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Topical Review

Signals that Regulate GLUT4 Translocation

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Introduction

Removal of excess glucose from the circulation involves the stimulation of glucose transport into muscle and adipose tissue. In these tissues, the increase in glucose uptake depends on the redistribution of intracellular vesicles containing the insulin-responsive glucose transporter GLUT4 to the cell surface membrane by a process called translocation. These plasma membrane-localized transporters subsequently facilitate the influx of plasma glucose into the cell. Recent insights into this regulated process show that, in addition to insulin, a heterogeneous set of factors is capable of mobilizing GLUT4 via alternate molecular pathways. Disconnect in the signal linking the insulin receptor to the GLUT4 protein has been described and is speculated to be a molecular and physiological basis of the insulin-resistant state in obesity and type 2 diabetes where tissues have an impaired response to physiological levels of insulin. Basic research dissecting the signaling pathways, particularly the pathways of insulin action, regulating peripheral tissue glucose uptake are essential for our understanding of this disease process and for the development of improved therapeutic strategies. In this review, some of the most salient features of the known insulin- and non-insulin-signaling mechanisms regulating GLUT4 translocation will be discussed.

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Signal Transduction from the Insulin Receptor

Insulin binding to the insulin receptor causes tyrosine autophosphorylation of the β-subunit and activation of its intrinsic tyrosine kinase (Fig. 1) (Cheatham & Kahn, 1995). The insulin receptor tyrosine kinase phosphorylates several intracellular proteins, including the insulin receptor substrate (IRS) proteins that provide docking sites for p85, the regulatory subunit of type I phosphatidylinositol 3-kinase (PI3K). This results in the activation of the catalytic p110 subunit of PI3K. Multiple studies using various pharmacological inhibitors, dominant-negative mutants, and constitutively active constructs are consistent with a necessary role of PI3K activity in insulin-stimulated GLUT4 translocation (Cheatham et al., 1994; Clarke et al., 1994; Kotani et al., 1995; Katagiri et al., 1996; Martin et al., 1996; Tanti et al., 1996; Frevert & Kahn, 1997). The lipid product generated by PI3K involved in linking PI3K activity to distal GLUT4 effector proteins apparently is phosphatidylinositol 3,4,5-trisphosphate (PIP_3) (Vollenweider et al., 1999). Increased levels of PIP_3 lead to activation of a protein kinase cascade involving stimulation of a 3′-phosphoinositide-dependent kinase-1 (PDK-1). Currently, substantial attention has focused on two potential PI3K/PDK-1 downstream targets, the protein kinase B/Akt (PKB) family of proteins and the atypical protein kinase C family members PKCλ, and PKCζ. The PI3K/PDK-1 signaling pathway targets the Akt and PKCλ/ζ enzymes and gives rise to their phosphorylation on Thr410 and Thr308, respectively (Alessi et al., 1997; Chou et al., 1998). Full activation of Akt further requires phosphorylation on Ser473 by the putative PDK-2 (Vanhaesebroeck & Alessi, 2000), whereas PKCλ/ζ activity appears to be dependent on autophosphorylation by a yet unknown mechanism (Standaert et al., 1999). Although studies suggest that both Akt and PKCλ/ζ act as essential downstream targets of PI3K activation mediating

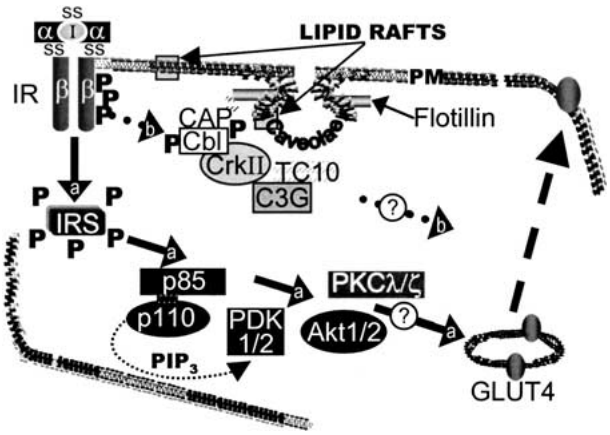

Fig. 1. Insulin signals regulating GLUT4 translocation. Solid arrows labeled *a* depict the PI3K pathway and dotted arrows labeled *b* depict the Cbl/CAP/TC10 cascade. *See* text for abbreviations and details.

insulin-stimulated GLUT4 translocation, understanding the specific roles and interrelationships between these serine/threonine kinases requires further investigation (Watson & Pessin, 2001).

