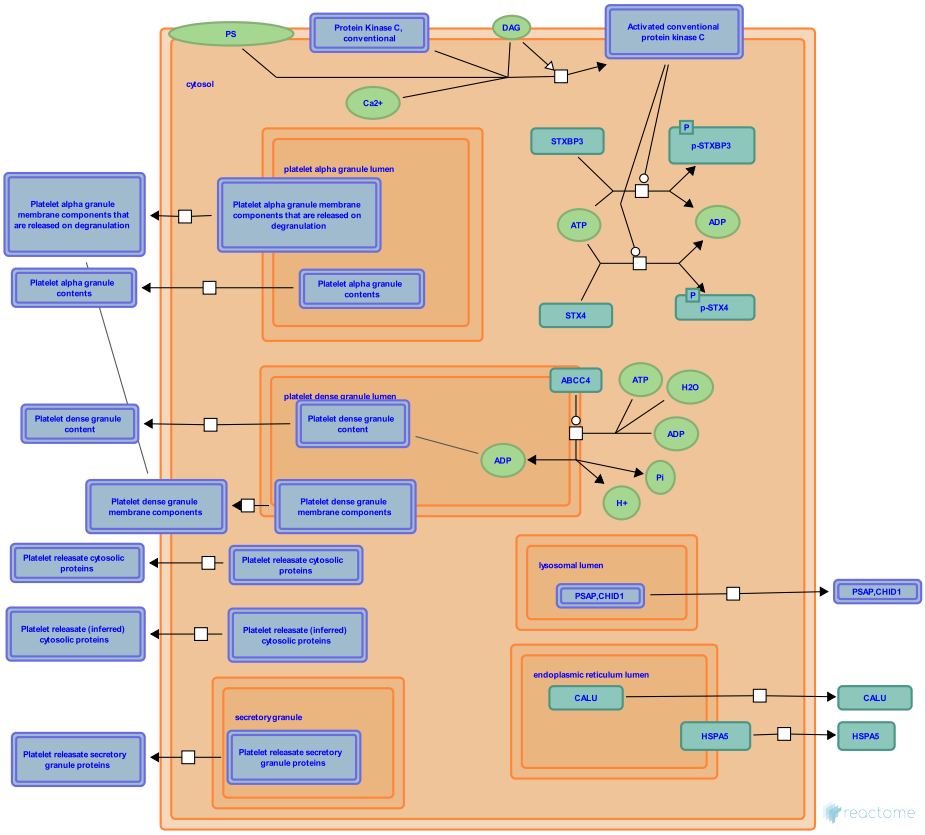
Response to elevated platelet cytosolic Ca2+



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16/05/2024

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.
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

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. ↗

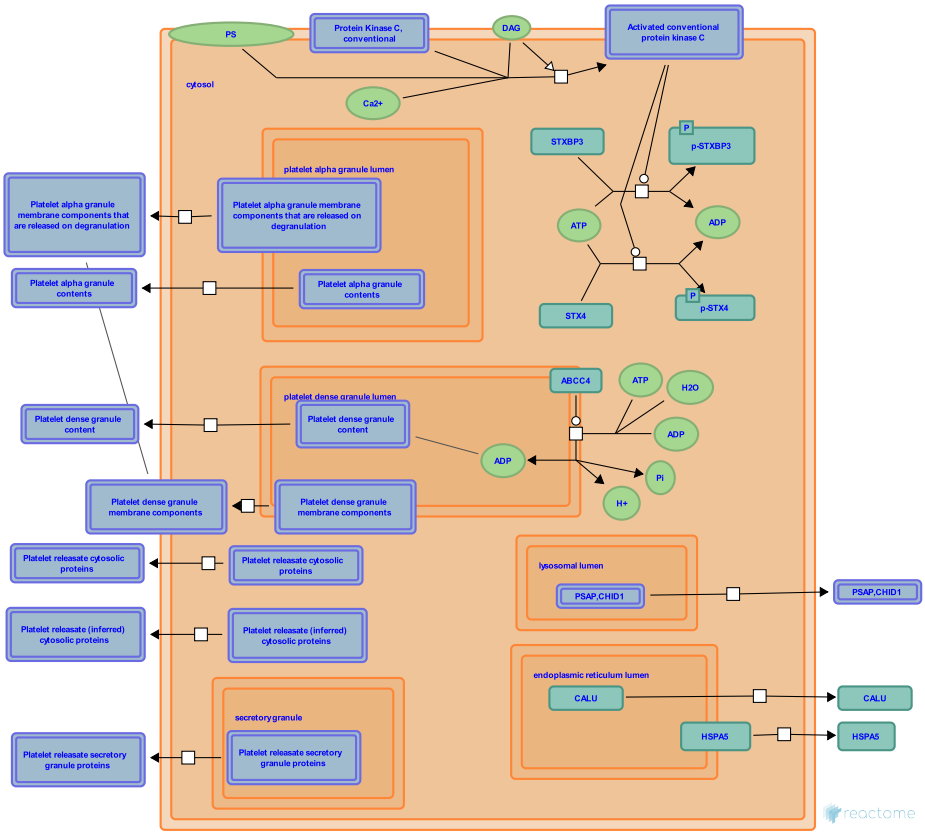
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 3 pathways and 1 reaction (see Table of Contents)

