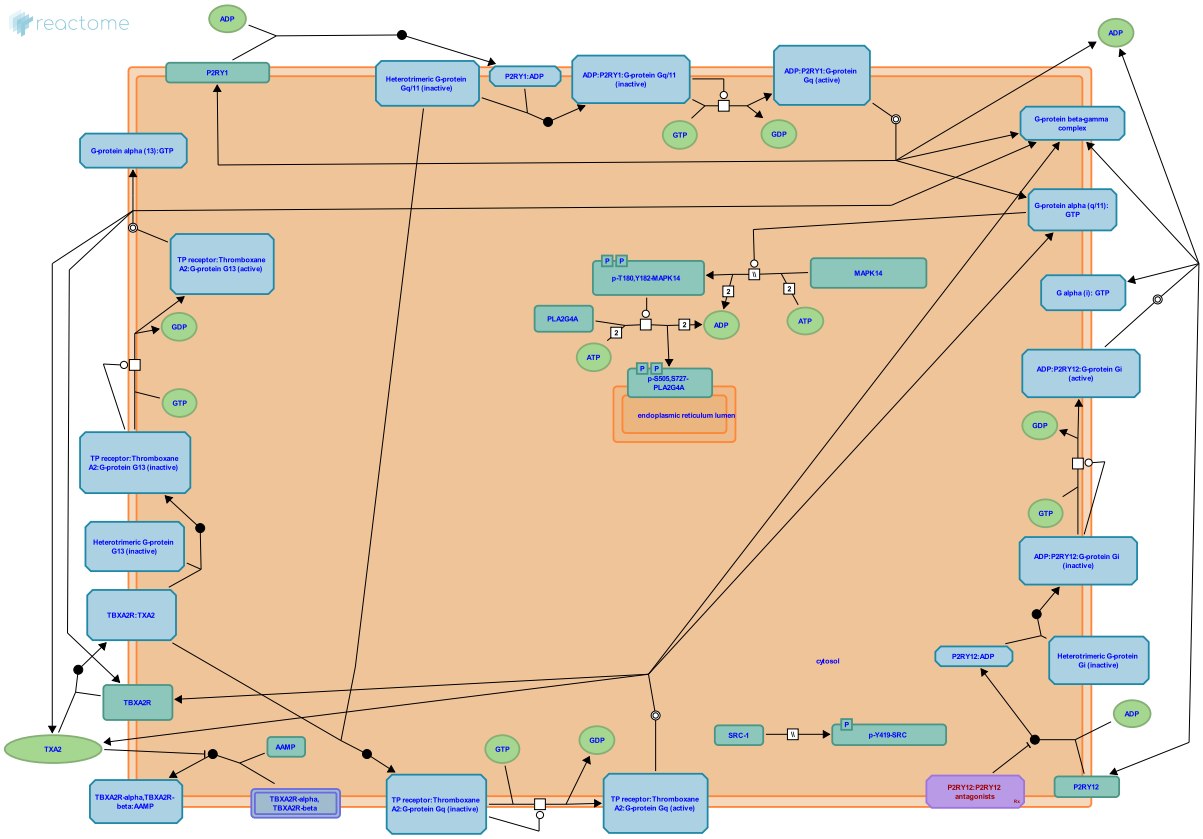
Signal amplification



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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.