Despite the essential nature of PI3K, substantial information suggests that PI3K-independent mechanisms stimulated by insulin also regulate GLUT4 translocation (Czech & Corvera, 1999; Elmendorf & Pessin, 1999). Recent studies have revealed that the PI3K signal gets a key assist from a cast of novel signaling intermediates corralled in certain regions of the plasma membrane of distinct lipid and protein compositions, referred to as lipid raft domains (Simons & Toomre, 2000; Marx, 2001; Bickel, 2002). Transduction of a PI3K-independent signal to these proteins apparently involves the tyrosine phosphorylation of a protein product of the c-Cbl proto-oncogene (Ribon & Saltiel, 1997). Two accessory proteins in adipocytes, termed APS and Cbl-associated adaptor protein (CAP), play a role in the tyrosine phosphorylation of Cbl and its subsequent signaling events (Ribon et al., 1998; Moodie, Alleman-Sposeto & Gustafson, 1999). APS appears to interact with both the insulin receptor and Cbl, bringing Cbl into the correct conformation or orientation to make it an efficient substrate for the insulin receptor tyrosine kinase (Ahmed, Smith & Pillay, 2000). Upon phosphorylation, the Cbl/CAP complex translocates to lipid raft microdomains.

Increasing evidence suggests that these plasma membrane regions play an important role in signal transduction by functioning as platforms for signaling receptors, including the insulin receptor (Simons & Toomre, 2000; Marx, 2001; Bickel, 2002). Caveolae represent a subset of lipid rafts that are formed from lipid rafts by polymerization of caveolins, hairpin-like palmitoylated integral membrane proteins that tightly bind cholesterol. Flotillin, a lipid raft protein, associates with CAP and serves to anchor the Cbl/Cap complex in this membrane compartment. Whether flotillin is resident in caveolae, in noncaveolar lipid rafts, or in both has not been firmly established (Bickel, 2002). Nevertheless, expression of dominant-interfering CAP mutants that cannot bind to Cbl inhibit Cbl translocation and insulin-stimulated glucose transport (Baumann et al., 2000). Translocation of phosphorylated Cbl recruits the adaptor protein Crkll to caveolae via SH2 domain interaction (Chiang et al., 2001). Crkll also forms a constitutive complex with the guanyl-exchange protein C3G. Once in the caveolae, C3G comes into close proximity with the G protein TC10, and catalyzes the exchange of GTP for GDP, resulting in the activation of this protein (Chiang et al., 2001). The localization of TC10 in caveolae is required for its activation by insulin (Watson et al., 2001). Expression of dominant interfering constructs of TC10 demonstrates that activation of this G protein is essential for insulin-stimulated glucose transport and GLUT4 translocation (Chiang et al., 2001). Once activated, TC10 seems to provide a second signal to the GLUT4 protein that functions in parallel with the activation of the PI3K pathway.

