PI5P, PP2A and IER3 Regulate PI3K/AKT Signaling

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08/09/2019
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: 69

This document contains 1 pathway and 7 reactions (see Table of Contents)
Phosphatidylinositol-5-phosphate (PI5P) may modulate PI3K/AKT signaling in several ways. PI5P is used as a substrate for production of phosphatidylinositol-4,5-bisphosphate, PI(4,5)P2 (Rameh et al. 1997, Clarke et al. 2008, Clarke et al. 2010, Clarke and Irvine 2013, Clarke et al. 2015), which serves as a substrate for activated PI3K, resulting in the production of PIP3 (Mandelker et al. 2009, Burke et al. 2011). The majority of PI(4,5)P2 in the cell, however, is produced from the phosphatidylinositol-4-phosphate (PI4P) substrate (Zhang et al. 1997, Di Paolo et al. 2002, Oude Weernink et al. 2004, Halstead et al. 2006, Oude Weernink et al. 2007). PIP3 is necessary for the activating phosphorylation of AKT. AKT1 can be de-activated by the protein phosphatase 2A (PP2A) complex that contains a regulatory subunit B56-beta (PPP2R5B) or B56-gamma (PPP2R5C). PI5P inhibits AKT1 dephosphorylation by PP2A through an unknown mechanism (Ramel et al. 2009). Increased PI5P levels correlate with inhibitory phosphorylation(s) of the PP2A complex. MAPK1 (ERK2) and MAPK3 (ERK1) are involved in inhibitory phosphorylation of PP2A, in a process that involves IER3 (IEX-1) (Letourneux et al. 2006, Rocher et al. 2007). It is uncertain, however, whether PI5P is in any way involved in ERK-mediated phosphorylation of PP2A or if it regulates another PP2A kinase.

**Literature references**


**Editions**

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PI4P is phosphorylated to PI(4,5)P2 by PIP5K1A-C at the plasma membrane

**Location:** PI5P, PP2A and IER3 Regulate PI3K/AKT Signaling

**Stable identifier:** R-HSA-1676082

**Type:** transition

**Compartments:** plasma membrane, cytosol

At the plasma membrane, phosphatidylinositol-4-phosphate 5-kinase type-1 alpha (PIP5K1A), beta (PIP5K1B), and gamma (PIP5K1C) phosphorylate phosphatidylinositol 4-phosphate (PI4P) to produce phosphatidylinositol 4,5-bisphosphate (PI(4,5)P2).

The following lists the above proteins with their corresponding literature references: PIP5K1A (Halstead et al. 2006, Zhang et al. 1997), PIP5K1B (Zhang et al. 1997), and PIP5K1C (Di Paolo et al. 2002).

This reaction is of particular interest because its regulation by small GTPases of the RHO and ARF families, not yet annotated here, ties the process of phosphatidylinositol phosphate biosynthesis to regulation of the actin cytoskeleton and vesicular trafficking, and hence to diverse aspects of cell motility and signalling (Oude Weernink et al. 2004, 2007).

Followed by: PI3K phosphorylates PIP2 to PIP3

**Literature references**


## Editions

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PI5P is phosphorylated to PI(4,5)P2 by PIP4K2 dimers at the plasma membrane

**Location:** PI5P, PP2A and IER3 Regulate PI3K/AKT Signaling

**Stable identifier:** R-HSA-1675776

**Type:** transition

**Compartments:** plasma membrane, cytosol

At the plasma membrane, phosphatidylinositol-5-phosphate 4-kinase type-2 alpha (PIP4K2A), beta (PIP4K2B) and gamma (PIP4K2C) homodimers and heterodimers (Clarke et al. 2010, Clarke and Irvine 2013, Clarke et al. 2015) phosphorylate phosphatidylinositol 5-phosphate (PI5P) to phosphatidylinositol 4,5-bisphosphate (PI(4,5)P2).

The following lists the above proteins with their corresponding literature references: PIP4K2A (Rameh et al. 1997, Clarke et al. 2008, Clarke and Irvine 2013), PIP4K2B (Rameh et al. 1997, Clarke and Irvine 2013) and PIP4K2C (Clarke and Irvine 2013, Clarke et al. 2015).