09/10/2024

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. ↗

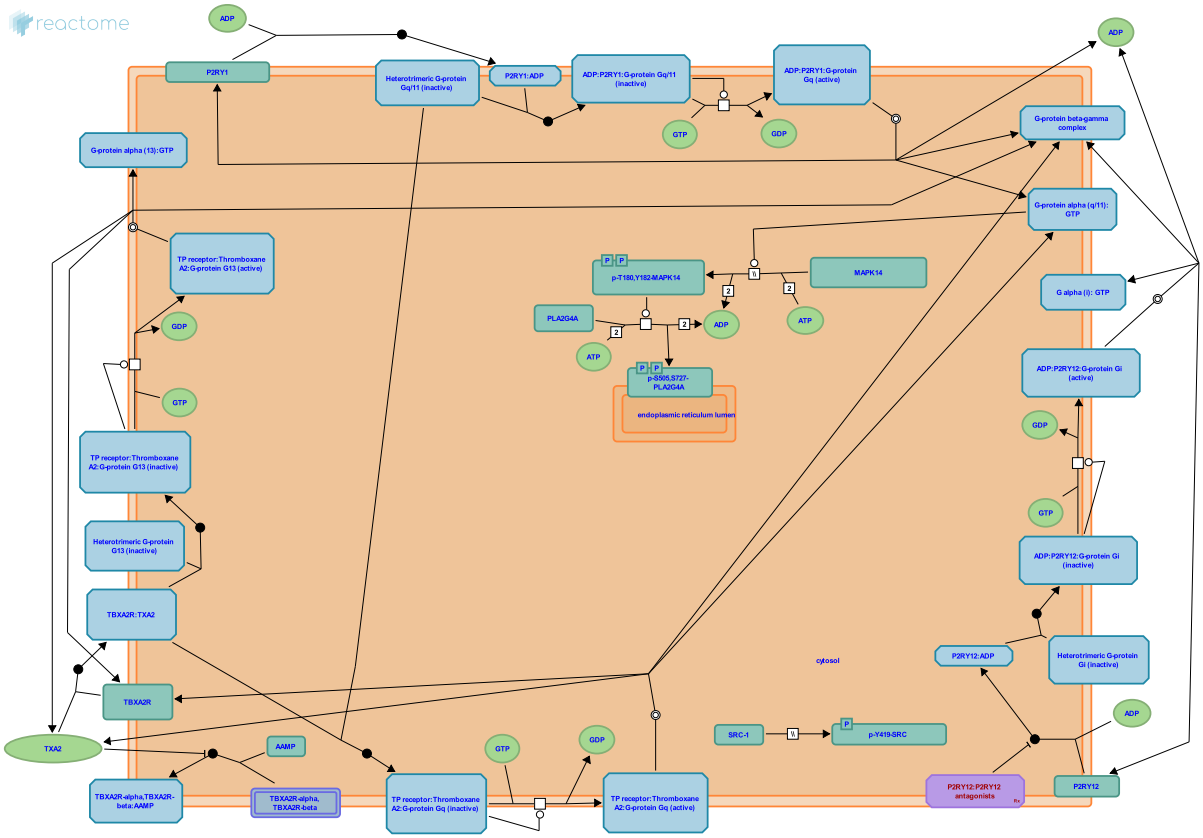
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 90

This document contains 4 pathways (see Table of Contents)

Signal amplification ↗

Stable identifier: R-HSA-392518



In the initial response to injury, platelets adhere to damaged blood vessels, responding to the exposure of collagen from the vascular epithelium. Once adhered they degranulate, releasing stored secondary agents such as ADP and ATP, and synthesized thromboxane A2. These amplify the response, activating and recruiting further platelets to the area and promoting platelet aggregation. Adenosine nucleotides secreted following platelet activation signal through P2 purinergic receptors on the platelet membrane. ADP activates P2Y1 and P2Y12 while ATP activates the ionotropic P2X1 receptor (Kunapuli et al. 2003). Activation of these receptors initiates a complex signaling cascade that ultimately results in platelet activation and thrombus formation (Kahner et al. 2006). ADP stimulation of P2Y1 and P2Y12 involves signaling via both the alpha and gamma:beta components of the heterotrimeric G-protein (Hirsch et al. 2001, 2006).

Literature references

Patrono, C., Davì, G. (2007). Platelet activation and atherothrombosis. *N Engl J Med, 357*, 2482-94. ↗

