SKELETAL MUSCLE, by virtue of its mass and capacity for substrate oxidation, has a critical role in determining whole body functional capacity and metabolism in health and disease (8). The loss of muscle mass, or sarcopenia, that occurs during ageing and that is the side effect of numerous disease conditions markedly reduces the ability of affected individuals to maintain normal levels of physical activity and metabolic health (6). Likewise, reduced muscle mitochondrial mass and oxidative capacity has been implicated in the etiology of metabolic diseases such as diabetes and obesity. In both cases, the most effective countermeasure is exercise training: endurance, resistance, or a combination of both. The remarkable plasticity of skeletal muscle in response to such exercise interventions has long been recognized (2) and the application of the tools in molecular and cell biology to questions related to exercise adaptation have significantly enhanced our understanding of underlying mechanisms. This Highlighted Topic series (Signals mediating skeletal muscle remodeling by activity) provides a timely review of this current understanding in a few key areas.

The first review, from Yan et al. (9) provides a thorough and insightful review on the phenotypic adaptations to endurance exercise and the potential coordination of mitochondrial biogenesis and angiogenesis, with peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) playing a central role. The work demonstrates what is possible with genetic manipulation and how such interventions have influenced our understanding of the molecular response to exercise. They are clear to point out that although the classic genetic models have provided a great deal of information on the genes involved in the response to exercise, these studies need to be viewed through the potential effects of genetic compensation and feedback mechanisms due to the dramatic change in gene expression (knockout or overexpression) and the prolonged alteration in gene expression. With the advent of tissue specific inducible genetic manipulations, these concerns will decrease and the effects of specific genes in the adaptive response will become clearer. McGee and Hargreaves (4) next provide a brief overview of the role of histone modifications in the adaptive response to endurance exercise. In their review, as well as in their research, they show that endurance exercise results in a transient change in histone acetylation, resulting in changes in chromosomal packaging and gene expression. Implicit in this discussion is the idea that lifelong exercise could potentially alter the epigenome, resulting in outcomes as diverse as improved health and the empirical observation of “muscle memory.”

Philp and colleagues (5) then review the recent paradigm shift in the control of muscle mass and strength, away from growth factors and toward a more direct mechanical role in the response to resistance exercise. Here they make a clear distinction between developmental muscle growth that is dependent on growth factors and load-induced muscle growth that can occur in a growth factor-independent manner. Much like amino acids, it seems that load can increase the activity of the growth controller mTORC1 in the absence of hormones and growth factors.

Marimuthu et al. (3) examine the signaling underlying disuse muscle atrophy. Their assertion that atrophy is not simply the reverse of load-induced muscle hypertrophy is important for how we study the progressive loss of muscle in aging, disease, diabetes, and inactivity. Also, central to our ability to discover treatments that can prevent muscle loss is the realization that not all atrophy is the same. In disease, inflammatory processes are central to the loss of muscle mass, whereas inactivity may result from a decrease in a mechanical signal. Therefore in translating this research, the authors make clear that what works to prevent cachexia-related atrophy may not maintain muscle following bedrest/spaceflight and vice versa.

The effects of dietary interventions on acute exercise performance have been well studied; however, the interactions between diet and training adaptations are less well understood. Hawley and colleagues (1) provide a review of the effect of nutrition on the adaptive responses to training. This work highlights the ability of exercise scientists to combine basic and applied research. These laboratories exemplify the rapid translation of basic research in exercise signaling, where laboratory findings are quickly applied to elite athletes and the value of a change in signaling meets its ultimate test.

Finally, the review by Jamie Timmons (7) describes the relationship between gene networks and responsiveness to training. This review reminds us that in every population there are people who respond better than others to an exercise stimulus. He presents the idea that a small number of differentially expressed genes and microRNAs may predispose muscle to respond to an exercise stimulus. This work highlights that the expression of 29 genes can predict the aerobic response to training. These are not the genes that acutely respond to exercise, but rather a subset of genes that prime the muscle to maximize the effects of a bout of exercise. Determining how these genes alter muscle and metabolism could provide a very powerful tool for optimizing training responses.
create a receptive environment is one of the biggest current challenges for exercise scientists.

This Highlighted Topic series in the *Journal of Applied Physiology* is a snapshot of the exciting work that attempts to understand the signals that are activated in response to exercise. Since exercise is the only known stimulus that can simultaneously prevent or ameliorate heart disease, diabetes, cancer, obesity, osteoporosis, sarcopenia, and cachexia, while improving learning and memory, understanding the local and global signals that result from exercise is a significant challenge. However, with the familiar nature of exercise often the public and other scientists underestimate the complexity of this research. As a result of this lack of respect, funding for this important area is a fraction of what is needed to accelerate our progress and move us toward viable clinical options for those who are unwilling or unable to exercise at a sufficient intensity. One of the biggest impediments for exercise scientists moving forward is earning respect of the scientific community and the public with quality research and effective outreach. Only then will exercise science take its rightful place with other modern molecular fields.

**REFERENCES**