark
*Correspondence: juleen.zierath@ki.se
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The health-promoting benefits of exercise have been recognized for centuries, yet the molecular and cellular mechanisms for the acute and chronic adaptive response to a variety of physical activities remain incompletely described. This Perspective will take a forward view to highlight emerging questions and frontiers in the ever-changing landscape of exercise biology. The biology of exercise is complex, highly variable, and involves a myriad of adaptive responses in multiple organ systems. Given the multitude of changes that occur in each organ during exercise, future researchers will need to integrate tissue-specific responses with large-scale omics to resolve the integrated biology of exercise. The ultimate goal will be to understand how these system-wide, tissue-specific exercise-induced changes lead to measurable physiological outcomes at the whole-body level to improve health and well-being.

Mens Sana in Corpore Sano—A Healthy Mind in a Healthy Body

The field of exercise science has roots in ancient Greek history, with early studies by Galen of Pergamon (131–201 AD) showing that exercise and proper nutrition could improve mental and physical health, aerobic fitness, and muscle strength. Just as today, competition was fierce among participants in the ancient Olympic Games, and coaches strived to develop new regimes to bring out the best performance in each athlete. Suffice it to say that the field of exercise science has deep historical roots in unraveling the mysteries of how humans can run faster and longer, lift and propel heavy objects, and outmaneuver the competitor. The modern-day history of exercise metabolism and how different exercise and diet manipulations alter skeletal muscle metabolism is reviewed in this issue of *Cell Metabolism* (Hawley et al., 2015). Great strides have been made, and the health-promoting benefits of exercise are now long appreciated, yet the molecular and cellular mechanisms for the acute and chronic adaptive response to a variety of physical activities remain incompletely described. This Perspective will take a forward view to highlight emerging questions and frontiers in the ever-changing landscape of exercise biology.

Mode of Exercise Leads to Different Adaptions

Basic concepts underlying the diverse metabolic responses and molecular mechanisms that underpin the adaptation of skeletal muscle to acute exercise and exercise training have been reviewed earlier (Egan and Zierath, 2013). Generally, exercise can be divided into either aerobic-based (endurance-based) or anaerobic-based (high-intensity speed and power output) work, representing two extremes of the energy systems (oxidative versus glycolytic) used. The functional adaptations to endurance exercise in some ways oppose the adaptions to resistance or sprinting training, but at the same time, both forms of exercise lead to similar increases in mitochondrial abundance and improvements in glycemic control (Egan and Zierath, 2013). In addition to the energy system used during each exercise bout, the frequency, intensity, and duration of each session will have a distinct impact on the metabolic and molecular responses of any given tissue (Egan and Zierath, 2013; Hawley et al., 2014). Long-term participation in vigorous exercise programs are associated with less disability and lower mortality and therefore influence the aging process and improve the quantity and quality of life (Chakravarty et al., 2008). While it may be obvious that many different forms of exercise exist, this fact is often overlooked when biologists address the molecular mechanisms that govern the response to exercise.

Throughout this Perspective we will refer to "exercise" in rather broad terms, but future studies in exercise biology should continue to be designed to dissect mechanisms controlling both the acute response to a single exercise bout, as well as the adaptive response to regular exercise training. Further research into conventional aerobic exercise regimes, as well as new high-intensity interval training (HIIT) programs, in which the participant performs low-volume HIIT consisting of repeated "all-out" cycling with short recovery (Gibala et al., 2006) or more a practical model of low-volume constant-load HIIT exercise (Little et al., 2010), is warranted, especially in people with metabolic disease. Resistance training to build and preserve skeletal muscle mass is also an essential component of any regular exercise training regime, as it leads to strength gains that are functionally useful for older adults or people with skeletal muscle disuse and wasting diseases (Phillips, 2009). Just as the athlete trains to improve speed, strength, and endurance, all three modalities are important for the general population to maximize overall improvements in health. Most people engage in some form of