Editions

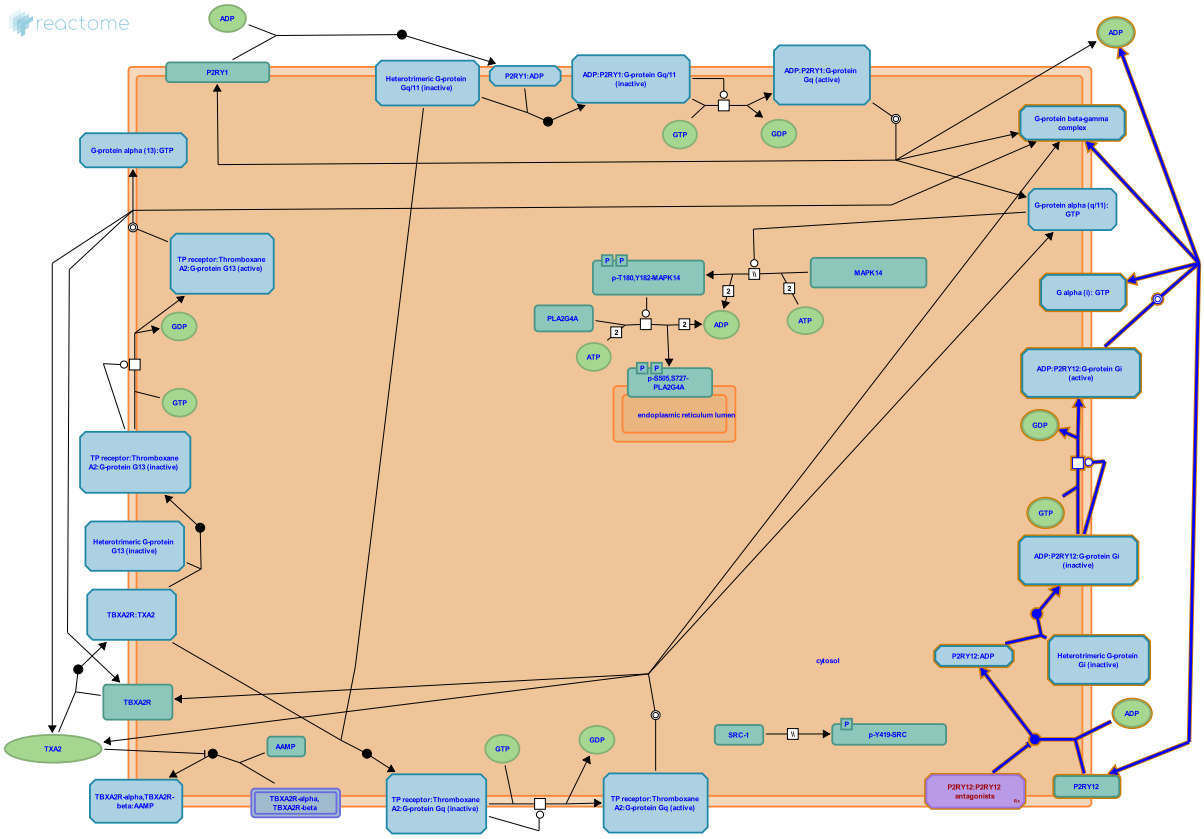
2009-06-03	Authored	Akkerman, JW.
2009-11-02	Reviewed	Poole, AW., Jones, ML., Harper, MT.
2009-11-03	Edited	Jupe, S.

ADP signalling through P2Y purinoceptor 12 ↗

Location: Signal amplification

Stable identifier: R-HSA-392170

Compartments: plasma membrane



Co-activation of P2Y1 and P2Y12 is necessary for complete platelet activation. P2Y1 is coupled to Gq and helps trigger the release of calcium from internal stores, leading to weak and reversible platelet aggregation. P2Y12 is Gi coupled, inhibiting adenylate cyclase, leading to decreased cAMP, a consequent decrease in cAMP-dependent protein kinase activity which increases cytoplasmic [Ca2+], necessary for activation (Woulfe et al. 2001).
In activated platelets, P2Y12 signaling is required for the amplification of aggregation induced by all platelet agonists including collagen, thrombin, thromboxane, adrenaline and serotonin. P2Y12 activation causes potentiation of thromboxane generation, secretion leading to irreversible platelet aggregation and thrombus stabilization.

Literature references

Vincent, D., Conley, PB., Yang, RB., Jantzen, HM., England, L., Li, G. et al. (2001). Identification of the platelet ADP receptor targeted by antithrombotic drugs. *Nature, 409*, 202-7. ↗

