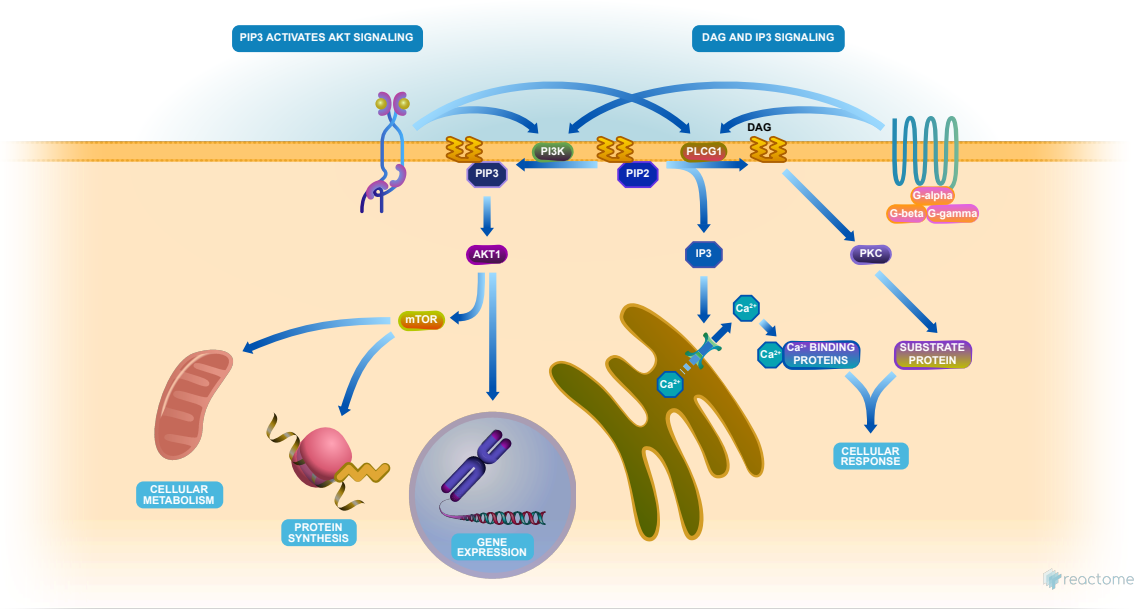
Intracellular signaling by second messengers



Annibali, D., D'Eustachio, P., Greene, LA., Nasi, S., Orlic-Milacic, M., Rothfels, K., Thorpe, L., Yuzugullu, H., Zhao, JJ.

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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

25/04/2024

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.

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Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

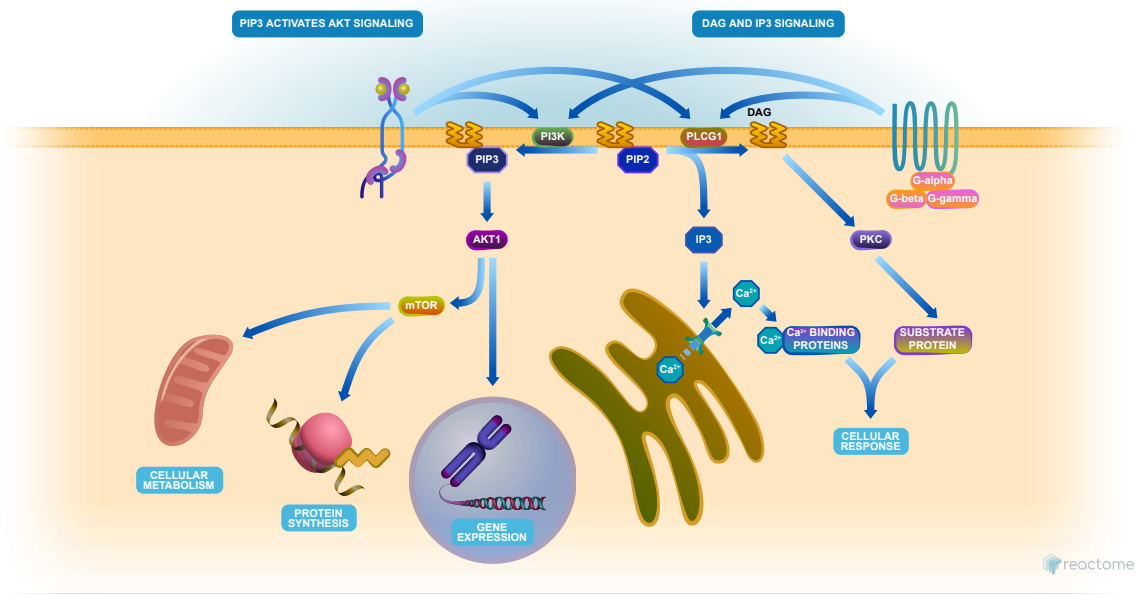
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 3 pathways (see Table of Contents)

Intracellular signaling by second messengers ↗

Stable identifier: R-HSA-9006925



Second messengers are generated within the cell as a downstream step in signal transduction cascades initiated by the interaction of an external stimulus with a cell surface receptor. Common second messengers include DAG, cAMP, cGMP, IP3, Ca2+ and phosphatidylinositols (reviewed in Kang et al, 2015; Raker et al, 2016; Li and Marshall, 2015; Pinto et al, 2015; Ahmad et al, 2015).