Clues to the identity of intermediates functioning distal to TC10 have come from studies aimed at examining the role of the microtubule- and actin-based cytoskeleton in the trafficking of GLUT4-containing vesicles. These studies have demonstrated that insulin elicits actin filament (F-actin) formation (Tsakiridis, Vranic & Klip, 1994; Marcusohn et al., 1995; Wang et al., 1998b; Asahi et al., 1999; Nakashima et al., 1999; Guilherme et al., 2000; Omata et al., 2000; Bose et al., 2001; Emoto, Langille & Czech, 2001; Patki et al., 2001) and reagents leading to actin depolymerization inhibit insulin-induced GLUT4 translocation and glucose uptake (Tsakiridis et al., 1994; Wang et al., 1998b; Asahi et al., 1999; Guilherme et al., 2000; Omata et al., 2000; Emoto et al., 2001; Patki et al., 2001). Thus, insulin signaling to polymerize cortical F-actin apparently represents a required pathway for optimal movement or fusion of GLUT4-containing membranes to the cell surface membrane. Recently Kanzaki et al. (2001) demonstrated that insulin could induce GLUT4 vesicle actin comet tails that are necessary for the efficient translocation. Interestingly, the actin-based GLUT4 vesicle motility was inhibited by both latrunculin B and a dominant-interfering actin-regulatory neural Wiskott-Aldrich syndrome protein (N-WASP) mutant. A more recent study found that expression of dominant interfering constructs of TC10 inhibited both cortical localization of N-WASP and F-actin formation in response to insulin (Jiang et al., 2002). These findings are consistent with the concept that N-WASP functions

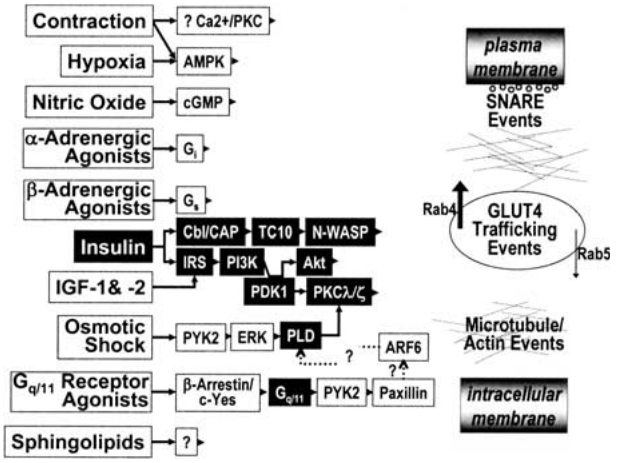

Fig. 2. Multiple signaling mechanisms implicated in augmenting plasma membrane GLUT4. Shown in black are recognized intermediates of insulin action. *See* text for other abbreviations and details.

downstream of TC10 in a PI3K-independent insulin signaling pathway to mobilize cortical F-actin, which in turn promotes GLUT4 responsiveness to insulin.

Insulin-independent Regulation of GLUT4 Translocation

It is clear that GLUT4 translocation can be induced by several regulators other than insulin. As recently reviewed by Czech and Corvera (1999), additional activators of GLUT4 translocation include the insulin-like growth factors 1 and 2 (IGF-1 and -2), contraction, hypoxia, nitric oxide, phorbol ester, β- and α-adrenergic agonists, and $G_{q/11}$-coupled receptor agonists (Fig. 2). With the exception of IGF-1 and IGF-2, a substantial amount of data suggests that many of these non-insulin stimuli regulate GLUT4 translocation by engaging PI3K-independent signaling mechanisms. For example, the stimulations of glucose transport in skeletal muscle caused by insulin and contraction are additive, but only the former is blocked by inhibitors of PI3K (Cortright & Dohm, 1997). In concert with this result, a number of studies have clearly demonstrated that proximal insulin-signaling steps are not components of the signaling mechanism by which exercise stimulates glucose uptake, since contractile activity does not stimulate the insulin receptor, IRS1 or PI3K function (Treadway et al., 1989; Goodyear et al., 1995; Wojtaszewski et al., 1996). Several signaling intermediaries potentially involved in contraction-induced GLUT4 translocation include calcium, PKC, glycogen, adenosine, nitric oxide, and 5′-AMP-activated kinase (AMPK) (Goodyear & Kahn, 1998; Richter, Derave & Wojtaszewski, 2001). As with the transduction of the insulin signal, the precise signaling mechanisms elicited by contraction may require more than one pathway (Fig. 2). For example, data indicate that AMPK transmits a portion of the signal by which muscle contraction increases glucose uptake, while other independent pathways also contribute to the response (Mu et al., 2001). Interestingly, whereas blockade of the AMPK signal only partially reduced contraction-stimulated glucose uptake, it completely blocked the insulin mimetic effects of hypoxia (Mu et al., 2001).

