Translocation of SLC2A4 (GLUT4) to the plasma membrane

D'Eustachio, P., Jassal, B., Klip, A., May, B.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of Creative Commons Attribution 4.0 International (CC BY 4.0) License. For more information see our license.

24/09/2021
**Introduction**

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

**Literature references**


Reactome database release: 77

This document contains 1 pathway and 15 reactions *(see Table of Contents)*
In adipocytes and myocytes insulin signaling causes intracellular vesicles carrying the GLUT4 (SLC2A4) glucose transporter to translocate to the plasma membrane, allowing the cells to take up glucose from the bloodstream (reviewed in Zaid et al. 2008, Leney and Tavare 2009, Bogan and Kandror 2010, Foley et al. 2011, Hoffman and Elmendorf 2011, Kandror and Pilch 2011, Jaldin-Fincati et al. 2017). In myocytes muscle contraction alone can also cause translocation of GLUT4.

Though the entire pathway leading to GLUT4 translocation has not been elucidated, several steps are known. Insulin activates the kinases AKT1 and AKT2. Muscle contraction activates the kinase AMPK-alpha2 and possibly also AKT. AKT2 and, to a lesser extent, AKT1 phosphorylate the RAB GTPase activators TBC1D1 and TBC1D4, causing them to bind 14-3-3 proteins and lose GTPase activation activity. As a result RAB proteins (probably RAB8A, RAB10, RAB14 and possibly RAB13) accumulate GTP. The connection between RAB:GTP and vesicle translocation is unknown but may involve recruitment and activation of myosins.

Myosins 1C, 2A, 2B, 5A, 5B have all been shown to play a role in translocating GLUT4 vesicles near the periphery of the cell. Following docking at the plasma membrane the vesicles fuse with the plasma membrane in a process that depends on interaction between VAMP2 on the vesicle and SNAP23 and SYNTAXIN-4 at the plasma membrane.

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-07-07</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2012-08-21</td>
<td>Reviewed</td>
<td>Klip, A.</td>
</tr>
</tbody>
</table>
RAB4A:GTP binds KIF3 and activates KIF3

Location: Translocation of SLC2A4 (GLUT4) to the plasma membrane

Stable identifier: R-HSA-2316347

Type: binding

Compartments: cytoplasmic vesicle membrane, cytosol

Inferred from: Rab4a:GTP Activates Kif3 (Mus musculus)

As inferred from mouse adipocytes, insulin signals via PKC-lambda to cause Rab4 to load GTP and associate with Kif3, which then has higher affinity for microtubules. Motor activity of Kif3 along microtubules is believed to transport vesicles containing Glut4 (Slc2a4) across the cytosol to the cortical actin network.

Followed by: RALA:GTP binds MYO1C:CALM1 and activates MYO1C

Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012-05-27</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2012-08-21</td>
<td>Reviewed</td>
<td>Klip, A.</td>
</tr>
</tbody>
</table>
p-AKT1,p-AKT2 phosphorylates AS160 (TBC1D4)

**Location:** Translocation of SLC2A4 (GLUT4) to the plasma membrane

**Stable identifier:** R-HSA-1445144

**Type:** omitted

**Compartments:** cytoplasmic vesicle membrane, cytosol

**Inferred from:** Akt Phosphorylates As160 (Tbc1d4) (Mus musculus)

As inferred from mouse, AKT2 and, to a lesser extent, AKT1 phosphorylate AS160 (TBC1D4) in response to insulin signaling (Howlett et al. 2007, Karlsson et al 2005). AS160, a RAB GTPase activating protein, interacts with IRAP (LNPEP) and is associated with cytoplasmic vesicles containing GLUT4 (SLC2A4).