Response to elevated platelet cytosolic Ca2+ ↗

Stable identifier: R-HSA-76005



Activation of phospholipase C enzymes results in the generation of second messengers of the phosphatidylinositol pathway. The events resulting from this pathway are a rise in intracellular calcium and activation of Protein Kinase C (PKC). Phospholipase C cleaves the phosphodiester bond in PIP2 to form 1,2 Diacylglycerol (DAG) and 1,4,5-inositol trisphosphate (IP3). IP3 opens Ca2+ channels in the platelet dense tubular system, raising intracellular Ca2+ levels. DAG is a second messenger that regulates a family of Ser/Thr kinases consisting of PKC isozymes (Nishizuka 1995). DAG achieves activation of PKC isozymes by increasing their affinity for phospholipid. Most PKC enzymes are also calcium-dependent, so their activation is in synergy with the rise in intracellular Ca2+. Platelets contain several PKC isoforms that can be activated by DAG and/or Ca2+ (Chang 1997).

Literature references

Watson, SP., Walker, TR. (1993). Synergy between Ca2+ and protein kinase C is the major factor in determining the level of secretion from human platelets. *Biochem J, 289*, 277-82. ↗

Editions

2004-08-13	Authored	de Bono, B.

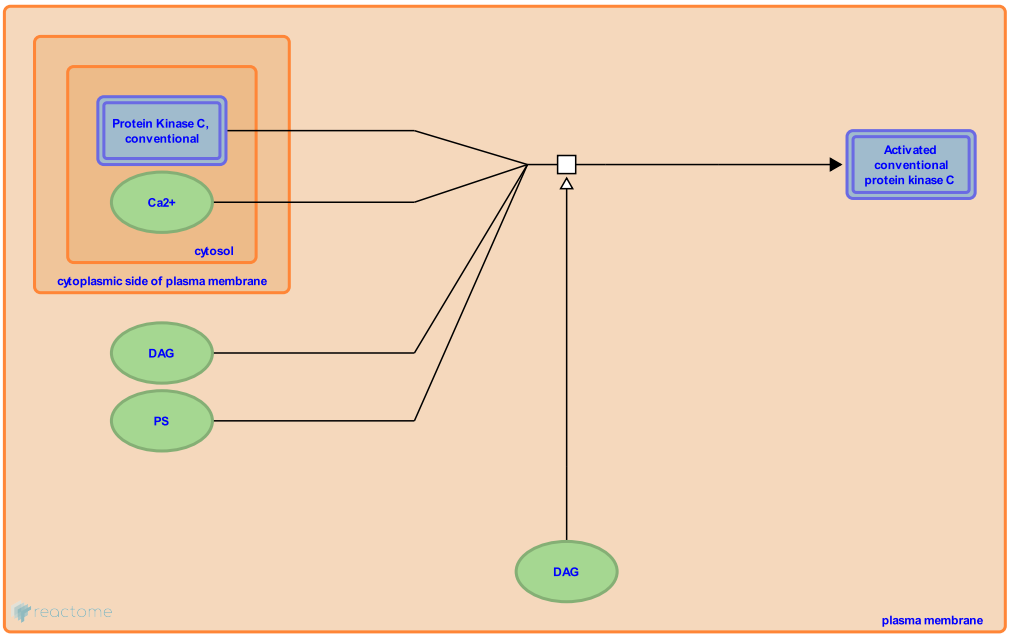
Activation of conventional Protein Kinase C ↗