Another group of agonists that have been reported to activate GLUT4 translocation and glucose transport by a PI3K-independent mechanism include hyperosmolarity, guanosine 5′-[γ-thio]triphosphate (GTPγS) and endothelin-1 (ET-1) (Baldini et al., 1991; Robinson et al., 1992; Lee, Hansen & Holloszy, 1995; Lund et al., 1995; Shibata et al., 1995; Yeh et al., 1995; Chen et al., 1997, 1999; Elmendorf, Chen & Pessin, 1998; Haruta et al., 1998; Wu-Wong et al., 1999; Bose et al., 2001). It has been demonstrated that the PI3K-independent mechanism initiated by these stimuli is also independent of Akt and requires tyrosine kinase activity (Chen et al., 1997; Elmendorf et al., 1998, Haruta et al., 1998; Wu-Wong et al., 1999; Bose et al., 2001). Initial work examining the tyrosine kinase signaling mechanism by which hyperosmolarity and GTPγS stimulated GLUT4 translocation suggested the involvement of the calcium-sensitive protein tyrosine kinase PYK2 (Chen et al., 1997; Elmendorf et al., 1998). In accordance, Sajan et al. (2002) recently found that the extracellular signal-regulated kinase (ERK) pathway components, growth-factor-receptor-bound-2 protein, son of sevenless (SOS), RAS, RAF and mitogen-activated protein (MAP) kinase/ERK kinase, MEK(-1), operating downstream of PYK2, were required for hyperosmolarity-stimulated GLUT4 translocation in rat adipocytes, L6 myotubes and 3T3-L1 adipocytes. Like PYK2/ERK pathway components, PKCλ/ζ enzymes were also required for hyperosmolarity-stimulated GLUT4 translocation. Interestingly, hyperosmolarity stimulated increases in phospholipase D (PLD) activity and generation of phosphatidic acid (PA), which directly activated PKCλ/ζ enzymes. As with PKCλ/ζ and glucose transport, hyperosmolarity-stimulated PLD activity was dependent on the ERK pathway. Moreover, PLD-generated PA was required for hyperosmolarity-induced activation of PKCλ/ζ enzymes and GLUT4 translocation. These findings mimic previously reported findings, suggesting that PLD action is required for insulin-stimulated GLUT4 translocation (Emoto et al., 2000), and further suggested that this PLD requirement for glucose transport is not related to PKCλ/ζ activation during the action of insulin, which, for the most part, activates PKCλ/ζ through non-PLD signaling pathways, as already discussed.