**Followed by:** 14-3-3 binds p-S5,T642-AS160 (TBC1D4)

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-07-07</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2012-08-21</td>
<td>Reviewed</td>
<td>Klip, A.</td>
</tr>
</tbody>
</table>
AS160 (TBC1D4) phosphorylated on serines 318, 341, 570, 588, and 751 and threonine 642 binds to all 14-3-3 proteins, although binding to 14-3-3 delta (YWHAZ) is comparatively low (Ramm et al. 2006, Howlett et al. 2007, Ngo et al. 2009, Treebak et al. 2009, Koumanov et al. 2011). As inferred from mouse, binding to 14-3-3 does not interfere with the interaction between AS160 and IRAP (LNPEP).

**Preceded by:** p-AKT1,p-AKT2 phosphorylates AS160 (TBC1D4)

**Followed by:** RAB8A,10,13,14 exchange GDP for GTP

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Edition</th>
<th>Date</th>
<th>Author/Editor</th>
<th>Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-07-07</td>
<td>Authored, Edited</td>
<td>May, B.</td>
<td>Klip, A.</td>
</tr>
</tbody>
</table>
**AMPK-alpha2 phosphorylates TBC1D1**

**Location:** Translocation of SLC2A4 (GLUT4) to the plasma membrane

**Stable identifier:** R-HSA-1454699

**Type:** transition

**Compartments:** cytosol, cytoplasmic vesicle membrane

**Inferred from:** Ampk-alpha2 Phosphorylates Tbc1d1 (Mus musculus)

In response to muscle contraction and insulin signaling, AMPK-alpha2 phosphorylates TBC1D1 on serine 237 and probably other residues (Frøsig et al. 2010, Vichaiwong et al. 2010). As inferred from rat L6 muscle cells TBC1D1 colocalizes with perinuclear vesicles bearing GLUT4 (SLC2A4) and may be involved in an early step that mobilizes them (Chen et al. 2008). Human TBC1D1 appears cytosolic and is believed to be concentrated near vesicle membranes (Park et al. 2011).

**Followed by:** 14-3-3 Binds p-S237-TBC1D1

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Authorship</th>
<th>Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-07-15</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2012-08-21</td>
<td>Reviewed</td>
<td>Klip, A.</td>
</tr>
</tbody>
</table>
**14-3-3 Binds p-S237-TBC1D1**

**Location:** Translocation of SLC2A4 (GLUT4) to the plasma membrane

**Stable identifier:** R-HSA-1454689

**Type:** binding

**Compartments:** cytosol

**Inferred from:** 14-3-3 Binds Phosphorylated Tbc1d1 (Mus musculus)

TBC1D1 phosphorylated on serine-237 binds 14-3-3 proteins in assays with yeast 14-3-3 proteins BMH1 and BMH2 (Chen et al. 2008, Frøsig et al. 2010). Binding with human 14-3-3 proteins is inferred.

**Preceded by:** AMPK-alpha2 phosphorylates TBC1D1

**Followed by:** RAB8A,10,13,14 exchange GDP for GTP

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-07-15</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2012-08-21</td>
<td>Reviewed</td>
<td>Klip, A.</td>
</tr>
</tbody>
</table>
RAB8A,10,13,14 exchange GDP for GTP

Location: Translocation of SLC2A4 (GLUT4) to the plasma membrane

Stable identifier: R-HSA-2255343

Type: transition

Compartments: cytoplasmic vesicle membrane

Inferred from: Rab8A/13/14 Exchange GDP for GTP (Rattus norvegicus), Rab8A/10/13/14 Exchange GDP for GTP (Mus musculus)

RAB8A/10/13/14 release GDP and bind GTP to yield the active complex. Guanine nucleotide exchange factors (GEFs) stimulate the reaction. GTPase-activating proteins (GAPs) oppose the reaction by stimulating the intrinsic GTPase activity of the RAB proteins.