Editions

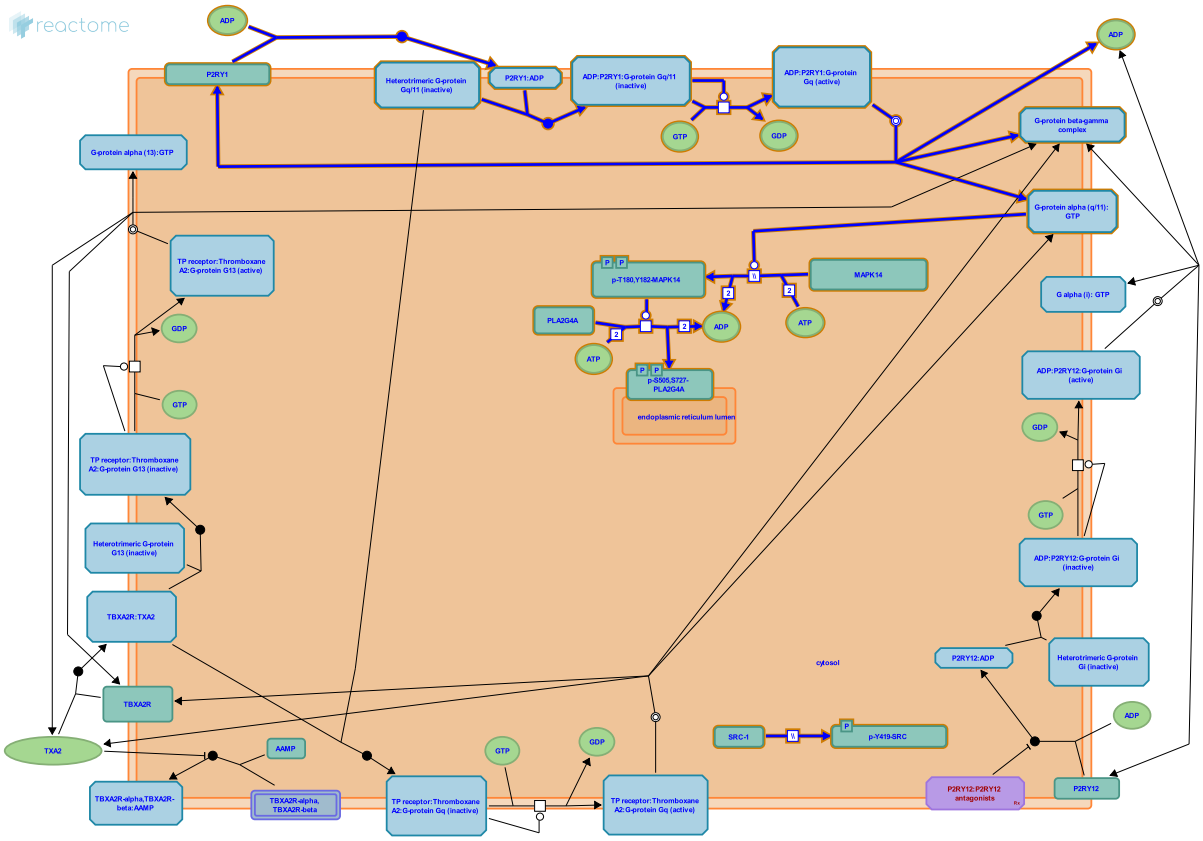
2009-02-27	Authored	Jassal, B.
2009-09-04	Reviewed	Akkerman, JW.
2009-09-10	Edited	Jupe, S.

ADP signalling through P2Y purinoceptor 1 ↗

Location: Signal amplification

Stable identifier: R-HSA-418592

Compartments: plasma membrane



Co-activation of P2Y1 and P2Y12 is necessary for complete platelet activation. P2Y1 is coupled to Gq and helps trigger the release of calcium from internal stores, leading to weak and reversible platelet aggregation. P2Y12 is Gi coupled, inhibiting adenylate cyclase, leading to decreased cAMP, a consequent decrease in cAMP-dependent protein kinase activity which increases cytoplasmic [Ca2+], necessary for activation (Woulfe et al. 2001).
In activated platelets, P2Y12 signaling is required for the amplification of aggregation induced by all platelet agonists including collagen, thrombin, thromboxane, adrenaline and serotonin. P2Y12 activation causes potentiation of thromboxane generation, secretion leading to irreversible platelet aggregation and thrombus stabilization.