Several lines of evidence suggest that activation of trimeric G protein-linked receptors leads to significant stimulatory effects on glucose transport (Obermaier-Kusser et al., 1988; Baldini et al., 1991; Robinson et al., 1992; Kanai et al., 1993; Elmendorf et al., 1998). Consistent with G protein involvement, adrenergic stimulation can induce GLUT4 translocation and glucose uptake in cardiac and skeletal muscle as well as white and brown adipocytes (Smith, Kuroda & Simpson, 1984; Rattigan, Appleby & Clark, 1991; Omatsu-Kanbe & Kitasato, 1992; Fischer et al., 1996; Omatsu-Kanbe, Zarnowski & Cushman, 1996; Shimizu et al., 1996; Tanishita et al., 1997; Han & Bonen, 1998; Kishi et al., 1998). Furthermore, platelet-activating factor, norepinephrine and bradykinin were shown to stimulate GLUT4 translocation in Chinese hamster ovary cells, L6 myotubes and 3T3-L1 adipocytes expressing their respective G_q-coupled receptors (Kishi et al., 1996, 1998). Recently, expression of constitutively active G_q (G_q/Q209L) was shown to stimulate GLUT4 translocation in 3T3-L1 adipocytes by a PI3K-independent mechanism (Kanzaki et al., 2000). Reminiscent of the tyrosine kinase dependency of the hyperosmolarity-, GTPγS- and ET-1-stimulated response, a tyrosine kinase is engaged in the pathway by which G_q/Q209L stimulates GLUT4 translocation (Kanzaki et al., 2000). Similar to the signal by which hyperosmolarity activates GLUT4 translocation, PYK2 has been shown to be a key intermediate in the ET-1/$G_{q/11}$ signal to the GLUT4 protein (Park et al., 2001). Recently, it has been shown that the ET-1 signal requires β-arrestin-mediated recruitment of the Src family kinase Yes to the $G_{q/11}$-coupled receptor to mediate ET-1 signaling to $G_{q/11}$ (Imamura et al., 2001). Distal to PYK2, the adhesion scaffold protein paxillin, a physiological target of PYK2, appears to be directed to F-actin-rich adhesion sites from the adipocyte cytoplasm in response to ET-1. A previous component shown to be required specifically for GLUT4 regulation by ET-1 but not insulin action is ARF6, a GTPase involved in actin rearrangements and membrane recycling (Bose et al., 2001; Lawrence & Birnbaum, 2001). Interestingly, recent reports identified a PYK2- and paxillin-binding protein family that contains an ARF-GAP (GTPase-activating protein) domain, linking PYK2 and paxillin functions to potential regulation of ARF6 (Donaldson, 2000). ARF6 has recently been shown to play a role in the acute synthesis of phosphatidylinositol 4,5-bisphosphate (PIP_2) in membrane ruffles through its ability to activate inositol 4-phosphate 5-kinase (Honda et al., 1999). ARF6 also activates PLD, generating phosphatidic acid, another activator of inositol 4-phosphate 5-kinase (Massenburg et al., 1994). PIP_2 in turn regulates multiple proteins involved in actin dynamics (Shibasaki et al., 1997). Thus, ARF6 may be downstream of PYK2 and paxillin in the ET-1 signaling pathway, perhaps causing cortical actin filament formation, thought to be required for optimal GLUT4 exocytosis (Shibasaki et al., 1997; Bose et al., 2001; Emoto et al., 2001).

As highlighted earlier, activation of GLUT4 translocation by insulin requires a PI3K-independent lipid raft-localized signaling event. Intriguingly, biochemical and morphological techniques have revealed that lipid rafts contain several proteins involved in regulating GLUT4 translocation and glucose transport. Work by some indicates that these proteins include the receptors for insulin and ET-1, as well as intermediary proteins such as $G_{q/11}$ and TC10 (Chun et al., 1994; Gustavsson et al., 1999; Kifor et al., 1998; Watson et al., 2001). In addition to the potential compartmentalizing aspect of the lipid raft plasma membrane microdomains, these domains are enriched in cholesterol and sphingomyelin and hydrolysis of sphingomyelin has itself been demonstrated to activate GLUT4 translocation and glucose transport (Brindley et al., 1996, 1999; Turinsky et al., 1996; David et al., 1998; Wang, O'Brien & Brindley, 1998a). The mechanism by which sphingomyelin turnover augments the level of GLUT4 in the plasma membrane is unclear, but reminiscent the effects of many other insulin mimetic stimuli, the signal in skeletal muscle and primary fat cells was found to be independent of the IR, IRS1 and PI3K (Turinsky et al., 1996; David et al., 1998).

Placing GLUT4 at the Cell Surface

Whatever insulin-dependent and -independent signaling mechanisms exist, these must act on the intracellular GLUT4-containing compartments. It is well documented that in the basal state, GLUT4 cycles slowly between the plasma membrane and one or more intracellular compartments, with the vast majority of the transporter residing in vesicular compartments within the cell interior (Kandror & Pilch, 1996b; Rea & James, 1997; Pessin et al., 1999). Insulin stimulation results in an overall increased accumulation of GLUT4 protein at the cell surface due to a 10- to 20-fold increase in the rate of exocytosis concomitant with a smaller decrease (2- to 3-fold) in the rate of GLUT4 endocytosis (Holman & Cushman, 1994; Czech, 1995; Kandror & Pilch, 1996a).