Location: Response to elevated platelet cytosolic Ca2+

Stable identifier: R-HSA-114553

Type: transition

Compartments: plasma membrane, cytosol



Protein Kinase C (PKC) is positively regulated by events that increase the plasma membrane concentration of diacylglycerol (DAG). Activation of PKC requires the coordinated binding of two membrane-targeting domains. The C1 domain binds diacylglycerol, the C2 domain binds phosphatidylserine. Each can bind the membrane independently, but with insufficient affinity for membrane recruitment and activation.
The conventional Protein Kinase C (cPKC) isoforms have two membrane-targetting domains, a C1 domain which binds to the membrane lipid diacylglycerol (DAG) and a C2 domain which binds membrane phospholipids such as phosphatidylserine, in a calcium-dependent manner. Association of both domains with the plasma membrane produces a conformational change that releases an autoinhibitory pseudosubstrate segment from the substrate-binding cavity, allowing substrate binding and downstream signaling.

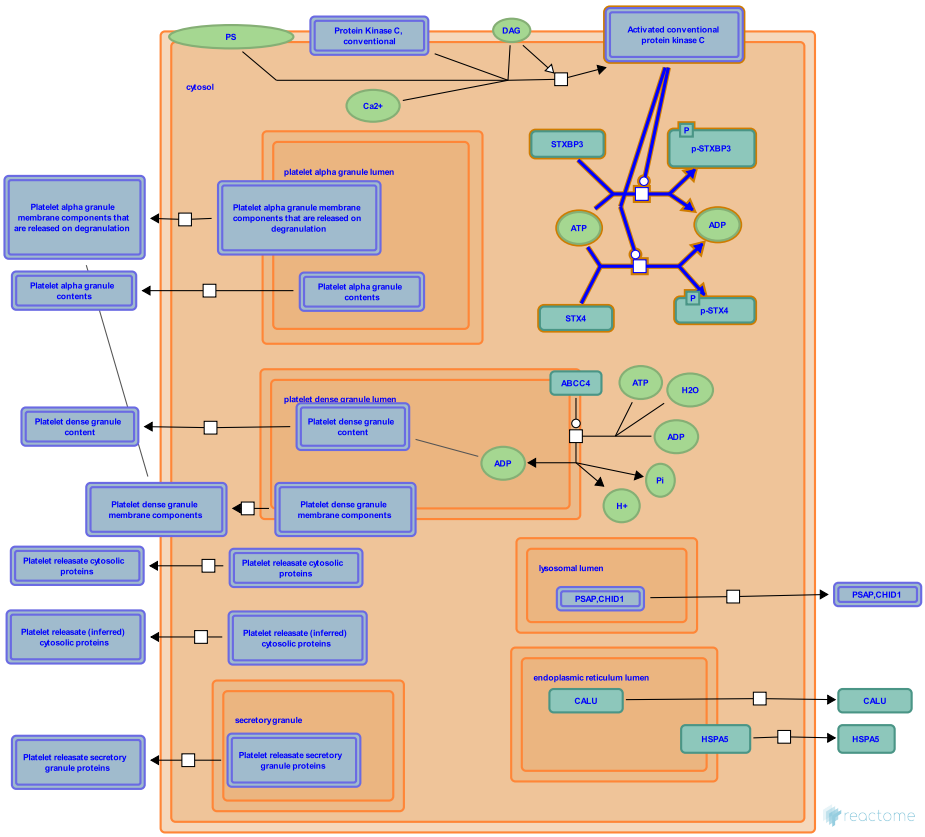
Literature references

Meyer, T., Oancea, E. (1998). Protein kinase C as a molecular machine for decoding calcium and diacylglycerol signals. *Cell, 95*, 307-18. ↗

Disinhibition of SNARE formation ↗

Location: Response to elevated platelet cytosolic Ca2+

Stable identifier: R-HSA-114516



The SNARE (SNAp REceptor) family of proteins are critical components of the machinery required for membrane fusion (Söllner et al. 1993, Wu et al. 2017). SNAREs can be grouped into three broad subfamilies: synaptosomal-associated proteins (SNAPs), vesicle-associated membrane proteins (VAMPs) and syntaxins. SNAPs contain two SNARE motifs and lack transmembrane domains, instead they are anchored to the membrane by thioester-linked acyl groups (Hong 2005). VAMPS or R-SNAREs have two subfamilies: short VAMPs or brevins and long VAMPs or longins. Syntaxins are evolutionarily less-well conserved, but except STX11 are transmembrane proteins (Hong 2005). Several SNARE proteins including Syntaxin-2 (STX2), STX4, STX11 and Vesicle-associated membrane protein 8 (VAMP8) are thought to be involved in platelet granule secretion (Golebiewska et al. 2013).