Preceded by: RAB8A,10,13,14 hydrolyze GTP, 14-3-3 binds p-5S,T642-AS160 (TBC1D4), 14-3-3 Binds p-S237-TBC1D1

Followed by: RAB8A,10,13,14 hydrolyze GTP, SLC2A4 (GLUT4) vesicle translocates and docks at the plasma membrane

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012-05-16</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2012-08-21</td>
<td>Reviewed</td>
<td>Klip, A.</td>
</tr>
</tbody>
</table>

https://reactome.org
RAB8A,10,13,14 hydrolyze GTP ↑

**Location:** Translocation of SLC2A4 (GLUT4) to the plasma membrane

**Stable identifier:** R-HSA-1445143

**Type:** transition

**Compartments:** cytoplasmic vesicle membrane

**Inferred from:** Rab8a/10/13/14 Hydrolyze GTP (Mus musculus)

RAB proteins have intrinsic weak GTPase activity that is enhanced by RAB-GTPase activating proteins (RAB-GAPs, Sano et al. 2007). The GTPase activity of RAB13 is inferred from other RAB proteins. AS160 (TBC1D4) and TBC1D1 are GAPs that activate the GTPase activity of RAB8A/10/13. Insulin signaling activates AKT, which phosphorylates and inactivates AS160 and TBC1D1, allowing GTP-bound (active) RABs to accumulate.

**Preceded by:** RAB8A,10,13,14 exchange GDP for GTP

**Followed by:** RAB8A,10,13,14 exchange GDP for GTP

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-07-07</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2012-08-21</td>
<td>Reviewed</td>
<td>Klip, A.</td>
</tr>
</tbody>
</table>
p-AKT2 phosphorylates Myosin 5A

**Location:** Translocation of SLC2A4 (GLUT4) to the plasma membrane

**Stable identifier:** R-HSA-1449597

**Type:** transition

**Compartments:** cytosol, plasma membrane

**Inferred from:** Akt2 Phosphorylates Myosin 5a (Mus musculus)

As inferred from mouse, AKT2 phosphorylates Myosin 5A on serine-1652. The phosphorylation promotes association of Myosin 5A with actin and ATPase activity of Myosin 5A.

**Followed by:** SLC2A4 (GLUT4) vesicle translocates and docks at the plasma membrane

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Authorship</th>
<th>Editor</th>
<th>Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-07-13</td>
<td>Authored, Edited</td>
<td>May, B.</td>
<td>Klip, A.</td>
</tr>
<tr>
<td>2012-08-21</td>
<td>Reviewed</td>
<td>Klip, A.</td>
<td>Klip, A.</td>
</tr>
</tbody>
</table>
p-AKT2 phosphorylates RGC2

**Location:** Translocation of SLC2A4 (GLUT4) to the plasma membrane

**Stable identifier:** R-HSA-1458463

**Type:** transition

**Compartments:** cytosol, plasma membrane

**Inferred from:** Akt2 Phosphorylates Rgc2 (Mus musculus)

As inferred from mouse, AKT2 (PKB-beta) phosphorylates RBC2 (RALGAPA2) on serine-486, serine-696, and threonine-715 in response to insulin. The phosphorylation prevents RBC1:RBC2 from activating RALA GTPase and allows RALA:GTP to accumulate.

**Followed by:** RALA exchanges GDP for GTP

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-07-17</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2012-08-21</td>
<td>Reviewed</td>
<td>Klip, A.</td>
</tr>
</tbody>
</table>
RALA exchanges GDP for GTP

**Location:** Translocation of SLC2A4 (GLUT4) to the plasma membrane

**Stable identifier:** R-HSA-2255342

**Type:** transition

**Compartments:** cytoplasmic vesicle membrane

**Inferred from:** RalA Exchanges GDP for GTP (Mus musculus)

RALA releases GDP and binds GTP, producing the active form of RALA. The reaction is accelerated by guanine nucleotide exchange factors (GEFs) and opposed by GTPase-activating proteins (GAPs) which enhance the conversion of RALA:GTP back to RALA:GDP by activating the GTPase activity of RALA.