Recent progress in vesicular-membrane trafficking has revealed that small GTP-binding proteins of the Rab family are necessary regulators. In the case of the endosomal recycling, sorting and exocytic movement of GLUT4, Rab4 (Cormont et al., 1996a, 2001; Mora et al., 1997; Shibata, Omata & Kojima, 1997; Shibata et al., 1996; Vollenweider et al., 1997), Rab5 (Cormont et al., 1996b; Huang, Imamura & Olefsky, 2001), and Rab11 (Kessler et al., 2000) have all been implicated. Rab4 was found to colocalize with the

GLUT4-enriched microsomal fraction and insulin stimulation results in a redistribution of Rab4 into the cytosolic fraction (Cormont et al., 1993). Furthermore, introduction of Rab4 C-terminal mutant, or high-level expression of wild-type Rab4 all result in an inhibition of insulin-stimulated GLUT4 translocation (Cormont et al., 1996a; Shibata et al., 1996; Mora et al., 1997). A more recent study found that a prenylation-deficient, and thus cytoplasmic, form of Rab4 inhibited GLUT4 translocation activated by both insulin and hyperosmolarity (Cormont et al., 2001). Although Rab4 appears to be an essential component in a step directly involved in the insulin- and osmotic shock-stimulated trafficking of the GLUT4-containing vesicle, movement of the exercise-responsive vesicular pool of GLUT4 appears to be regulated by a different mechanism (Sherman et al., 1996; Cormont et al., 2001). Work by Knight et al. (2000) further shows that Rab4 or a Rab4-associated protein acts at one or more steps in propagating the insulin signal, in addition to any role it may play in the regulation of GLUT4 vesicle translocation.

In contrast to Rab4, the subcellular distribution of Rab5 is compatible with a role in the endocytosis of GLUT4 (Cormont et al., 1996b). In line with Rab5 being associated with the sorting endosome and participating in endosomal membrane fusion reactions in the early endocytic pathway, Rab5 antibody injection increased the basal cell-surface GLUT4 level, did not change the insulin-stimulated surface GLUT4 level, and inhibited GLUT4 internalization after insulin withdrawal (Huang et al., 2001). Interestingly, active Rab5 (Rab5-GTP) was readily detected in unstimulated 3T3-L1 cells. After insulin stimulation for 10 and 20 min, the Rab5-GTP level was reduced by 65–75% of the basal level. At 10 min after insulin was removed, Rab5-GTP had recovered to basal levels. These results indicate that Rab5 is activated in the basal state and is inactivated during the process of insulin-stimulated GLUT4 translocation, becoming reactivated when insulin's effects dissipate, thus allowing GLUT4 endocytosis to proceed normally. Intriguingly, the insulin-stimulated inactivation of Rab5 appears to require PI3K activity; whereas the action of insulin on the dynamin- and clathrin-dependent process of plasma membrane GLUT4 retrieval is independent of PI3K (Pessin et al., 1999). Furthermore, an insulin-induced change in Rab5 subcellular localization independent of PI3K has been reported (Cormont et al., 1996b), suggesting that insulin-induced Rab5 movement and Rab5-GTP loading are differentially regulated. Whatever precise PI3K-dependent and -independent Rab5 mechanisms are in place, recent work by Huang et al. (2001) has physically associated Rab5 with the motor protein dynein. These investigators found that the insulin-induced deactivation of Rab5 causes the dissociation of dynein from microtubules. This suggests that when Rab5 is active and dynein binds to microtubules, internalization of GLUT4 is facilitated. After insulin stimulation, the decreased activity of Rab5 and dissociation of dynein from microtubules would enhance accumulation of the transporter at the cell surface and may foster the release of GLUT4 vesicles from microtubules to allow exocytosis to the cell surface.

