The balancing act between the cellular processes of protein synthesis and breakdown: exercise as a model to understand the molecular mechanisms regulating muscle mass

Blake B. Rasmussen1 and Erik A. Richter2

1Division of Rehabilitation Sciences, Department of Physical Therapy, and Sealy Center on Aging, University of Texas Medical Branch, Galveston, Texas; and 2Copenhagen Muscle Research Centre, and Molecular Physiology Group, Section of Human Physiology, Department of Exercise and Sport Sciences, University of Copenhagen, Copenhagen, Denmark

The more we learn about skeletal muscle biology the more it becomes clear how important muscle tissue is for maintaining overall health. Specifically, muscle is important to provide sufficient strength/force production for locomotion and performing regular activities associated with daily living. In addition, skeletal muscle is important for metabolic health, including lipid and glucose metabolism and insulin sensitivity. The cellular processes of protein synthesis and protein breakdown are both important in maintaining muscle tissue because breakdown is vital for removing damaged proteins and synthesis for making new proteins. Recent work from several laboratories have clearly shown that the balance between protein synthesis and protein breakdown is fundamental in maintaining overall muscle mass and is a major contributor to what is typically referred to as muscle plasticity. Exercise (both aerobic and resistance) and nutritional balance can dramatically alter muscle protein synthesis and breakdown rates and are likely to be useful interventions to counteract muscle wasting and degeneration in a variety of conditions, including sarcopenia, physical inactivity (e.g., bed rest, spaceflight, or simply lack of regular exercise), during rehabilitation following surgery or trauma, and cancer cachexia. New developments in the field of human muscle protein metabolism have begun to unravel the cellular and molecular signaling mechanisms that regulate muscle protein synthesis and breakdown. The use of exercise and nutrition as interventions to alter these cellular processes has been extremely valuable in this effort. Therefore, this Highlighted Topic series (Regulation of Protein Metabolism in Exercise and Recovery) is coming at a time when much new work has been published and when the integration and review of this material will be very useful for those working in the fields of protein metabolism, exercise physiology, and muscle biology. Each of the six reviews is from an established laboratory within the field and focuses primarily on the regulation of the processes of muscle protein synthesis and/or breakdown. In addition to discussing the effect of acute and chronic exercise on protein turnover, other topics include a thorough examination of the most recent knowledge of the cellular mechanisms controlling muscle protein synthesis and breakdown, the effect of nutrition (particularly the essential amino acids), muscle loss with aging (sarcopenia), and potential sex-based differences.

The first review is by Miyazaki and Esser (5) and provides a thorough, up-to-date discussion of the cellular mechanisms regulating muscle protein synthesis. Their review focuses primarily on work performed in animals and in cell culture and highlights several key findings, including the central role of the mammalian target of rapamycin complex 1 (mTORC1) signaling pathway in regulating muscle protein synthesis. The authors point out three primary activators of mTORC1 in muscle: 1) growth factors/insulin, 2) amino acids, and 3) mechanotransduction. Growth factors such as insulin and IGF-I are upstream regulators of mTORC1, and this review focuses on new developments in the process, including the control of tuberous sclerosis complex 1/2 (TSC1/2), Akt, and Ras homolog enriched in brain (Rheb). The mechanism(s) of how essential amino acids activate mTORC1 is still rather uncertain; however, the authors discuss recent work showing that human vacuolar protein sorting 34 (hVps34) and the Ras-related GTPase (Rag) proteins appear to be involved. Mechanical overload increases muscle cell size, and the activation of mTORC1 is necessary for producing this effect. Interestingly, the activation of mTORC1 following mechanical overload appears to be independent of Akt/phosphatidylinositol 3-kinase (PI3K), growth factors, or amino acids. A nice discussion of how loading/stretch activates phospholipase D1, produces phosphatidic acid, and activates mTORC1 is provided. The authors conclude that mechanotransduction is likely acting synergistically with changes in amino acid and growth factor availability.

The next review by Drummond et al. (2) examines the cell signaling pathways associated with the regulation of human muscle protein synthesis. The review focuses on recent work in humans in which resistance exercise and/or essential amino acids both potently stimulate the rate of muscle protein synthesis after exercise. Although the cellular mechanisms/signaling pathways responsible for stimulating protein synthesis in human muscle are not completely understood, it does appear that activation of the mTORC1 signaling pathway is playing an important regulatory role in controlling translation initiation and elongation. Most of their work has been in young men and women; however, recently studies into the aging field have shown key differences in gene expression, cell signaling, and rates of protein synthesis to exist between young and older humans during postexercise recovery. Whether or not these...
differences contribute to sarcopenia or can be reversed with resistance exercise training and/or leucine-enriched essential amino acid supplementation remains to be determined.