Literature references

Jin, J., Kunapuli, SP., Daniel, JL. (1998). Molecular basis for ADP-induced platelet activation. II. The P2Y1 receptor mediates ADP-induced intracellular calcium mobilization and shape change in platelets. *J Biol Chem, 273*, 2030-4. ↗

Editions

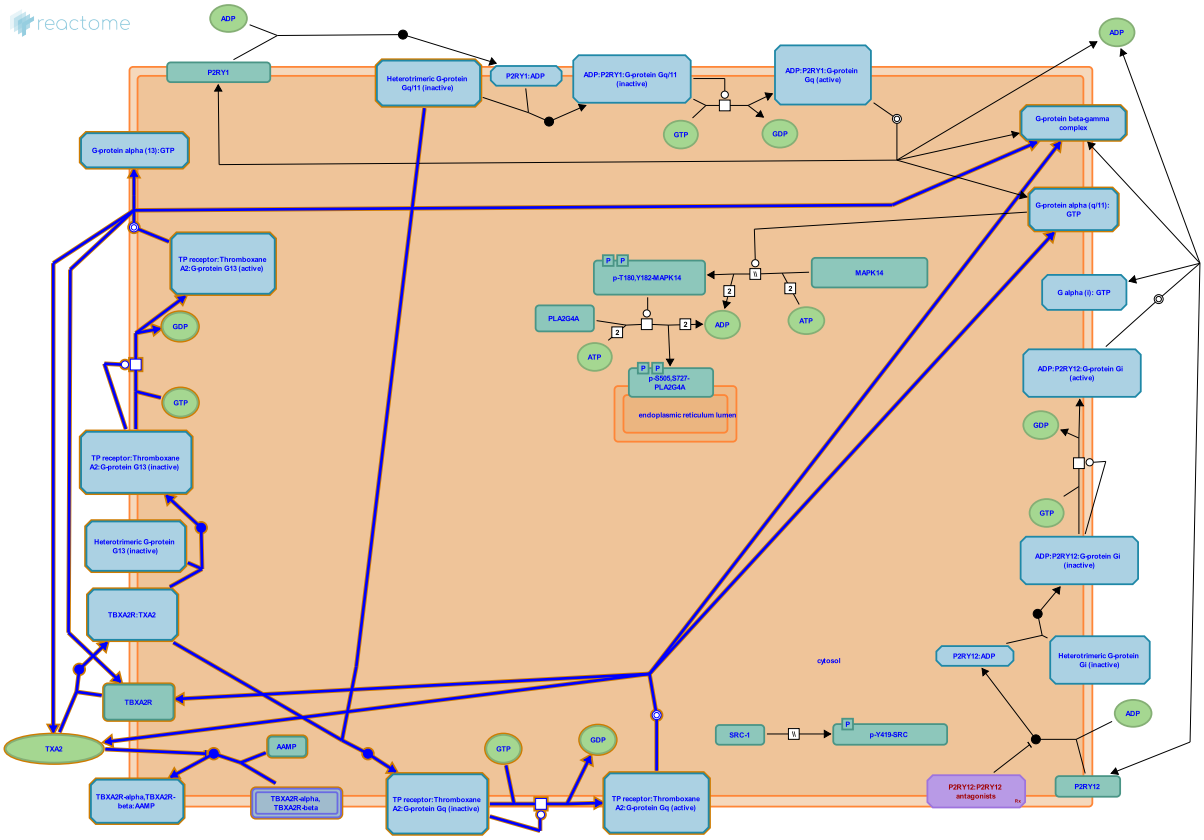
2009-04-24	Authored	Jupe, S.
2009-09-04	Reviewed	Akkerman, JW.
2009-09-10	Edited	Jupe, S.

Thromboxane signalling through TP receptor ↗

Location: Signal amplification

Stable identifier: R-HSA-428930

Compartments: plasma membrane



Thromboxane (TXA2) binds to the thromboxane receptor (TP). There are 2 splice variant forms of TP, differing in their cytoplasmic carboxyl terminal tails. TP beta was first identified in endothelial cells. TP alpha was identified in platelets and placenta. The major signalling route for TP is Gq-mediated stimulation of PLC and consequent increase in cellular calcium. TP also couples to G13, leading to stimulation of Rho and Rac.

Literature references

Nakahata, N. (2008). Thromboxane A2: physiology/pathophysiology, cellular signal transduction and pharmacology. *Pharmacol Ther, 118*, 18-35. ↗

Editions

2009-06-03	Authored	Akkerman, JW.
2009-11-02	Reviewed	Poole, AW., Jones, ML., Harper, MT.
2009-11-03	Edited	Jupe, S.

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