**Followed by:** PI3K phosphorylates PIP2 to PIP3

**Literature references**


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## Editions

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In unstimulated cells, PI3K class IA exists as an inactive heterodimer of a p85 regulatory subunit (encoded by PIK3R1, PIK3R2 or PIK3R3) and a p110 catalytic subunit (encoded by PIK3CA, PIK3CB or PIK3CD). Binding of the iSH2 domain of the p85 regulatory subunit to the ABD and C2 domains of the p110 catalytic subunit both stabilizes p110 and inhibits its catalytic activity. This inhibition is relieved when the SH2 domains of p85 bind phosphorylated tyrosines on activated RTKs or their adaptor proteins. Binding to membrane-associated receptors brings activated PI3K in proximity to its membrane-localized substrate, PIP2 (Mandelker et al. 2009, Burke et al. 2011).

**Preceded by:** PI4P is phosphorylated to PI(4,5)P2 by PI5K1A-C at the plasma membrane, PI5P is phosphorylated to PI(4,5)P2 by PIP4K2 dimers at the plasma membrane

**Literature references**


Burke, JE., Vadas, O., Berndt, A., Finegan, T., Perisic, O., Williams, RL. (2011). Dynamics of the phosphoinositide 3-kinase p110\(^\gamma\) interaction with p85\(^\alpha\) and membranes reveals aspects of regulation distinct from p110\(^\alpha\). *Structure*, 19, 1127-37.
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The protein phosphatase 2A (PP2A) complex containing a regulatory subunit B56 beta (PPP2R5B) or B56 gamma (PPP2R5C) dephosphorylates activated AKT1 on threonine residue T308 and serine residue S473, thus halting PI3K/AKT signaling (Rocher et al. 2007). Phosphatidylinositol-5-phosphate (PI5P) negatively regulates PP2A-mediated dephosphorylation of AKT1 by promoting, through an unknown mechanism, an inhibitory phosphorylation on tyrosine residue Y307 (Chen et al. 1992) of the catalytic subunit of PP2A (Ramel et al. 2009).

**Literature references**


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Inhibition of PP2A activity by phosphorylation of the catalytic subunit at tyrosine Y307

**Location:** PI5P, PP2A and IER3 Regulate PI3K/AKT Signaling

**Stable identifier:** R-HSA-8857925

**Type:** transition

**Compartments:** cytosol, plasma membrane

SRC family tyrosine kinases, such as SRC and LCK, as well as receptor tyrosine kinases, such as EGFR and insulin receptor, can phosphorylate the catalytic subunit of serine/threonine protein phosphatase PP2A at tyrosine residue Y307. Phosphorylation at Y307 inhibits the catalytic activity of PP2A. Phosphatidylinositol-5-phosphate (PI5P) positively regulates phosphorylation of the catalytic subunit of PP2A at Y307.

**Literature references**


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[https://reactome.org](https://reactome.org)
IER3 recruits MAPKs to PP2A-B56-beta,gamma

**Location:** PI5P, PP2A and IER3 Regulate PI3K/AKT Signaling

**Stable identifier:** R-HSA-6811472

**Type:** binding

**Compartments:** cytosol

IER3 (IEX-1) recruits both an activated MAPK (MAPK1 (ERK2) or MAPK3 (ERK1)) and the protein phosphatase 2A (PP2A) complex containing regulatory subunits B56-beta (PPP2R5B) or B56-gamma (PPP2R5C), through an interaction with the B56 subunit, forming a tripartite complex (Letourneux et al. 2006, Rocher et al. 2007).

**Followed by:** MAPKs phosphorylate PP2A

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MAPKs phosphorylate PP2A

**Location:** PI5P, PP2A and IER3 Regulate PI3K/AKT Signaling

**Stable identifier:** R-HSA-6811454

**Type:** transition

**Compartments:** cytosol

Activated MAPK1 (ERK2) or MAPK3 (ERK1), recruited to the PP2A complex through IER3 (IEX-1), phosphorylate the regulatory subunit PPP2R5B (B56-beta) or PPP2R5C (B56-gamma) of the PP2A complex on serine residue S368 or S337, respectively. ERK-mediated phosphorylation of the PP2A regulatory subunits causes dissociation of the PP2A complex and prevents PP2A-mediated dephosphorylation of AKT1 (Letourneux et al. 2006, Rocher et al. 2007).

**Preceded by:** IER3 recruits MAPKs to PP2A-B56-beta,gamma

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