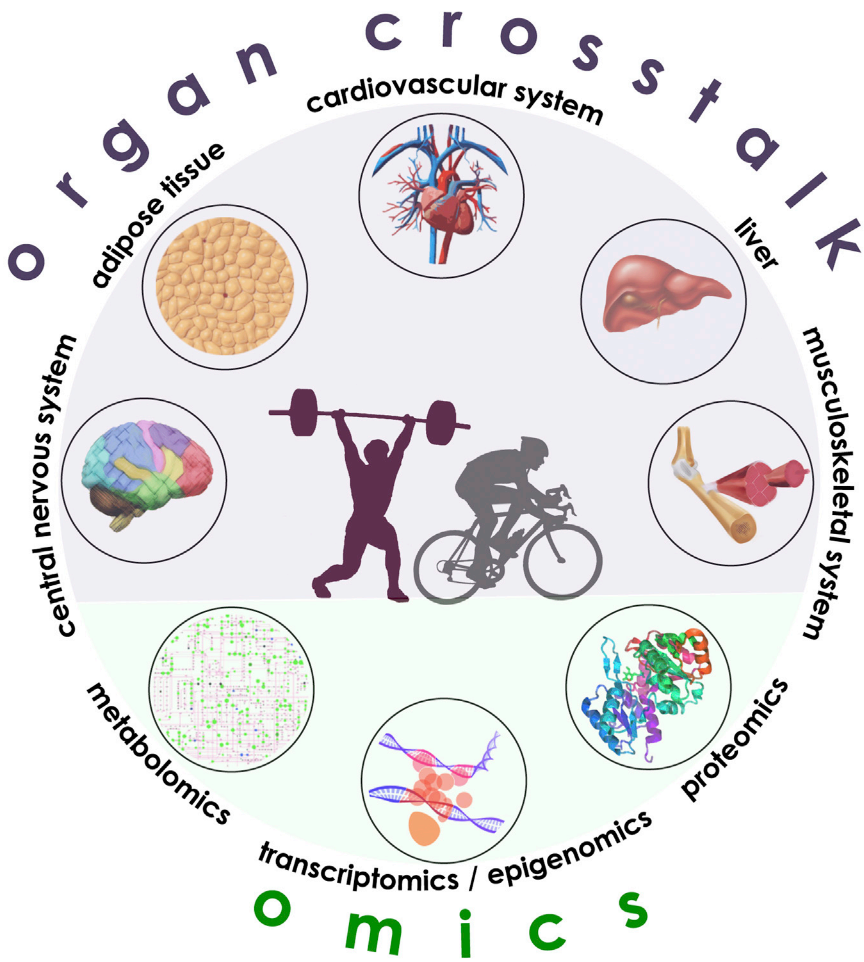

Figure 1. An Omics Approach to Decipher the Molecular Basis of Exercise Adaptation
The integrated biology of the acute and adaptive response to endurance and strength exercise training requires the involvement of multiple organs to achieve physiological improvements in work performance. Future challenges will be the integration of an individual's genetic and epigenetic background, with the tissue-specific gene expression, proteome, and metabolomic profiles to predict improvements in whole-body glucose homeostasis, strength, and aerobic capacity.

concurrent training in which they simultaneously incorporate both resistance and endurance exercise training bouts. While this regime may prevent disease and improve athletic performance, it may attenuate gains in muscle mass, strength, and power compared with undertaking resistance training alone (Fyfe et al., 2014). Nevertheless, detailed molecular studies of different exercise training regimes in healthy and diseased cohorts are lacking. In addition, the development and implementation of exercise-nutrient protocols that take into account the timing and type (carbohydrate/protein/fat) of nutrients an individual ingests either before or after acute exercise are urgently needed to maximize health benefits. For example, brief, intense interval exercise bouts undertaken immediately before breakfast, lunch, and dinner have a greater impact on blood glucose control than a single bout of moderate, continuous exercise undertaken before an evening meal (Francois et al., 2014). While the molecular mechanism for this improvement is unknown, prior intense exercise before each meal may promote a transient exercise-induced translocation of glucose transporters (GLUT4) to the cell surface to increase skeletal muscle glucose uptake and consequently reduce blood sugar levels (Holloszy, 2003). Thus, the timing of exercise appears to have a great impact on glycemic control, implicating the importance of regular exercise training in the prevention of insulin resistance in type 2 diabetes.

A long-term goal is to design exercise-nutrient programs to optimally target skeletal muscle, the cardiovascular system, and the CNS to improve aerobic capacity, strength, and metabolic health (Figure 1). Such approaches should be tempered with the understanding that there is large heterogeneity in the adaptive response of individuals to exercise training (Bouchard et al., 2012; Church-ward-Venne et al., 2015; Osler et al., 2015). Genetic and epigenetic studies may elucidate the underlining biology of the individual response to exercise (Denham et al., 2014; Loos et al., 2015). Understanding and integrating the genomic, transcriptomic, proteomic, and metabolomic landscape will provide a fingerprint of the integrative response of the whole body to exercise. Ultimately, the mode and duration of the exercise intervention and the unique molecular fingerprint of the participant may one day be taken into consideration when designing exercise training programs to optimize health.

Organ Crosstalk

Exercise perturbs whole-body homeostasis, and ultimately every cell and organ in the body needs to cope and adapt to the increased mechanical, metabolic, and thermoregulatory demands associated with the increased work load (Hawley et al., 2014). Although researchers often reduce the study of any given exercise adaptation to an isolated tissue, one must keep in mind that the adaptive response to exercise involves the entire body. An area of fertile research on the horizon is the identification of systemic factors that integrate the individual organ response with the entire body. Since the 1960's when Goldstein (1961) hypothesized that a circulatory skeletal muscle-derived "humoral" factor (Goldstein factor) imparted control over glucose homeostasis during exercise, investigators have searched for systemic factors that communicate information from the working skeletal muscle to the whole body. Subsequent work provided evidence that the increase in skeletal muscle insulin sensitivity in response to muscle contraction requires the presence of a basal serum factor, rather than a factor that is produced during the actual exercise bout (Gao et al., 1994). Thus, both baseline and exercise-responsive factors can communicate information about the