Literature references

Kim, S., Kang, DS., Lee, C., Suh, PG., Yang, YR., Ryu, SH. (2016). Roles of phosphoinositide-specific phospholipase Cγ1 in brain development. *Adv Biol Regul, 60*, 167-73. ↗

Ulrich, H., Gomes, KN., Goulart, VA., Kihara, AH., Resende, RR., Pinto, MC. et al. (2015). Calcium signaling and cell proliferation. *Cell. Signal., 27*, 2139-49. ↗

Becker, C., Steinbrink, K., Raker, VK. (2016). The cAMP Pathway as Therapeutic Target in Autoimmune and Inflammatory Diseases. *Front Immunol, 7*, 123. ↗

Patel, S., Levine, TP. (2016). Signalling at membrane contact sites: two membranes come together to handle second messengers. *Curr. Opin. Cell Biol., 39*, 77-83. ↗

Murata, T., Ahmad, F., Degerman, E., Shimizu, K., Manganiello, V., Maurice, D. (2015). Cyclic nucleotide phosphodiesterases: important signaling modulators and therapeutic targets. *Oral Dis, 21*, e25-50. ↗

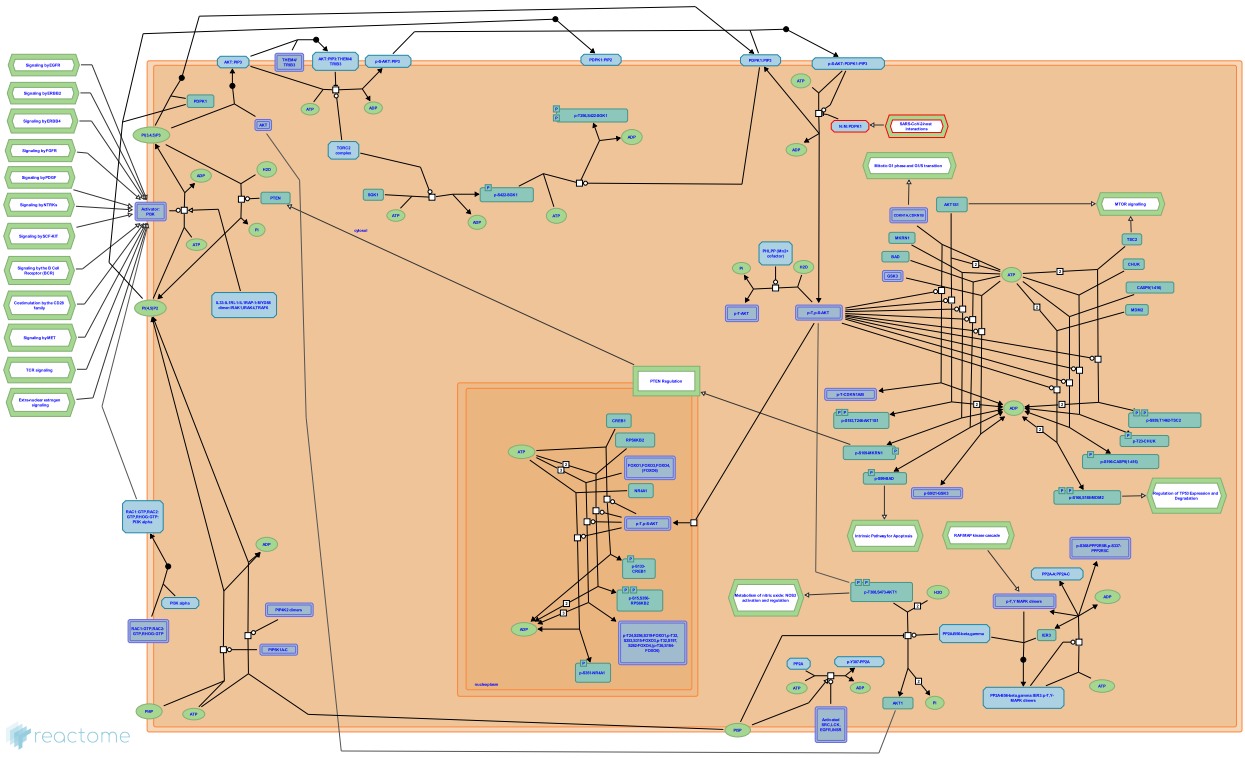
Editions

2017-05-24	Authored, Edited	Rothfels, K.
2017-06-22	Reviewed	D'Eustachio, P.