GLUT4 membrane fusion events bring finality to the translocation process and entail the pairing of protein complexes in the vesicle compartment (v-SNAREs, for vesicle SNAP receptors) with cognate receptor complexes at the target membrane (t-SNAREs, for target membrane SNAP receptors). Several v- and t-SNARE proteins have been identified that specifically participate in the docking and fusion of GLUT4 vesicles with the plasma membrane (Rea & James, 1997; Elmendorf & Pessin, 1999; Pessin et al., 1999; Foster et al., 2000). The syntaxin 4-SNAP-23 complex appears to function as the required plasma membrane t-SNARE, whereas VAMP2 is the predominant v-SNARE for insulin-stimulated GLUT4 vesicle docking and fusion (Cheatham et al., 1996; Volchuk et al., 1996; Araki et al., 1997; Olson, Knight & Pessin, 1997; Martin et al., 1998). Several accessory proteins (Munc18c, Synip, VAP33 and pantophysin) have been shown to play important functional rotes in regulation of insulin-stimulated t- and v-SNARE interactions (Tamori et al., 1998; Thurmond et al., 1998, 2000; Min et al., 1999; Foster et al., 2000; Thurmond & Pessin, 2000). It seems likely that several of the SNARE proteins involved in insulin-stimulated GLUT4 translocation also facilitate the translocation of GLUT4 induced by the various non-insulin stimuli. Expression of a dominant interfering mutant of syntaxin 4, which previously was demonstrated to block insulin-stimulated GLUT4 translocation, also prevented the insulin mimetic actions of hyperosmolarity (Chen et al., 1997). Interestingly, GTPγS-stimulated GLUT4 translocation appears to utilize VAMP3 as a v-SNARE rather than the VAMP2 isoform used predominantly by insulin, thereby suggesting the presence of two independently regulated pools of GLUT4 storage compartments (Millar et al., 1999). In support of this idea, skeletal muscle has also been shown to contain two pools of GLUT4 vesicles, one that responds to insulin and another that is responsive to exercise and contraction (Coderre et al., 1995; Aledo & Hundal, 1996). Although it was tempting to speculate that exercise utilized a VAMP3 pool of transporters, VAMP3 null mice did not display any impairment in exercise-contraction-stimulated glucose uptake (Yang et al., 2001).

Conclusion

The complexity in the signaling network regulating GLUT4 translocation has become even more apparent

in recent years. This is because studies aimed at finding commonality in the molecular mechanisms by which a large heterogeneous set of factors activate GLUT4 translocation bring to light unexpected discord. For example, a number of studies led to the proposal that hypoxia mimics the effects of contraction on glucose uptake, however, recent new data strongly support the idea that although AMPK may be the sole mediator of hypoxia-stimulated GLUT4 translocation, the effects of contraction require not only AMPK but another parallel signal. Undoubtedly the multiplicity of signals elicited by a single stimulus probably reflects the required engagement of several downstream events to permit the efficient translocation of GLUT4 to the plasma membrane. The identification of two distinct signals employed by insulin to activate GLUT4 translocation fits well into this paradigm and studies with other agonists, such as hyperosmolarity and ET-1, rally the idea that insulin may even engage additional distinct mechanisms. For example, studies show that $G_{q/11}$ plays a role in the insulin-signaling network activating GLUT4 translocation; however, studies have not linked it to the PI3K and TC10 pathways (Imamura et al., 1999; Kanzaki et al., 2000). In addition, there is evidence that PLD, an enzyme hypothesized to be associated with the GLUT4-containing membranes and to act in a constitutive manner to promote the mechanism of GLUT4 translocation by insulin, also may mediate the insulin mimetic action of hyperosmolarity and $G_{q/11}$. Although a picture is emerging that lipid rafts compartmentalize many of the GLUT4-directed signals, it is currently unclear as to whether there is a functional significance to this or not. Nonetheless, substantial progress has been made in identifying several key players in the molecular events mediating GLUT4 translocation. The future goal is to now link all the separate sections of this puzzle into one single coherent picture to provide important and novel therapeutic approaches to the treatment of type 2 diabetes.

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