Skeletal muscle is the largest organ in humans, comprising ~50% of the total body mass. While this tissue functions to sustain normal daily physical activity, skeletal muscle is also involved in regulating metabolic homeostasis. For example, early studies in skeletal muscle revealed that glucose transport was stimulated not just by insulin but also by muscle contraction/exercise in an insulin-independent manner. More recently, it has also become evident that the homeostatic regulation of lipid metabolism also involves skeletal muscle. Indeed, dysregulation of skeletal muscle lipid metabolism is now known to be closely associated with the development of insulin resistance in this tissue. The discoveries of the nuclear encoded transcriptional coactivator peroxisome proliferator-activated receptor (PPAR)γ coactivator-1α (PGC-1α) and the corepressor RIP140 and their roles in mitochondrial biogenesis and the expression of genes involved in the regulation of oxidative phosphorylation and lipid metabolism have begun to provide a molecular underpinning for some of our understandings of skeletal muscle carbohydrate and muscle metabolism.

On June 2–4, 2009, the University of Guelph (Guelph, Ontario, Canada) hosted a conference entitled Muscles as Molecular and Metabolic Machines. This conference was held under the auspices of the triennial meeting of the International Research Group on Biochemistry of Exercise. The conference was sponsored, in part, by the Institute of Musculoskeletal Health and Arthritis of the Canadian Institutes of Health Research. In this issue of this Journal, a series of review articles based on some of the presentations at the conference addresses selected aspects of the molecular regulation of skeletal muscle metabolism.

In the first review (8), Watt and Spriet provide a perspective on the molecular regulation of intramuscular triacylglycerol hydrolysis. For many years, research on the regulation of skeletal muscle metabolism was focused on carbohydrate utilization, while energy provision by lipids was long viewed as being largely dependent on the blood-borne delivery of fatty acids derived from adipocyte triacylglycerol hydrolysis, particularly during exercise when the metabolic rate is increased. In addition, utilization of intramuscular triacylglycerol as an energy source was controversial, owing largely to methodological difficulties (7). These views have changed substantially with the realization that fatty acid entry into muscle is a highly regulated protein-mediated process (1), and with the discovery six years ago of adipose triglyceride lipase (ATGL), a key enzyme regulating triacylglycerol hydrolysis in adipocytes and other tissues, including skeletal muscle. Watt and Spriet review the recent evidence of the central regulatory role of ATGL in triacylglycerol hydrolysis and the regulation of ATGL. They also develop an interesting argument suggesting that ATGL-mediated triacylglycerol hydrolysis provides intracellular ligands (fatty acids) for PPARα/γ action, thereby driving transcription of selected genes involved in fatty acid catabolism to enhance fatty acid oxidation. Taking all the evidence together, Watt and Spriet suggest that ATGL is a mediator of whole body lipid homeostasis.

In the second review (2), Lauritzen and Schertz address issues concerning contraction-mediated GLUT4 trafficking in skeletal muscle, a tissue that can account for the uptake of 80–90% of a glucose load. Hence, this tissue is key for regulating whole body glucose homeostasis. It is well known that insulin (6) and muscle contraction (5) induce independently the translocation of the glucose transporter GLUT4 to stimulate glucose transport. Compared with insulin, muscle contraction-induced GLUT4 translocation is not as well understood. Lauritzen and Schertz review the substantial technical difficulties involved in determining GLUT4 translocation in skeletal muscle. While various muscle cell lines provide some ease for examining GLUT4 trafficking, the authors point out that such models are not necessarily suitable for understanding this process in skeletal muscle in vivo. In particular, skeletal muscle t-tubules have a considerably larger surface area than the plasma membrane and are known to be a critically important site involved in GLUT4-mediated glucose transport. Importantly, the authors remind us that selected cell line models have few (C2C12 myotubes) or no t-tubules (rat L6 myotubes); hence, although providing interventional opportunities for study, they are not ideally representative of mature skeletal muscle. The authors therefore examine in detail the advantages, difficulties, and limitations of different modern approaches for examining GLUT4 trafficking in skeletal muscle in vivo. Taken all together, Lauritzen and Schertz have illustrated the difficulty in resolving the mechanisms regulating GLUT4 trafficking in skeletal muscle and the need for technical developments to elucidate this process.

In the third review, Lira et al. (3) examine the effects of PGC-1α, a major regulator of exercise-induced phenotypic adaptation and substrate utilization. The discovery of PGC-1α, little more than a decade ago (4, 9), has provided a much needed molecular basis for understanding activity-induced phenotypic changes in skeletal muscle as well as the often similar processes that are adversely altered in type 2 diabetes. Lira et al. review the role of PGC-1α in exercise-mediated muscle adaptation and the insulin-sensitizing role of PGC-1α. They summarize much recent information indicating that, in muscle, an orchestrated signaling network (Ca2+-dependent pathways, reactive oxygen species (ROS), nitric oxide (NO), AMP-dependent protein kinase (AMPK), p38 mitogen-activated protein kinase (MAPK)) is involved in the control of contractile protein expression, angiogenesis, mitochondrial biogenesis, and other adaptations. Particularly, the p38α MAPK/PGC-1α regulatory axis is required for exercise-induced mitochondrial biogenesis and angiogenesis but not for fiber type transformation in skeletal muscle. Lira et al. question whether the insulin-sensitizing role of PGC-1α can be examined adequately in PGC-1α knockout or PGC-1α transgenic mice. They propose that massive alterations in PGC-1α expression have deleterious metabolic effects, whereas a modest PGC-1α upregulation based on physiological and metabolic considerations can

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improve skeletal muscle insulin sensitivity. Lira et al. provide substantial evidence that the p38γ MAPK/PGC-1α regulatory axis is critical for exercise-induced metabolic adaptations and that upregulation of PGC-1α within physiological limits exerts insulin-sensitizing effects in skeletal muscle.

In a future issue of this Journal two additional reviews are forthcoming. Fritah, Christian, and Parker will provide an update on the metabolic effects and the regulation of RIP140, a corepressor that has diverse functions, including a PGC-1α antagonistic effect. Laurie Goodyear will provide a review on the metabolic effects of the AS160 paralog TBC1D1.

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