PIP3 activates AKT signaling ↗

Location: Intracellular signaling by second messengers

Stable identifier: R-HSA-1257604



Signaling by AKT is one of the key outcomes of receptor tyrosine kinase (RTK) activation. AKT is activated by the cellular second messenger PIP3, a phospholipid that is generated by PI3K. In ustimulated cells, PI3K class IA enzymes reside in the cytosol as inactive heterodimers composed of p85 regulatory subunit and p110 catalytic subunit. In this complex, p85 stabilizes p110 while inhibiting its catalytic activity. Upon binding of extracellular ligands to RTKs, receptors dimerize and undergo autophosphorylation. The regulatory subunit of PI3K, p85, is recruited to phosphorylated cytosolic RTK domains either directly or indirectly, through adaptor proteins, leading to a conformational change in the PI3K IA heterodimer that relieves inhibition of the p110 catalytic subunit. Activated PI3K IA phosphorylates PIP2, converting it to PIP3; this reaction is negatively regulated by PTEN phosphatase. PIP3 recruits AKT to the plasma membrane, allowing TORC2 to phosphorylate a conserved serine residue of AKT. Phosphorylation of this serine induces a conformation change in AKT, exposing a conserved threonine residue that is then phosphorylated by PDPK1 (PDK1). Phosphorylation of both the threonine and the serine residue is required to fully activate AKT. The active AKT then dissociates from PIP3 and phosphorylates a number of cytosolic and nuclear proteins that play important roles in cell survival and metabolism. For a recent review of AKT signaling, please refer to Manning and Cantley, 2007.

Editions

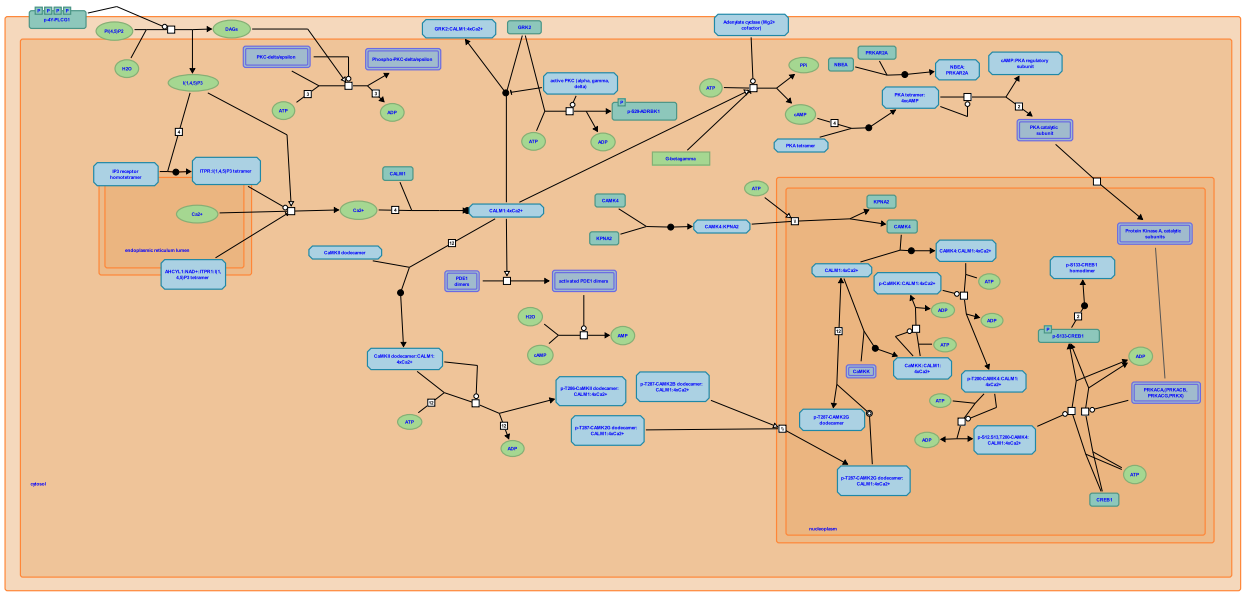
2007-11-08	Reviewed	Greene, LA.
2012-06-21	Revised	Orlic-Milacic, M.
2012-08-13	Reviewed	Zhao, JJ., Yuzugullu, H., Thorpe, L.

DAG and IP3 signaling ↗

Location: Intracellular signaling by second messengers

Stable identifier: R-HSA-1489509

Compartments: plasma membrane, extracellular region, cytosol



This pathway describes the generation of DAG and IP3 by the PLCgamma-mediated hydrolysis of PIP2 and the subsequent downstream signaling events.

Literature references

Snyder, SH., Nikolaidis, N., van Rossum, DB., Gill, DL., Patterson, RL. (2005). Phospholipase C-gamma: diverse roles in receptor-mediated calcium signaling. *Trends Biochem Sci, 30*, 688-97. ↗

Editions

2006-10-10	Authored	Annibali, D., Nasi, S.
2007-11-08	Reviewed	Greene, LA.

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