**Preceded by:** RALA hydrolyzes GTP, p-AKT2 phosphorylates RGC2

**Followed by:** RALA:GTP binds MYO1C:CALM1 and activates MYO1C, RALA hydrolyzes GTP

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012-05-16</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2012-08-21</td>
<td>Reviewed</td>
<td>Klip, A.</td>
</tr>
</tbody>
</table>
RALA:GTP binds MYO1C:CALM1 and activates MYO1C

**Location:** Translocation of SLC2A4 (GLUT4) to the plasma membrane

**Stable identifier:** R-HSA-2316349

**Type:** binding

**Compartments:** cytoplasmic vesicle membrane, cytosol

**Inferred from:** RalA:GTP binds Myo1c:Calm1 and F-actin (Mus musculus)

As inferred from mouse, insulin causes phosphorylation and inactivation of the Ral GTPase activating complex RGC, causing RALA:GTP to accumulate and associate with the unconventional myosin MYO1C. MYO1C, with calmodulin as a light chain, motors across cortical actin and interacts with the exocyst complex to tether vesicles at the plasma membrane (Chen et al. 2007).

**Preceded by:** RALA exchanges GDP for GTP, RAB4A:GTP binds KIF3 and activates KIF3

**Followed by:** SLC2A4 (GLUT4) vesicle translocates and docks at the plasma membrane

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012-05-27</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2012-08-21</td>
<td>Reviewed</td>
<td>Klip, A.</td>
</tr>
</tbody>
</table>
RALA hydrolyzes GTP

**Location:** Translocation of SLC2A4 (GLUT4) to the plasma membrane

**Stable identifier:** R-HSA-1458485

**Type:** transition

**Compartments:** cytoplasmic vesicle membrane

**Inferred from:** RalA Hydrolyzes GTP (Mus musculus)

RALA is a guanine nucleotide binding protein that hydrolyzes bound GTP to yield GDP and phosphate. RGC1 and RGC2 are GAPs (GTPase-activating proteins) that activate the GTPase activity of RALA. Insulin activates AKT, which phosphorylates RGC2, inactivating the GAP activity of RGC1:RGC2 and allowing RALA:GTP to accumulate.

**Preceded by:** RALA exchanges GDP for GTP

**Followed by:** RALA exchanges GDP for GTP

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Year</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-07-17</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2012-08-21</td>
<td>Reviewed</td>
<td>Klip, A.</td>
</tr>
</tbody>
</table>

https://reactome.org
p-AKT2 phosphorylates C2CD5 ➔

**Location:** Translocation of SLC2A4 (GLUT4) to the plasma membrane

**Stable identifier:** R-HSA-5260201

**Type:** transition

**Compartments:** cytosol, plasma membrane

**Inferred from:** p-Akt2 phosphorylates C2cd5 (Mus musculus)

The protein kinase B beta (AKT) pathway mediates insulin-stimulated glucose transport by increasing glucose transporter GLUT4 translocation from intracellular stores to the plasma membrane. C2 domain-containing protein 5 (C2CD5 aka C2 domain-containing phosphoprotein 138kDa) has been shown to be required for optimal insulin-stimulated GLUT4 translocation and fusion of GLUT4 vesicles with the plasma membrane in adipocytes. It is also able to bind Ca2+ and lipid membranes in its C2 domain. C2CD5 is a substrate for RAC-beta serine/threonine-protein kinase (AKT2), which phosphorylates C2CD5 at serine 197. Phosphorylated C2CD5 optimises GLUT4 translocation to the plasma membrane. The role of human C2CD5 is inferred from the role of the orthologous mouse protein (Xie et al. 2011).