The review by Rose and Richter (6) focuses on molecular signaling in muscle during (rather than after) exercise that contributes to reducing global muscle protein synthesis during exercise. Whether protein degradation is increased during exercise is not yet clear. The blunting of protein synthesis during exercise is thought to be mediated at least in part by decreased mRNA translation initiation and elongation involving changes in eukaryotic initiation factor 4E-(eIF4E)-binding protein 1 (4E-BP1) and eukaryotic elongation factor 2 (eEF2) phosphorylation, respectively. It is discussed that signaling to translation and initiation factors is mediated by changes in intracellular Ca$^{2+}$ concentration and energy turnover elicited by neuromuscular excitation-contraction coupling and resulting muscle contractions. In particular, a signaling cascade involving Ca$^{2+}$/calmodulin-eEF2 kinase-eEF2 is implicated as being important for blunting RNA translation during exercise. The physiological significance of the reduced muscle protein synthesis during exercise is uncertain; however, the authors provide plausible mechanisms by which the inhibition of protein synthesis during exercise contributes to the postexercise stimulation of muscle protein anabolism.

In the review by Burd et al. (1), the authors primarily focus on resistance exercise training, protein supplementation, and potential sex-based differences. Their work clearly shows that an acute bout of resistance exercise increases the rate of muscle protein synthesis for at least 24–48 h in untrained human subjects and that resistance exercise training results in a shorter duration of enhanced postexercise protein synthesis. The authors also describe the term “window of anabolic opportunity” in which nutrient sensitivity of human skeletal muscle appears to be enhanced during the first 24 h following resistance exercise; however, it is likely that protein intake during the first few hours postexercise produces a large protein anabolic response because rates of muscle protein synthesis are higher during the early postexercise time course. Another interesting point of discussion is the difference between endurance-type and resistance exercise muscle contractions in which it appears that resistance exercise primarily stimulates the rate of myofibrillar protein synthesis, whereas endurance exercise targets mitochondrial protein synthesis. Finally, the authors point out that only minor differences in protein metabolism following resistance exercise or feeding exist between men and women, although these differences may become important during the aging process.

Aging and sarcopenia is the topic of the review by Koopman and van Loon (3), who begins by pointing out that differences in basal muscle protein synthesis and breakdown rates appear to be similar between young and older humans. Therefore, work in their laboratory has focused on whether or not differences in the exercise and/or feeding response may help to explain why muscle loss occurs during the aging process. They provide evidence that human skeletal muscle maintains its ability to respond to anabolic stimuli such as resistance exercise and protein intake, although the ability to respond to feeding appears to be somewhat less in the elderly. Their work obviously shows the usefulness of combining resistance exercise training with nutritional supplementation to promote muscle protein synthesis and growth; however, it does appear that an excess amount of protein intake is not necessary to produce maximal hypertrophy in older human skeletal muscle.

The final review by Kumar et al. (4) highlights the importance of measuring in vivo rates of muscle protein synthesis and breakdown concurrently with assessment of biochemical regulatory pathways to provide a better picture of what is happening within the muscle cell during and following exercise. An interesting discussion follows in which the authors examine the relationship between the kinetic measurement of muscle protein turnover rates and the phosphorylation of proteins associated with the control of muscle protein synthesis and breakdown following resistance or endurance exercise. In many circumstances, there is not a direct relationship, which suggests that much more work is needed to better understand the control of these cellular processes. Other significant points in this review include the concept of “anabolic resistance” in which the authors original data suggest that the muscle protein anabolic response to feeding and resistance exercise is blunted in older individuals. Finally, those interested in the effects of nutrition and exercise on muscle protein turnover in humans will enjoy the comprehensive tables highlighting all of the research in the field over the last several years.

In summary, the reviews presented in this Highlighted Topic series demonstrate that the balance between the cellular processes of muscle protein synthesis and breakdown are critical in controlling overall muscle mass. Exercise is an excellent model to study muscle protein turnover because it has major effects on the rates of both synthesis and breakdown and should prove helpful in deciphering the cellular mechanisms responsible for regulating these processes. The reviews within this series provide an excellent assessment of the current state of the muscle protein metabolism field. It is our hope that future work will continue to improve our understanding of how these processes are regulated in an effort to develop new interventions, treatments, and rehabilitation strategies to improve muscle mass and function in a variety of muscle-wasting conditions.

REFERENCES


