ContRac1ion-Mediated Glucose Uptake: A Central Role for Rac1

Leonidas S. Lundell and Anna Krook

Skeletal muscle glucose uptake can be regulated in response to different stimuli, with insulin and contraction being central. While the processes underlying insulin-induced glucose uptake have been extensively characterized, the processes underlying contraction-induced glucose uptake remain elusive. In this issue of *Diabetes*, Sylow et al. (1) provide another piece to this puzzle. They report that Rac1 is essential for contraction-induced GLUT4 translocation.

Contraction induces glucose uptake in skeletal muscle both independently (2) and synergistically (3) with insulin. Several different mechanisms have been proposed, which appear to be activated in parallel following muscle contraction (Fig. 1). Key pathways include activation of the AMP-sensitive protein kinase (AMPK) through changes in the AMP:ATP ratio in response to increasing energy demands (4). Increased Ca^{2+}/calmodulin-dependent protein kinase I (CaMKI) influx during muscle depolarization results in activation of calcium signaling cascades via CaMKI (5) and protein kinase C (PKC) (6). Downstream candidates include the Rab-GTPase-activating protein TBC1D1 (7), and evidence supports a role of increased free radical content in contraction-mediated glucose uptake as a consequence of increased respiratory activity (8).

Rac1 is a small GTPase and member of the Rho family, which has previously been implicated in a wide range of processes including membrane dynamics, cell adhesion, and proliferation (9). Previous work has identified Rac1 as a downstream mediator of insulin-stimulated glucose transport in cultured skeletal muscle, where in vitro siRNA silencing leads to abrogated actin remodeling and prevents insulin-induced GLUT4 translocation (10). In the current study, Sylow et al. (1) provide evidence for a role for Rac1 in mediating contraction-induced GLUT4 membrane translocation, demonstrating that in vivo, Rac1 is activated in response to exercise in both human and mouse skeletal muscle. Consistent with a role for Rac-1 in contraction-induced glucose uptake, ex vivo contraction of mouse muscle lacking Rac1 displayed impaired contraction-induced glucose transport. Furthermore, pharmacological inhibition of Rac1 in vitro reduced insulin-stimulated glucose uptake. Interestingly, the authors present two lines of evidence that contraction-mediated Rac1 activation is AMPK-independent. Mice with a targeted deletion of AMPK kinase activity displayed a normal Rac1 activation. Additionally AICAR, a pharmacological AMPK activator, did not lead to increased Rac1 activation (1).

While providing new molecular insight into regulation of GLUT4 traffic, a number of key questions remain to be resolved. Since the authors exclude a role for AMPK as an upstream regulator of Rac1, what then are the remaining contenders for this role? Possible candidates include TBC1D1 with its calcium-binding motifs, as well as several PKC isoforms that are activated by an AMPK-independent mechanism (Fig. 1). Furthermore, Sylow et al. show that exercise leads to Rac1 phosphorylation and GTP loading. The molecular pathways regulating these events are imprecisely established and could take very different forms, for example kinase-mediated phosphorylation (11), GDP to GTP exchange by stimulation of guanine nucleotide exchange factor activation (12), decreased GTP hydrolysis by inhibition of GTPase activating proteins (13), or inhibition of GDP dissociation by guanosine nucleotide dissociation inhibitors (9). In addition, the effectors lying downstream of Rac1 involved in actin remodeling remain to be characterized, and future studies to address this mechanism are warranted (10). The direct effect of exercise in Rac1-depleted mice will also be interesting in further studies, both with respect to glucose uptake and in relationship to exercise performance and muscle ergogenics.

While evidence from rodent models of type 2 diabetes indicates that insulin-stimulated but not exercise-stimulated glucose transport is impaired in skeletal muscle from diabetic rodents (14), the data from type 2 diabetic patients is less clear. Indeed, AICAR-stimulated and hypoxia-stimulated glucose uptake is reduced in skeletal muscle from type 2 diabetic patients (4,15). Furthermore, upon a careful examination of the limited number of subjects that have been studied, contraction-induced GLUT4 translocation may also be reduced in skeletal muscle from type 2 diabetic patients (16). This has led to the proposal that insulin resistance in human skeletal muscle involves defective GLUT4 traffic and targeting (17). A broader challenge in dissecting the disease mechanism for skeletal muscle insulin resistance in type 2 diabetes is to understand whether Rac1 activation is altered in the context of human pathophysiology, and to determine whether Rac1 represents a convergence point linking insulin-induced and contraction-induced signals to the control of GLUT4 translocation. Answers to these questions will potentially increase the molecular understanding of contraction-induced glucose uptake and provide novel entry points for possible therapeutic interventions in type 2 diabetes.

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From the Department of Physiology and Pharmacology, Section for Integrative Physiology, Karolinska Institutet, Stockholm, Sweden.
Corresponding author: Anna Krook, anna.krook@ki.se.
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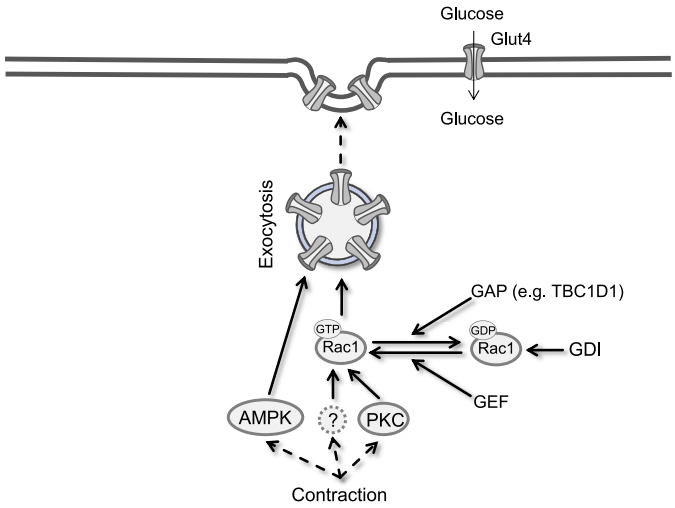

FIG. 1. Possible upstream and direct regulators of Rac1 activity. Contraction stimulates GLUT4 exocytosis by activating a range of different molecules, including AMPK, PKC, and TBCD1. Evidence presented by Sylow et al. (1) indicates that AMPK is not involved in Rac1 activation. Other possible pathways include TBC1D1 and PKC. Rac1 cycling between active, GTP bound state and inactive, GDP bound state is another possible node by which Rac1 regulates GLUT4 exocytosis.

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