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th></th>
<th>Authors, Edited</th>
<th>Jassal, B.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014-02-07</td>
<td>Authored, Edited</td>
<td></td>
</tr>
<tr>
<td>2015-02-11</td>
<td>Reviewed</td>
<td>D'Eustachio, P.</td>
</tr>
</tbody>
</table>
SLC2A4 (GLUT4) vesicle translocates and docks at the plasma membrane

**Location:** Translocation of SLC2A4 (GLUT4) to the plasma membrane

**Stable identifier:** R-HSA-2316352

**Type:** omitted

**Compartments:** cytoplasmic vesicle membrane, plasma membrane

**Inferred from:** Translocation of Glut4 Vesicle and Docking at the Plasma Membrane (Mus musculus)

As inferred from mouse, GLUT4 (SLC2A4) initially translocates from endosomes to insulin-responsive vesicles (IRVs, GSVs). RAB11 appears to play a role in this process. IRVs bearing GLUT4 are then translocated across the cortical actin network to the plasma membrane. Unconventional myosin 5A (MYO5A) interacts with RAB10 or RAB8A on the vesicle and participates in transport of the IRV. Myosin 1C appears to act close to the plasma membrane and may facilitate fusion of the vesicle with the plasma membrane. RAB:GTP complexes coupled to the vesicles may interact with myosins to regulate their activity. Non-muscle myosin IIA (MYH9) appears to interact with the SNAP23 complex to dock the IRV at the inner membrane face.

**Preceded by:** RALA:GTP binds MYO1C:CALM1 and activates MYO1C, RAB8A,10,13,14 exchange GDP for GTP, p-AKT2 phosphorylates Myosin 5A

**Followed by:** SLC2A4 (GLUT4) vesicle fuses with the plasma membrane

**Editions**

<table>
<thead>
<tr>
<th>Edition</th>
<th>Author/Editor</th>
<th>Date</th>
<th>Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012-05-27</td>
<td>Authored, Edited</td>
<td>May, B.</td>
<td></td>
</tr>
<tr>
<td>2012-08-21</td>
<td>Reviewed</td>
<td>Klip, A.</td>
<td></td>
</tr>
</tbody>
</table>
SLC2A4 (GLUT4) vesicle fuses with the plasma membrane

**Location:** Translocation of SLC2A4 (GLUT4) to the plasma membrane

**Stable identifier:** R-HSA-1449574

**Type:** omitted

**Compartments:** cytoplasmic vesicle membrane, plasma membrane

**Inferred from:** Fusion of Glut4 Vesicle with the Plasma Membrane (Mus musculus)

After docking at the membrane VAMP2 on the vesicle interacts with SYNTAXIN-4 and SNAP23 on the plasma membrane to catalyze fusion of the vesicle with the plasma membrane. STXBP3 (MUNC18C) bound to STX4 prevents fusion until STXBP3 is phosphorylated.

**Preceded by:** SLC2A4 (GLUT4) vesicle translocates and docks at the plasma membrane

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-07-13</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2012-08-21</td>
<td>Reviewed</td>
<td>Klip, A.</td>
</tr>
</tbody>
</table>
Table of Contents

Introduction 1

Translocation of SLC2A4 (GLUT4) to the plasma membrane 2

RAB4A:GTP binds KIF3 and activates KIF3 4

p-AKT1,p-AKT2 phosphorylates AS160 (TBC1D4) 5

14-3-3 binds p-S5,T642-AS160 (TBC1D4) 6

AMPK-alpha2 phosphorylates TBC1D1 7

14-3-3 binds p-S237-TBC1D1 8

RAB8A,10,13,14 exchange GDP for GTP 9

RAB8A,10,13,14 hydrolyze GTP 10

p-AKT2 phosphorylates Myosin 5A 11

p-AKT2 phosphorylates RGC2 12

RALA exchanges GDP for GTP 13

RALA:GTP binds MYO1C:CALM1 and activates MYO1C 14

RALA hydrolyzes GTP 15

p-AKT2 phosphorylates C2CD5 16

SLC2A4 (GLUT4) vesicle translocates and docks at the plasma membrane 17

SLC2A4 (GLUT4) vesicle fuses with the plasma membrane 18

Table of Contents