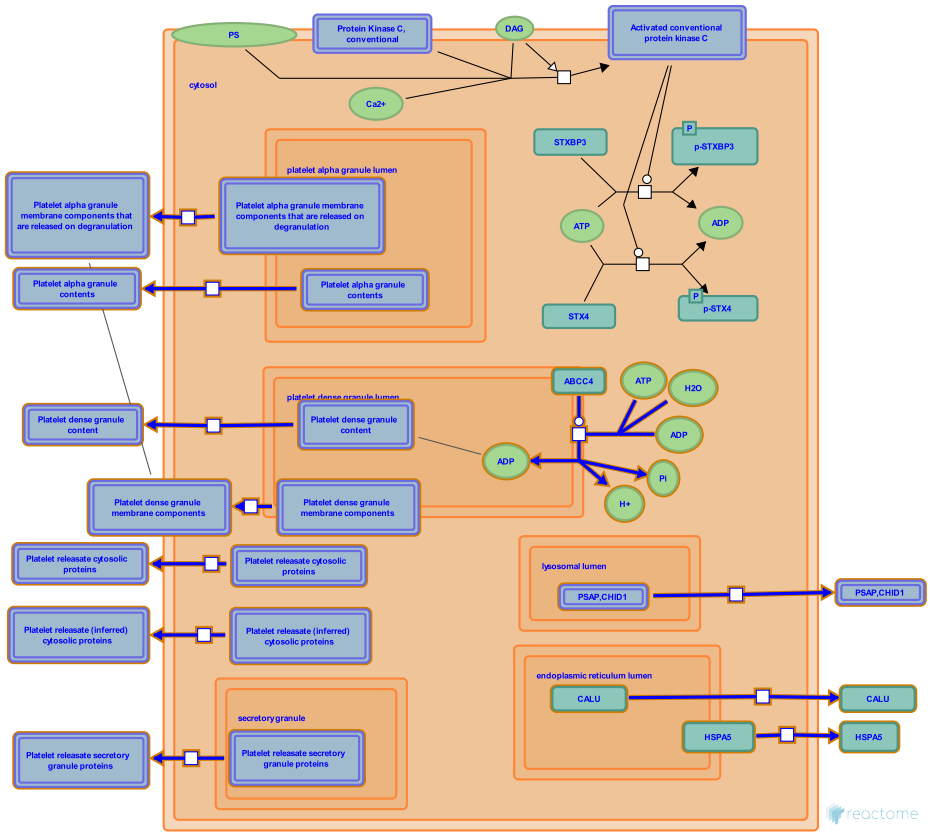
Literature references

Karatekin, E., Thiyagarajan, S., Wu, Z., O'Shaughnessy, B. (2017). Regulation of Exocytotic Fusion Pores by SNARE Protein Transmembrane Domains. *Front Mol Neurosci, 10*, 315. ↗

Platelet degranulation ↗

Location: Response to elevated platelet cytosolic Ca2+

Stable identifier: R-HSA-114608



Platelets function as exocytotic cells, secreting a plethora of effector molecules at sites of vascular injury. Platelets contain a number of distinguishable storage granules including alpha granules, dense granules and lysosomes. On activation platelets release a variety of proteins, largely from storage granules but also as the result of apparent cell lysis. These act in an autocrine or paracrine fashion to modulate cell signaling.

Alpha granules contain mainly polypeptides such as fibrinogen, von Willebrand factor, growth factors and protease inhibitors that that supplement thrombin generation at the site of injury. Dense granules contain small molecules, particularly adenosine diphosphate (ADP), adenosine triphosphate (ATP), serotonin and calcium, all recruit platelets to the site of injury. The molecular mechanism which facilitates granule release involves soluble NSF attachment protein receptors (SNAREs), which assemble into complexes to form a universal membrane fusion apparatus. Although all cells use SNAREs for membrane fusion, different cells possess different SNARE isoforms. Platelets and chromaffin cells use many of the same chaperone proteins to regulate SNARE-mediated secretion (Fitch-Tewfik & Flaumenhaft 2013).

Literature references

Page, CP., Vermylen, J., Gresele, P., Fuster, V. (2002). Platelets in thrombotic and non-thrombotic disorders. *Cambridge University Press,* 435-437.

McRedmond, JP., Toomey, S., Fitzgerald, DJ., Cahill, DJ., Belton, O., Maguire, PB. et al. (2004). Characterization of the proteins released from activated platelets leads to localization of novel platelet proteins in human atherosclerotic lesions. *Blood, 103,* 2096-104. ↗

Table of Contents