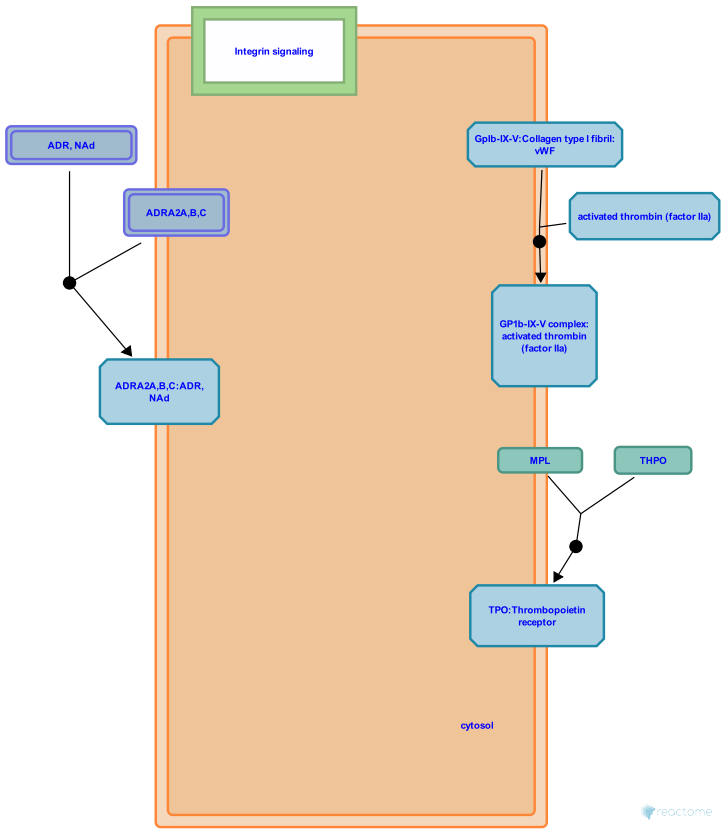
Platelet Aggregation (Plug Formation)



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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. ↗

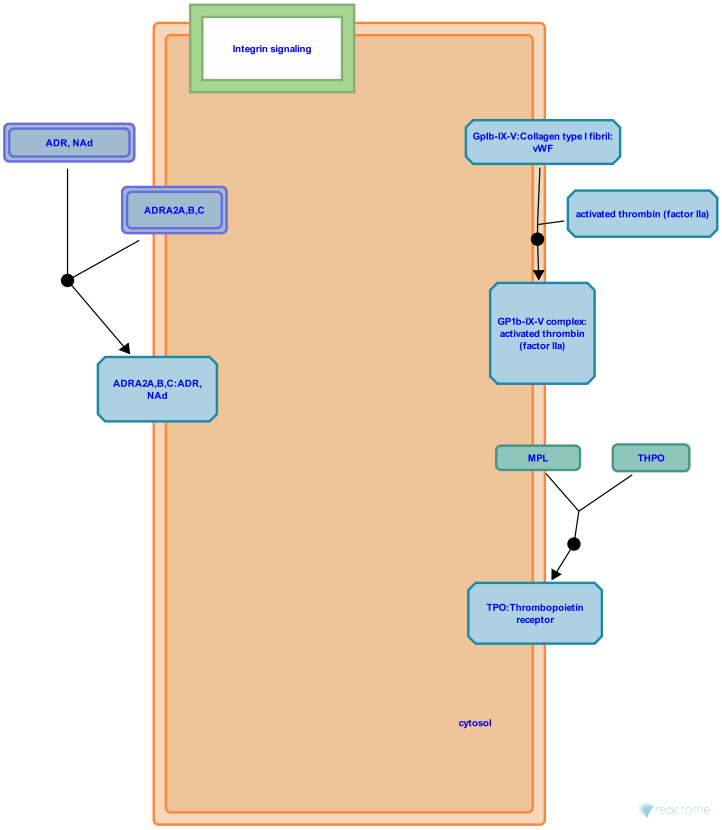
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Platelet Aggregation (Plug Formation) ↗

Stable identifier: R-HSA-76009



The tethering of platelets to the site of vascular injury is the first step in the formation of a platelet thrombus. Firm adhesion of these tethered platelets, as well as the additional recruitment of others onto their surface leads to the formation of large platelet aggregates. The formation of a thrombus is strictly dependent on the formation of interplatelet bonds.

Literature references

Varga-Szabo, D., Pleines, I., Nieswandt, B. (2008). Cell adhesion mechanisms in platelets. *Arterioscler Thromb Vasc Biol, 28*, 403-12. ↗

Ruggeri, ZM., Mendolicchio, GL. (2007). Adhesion mechanisms in platelet function. *Circ Res, 100*, 1673-85. ↗

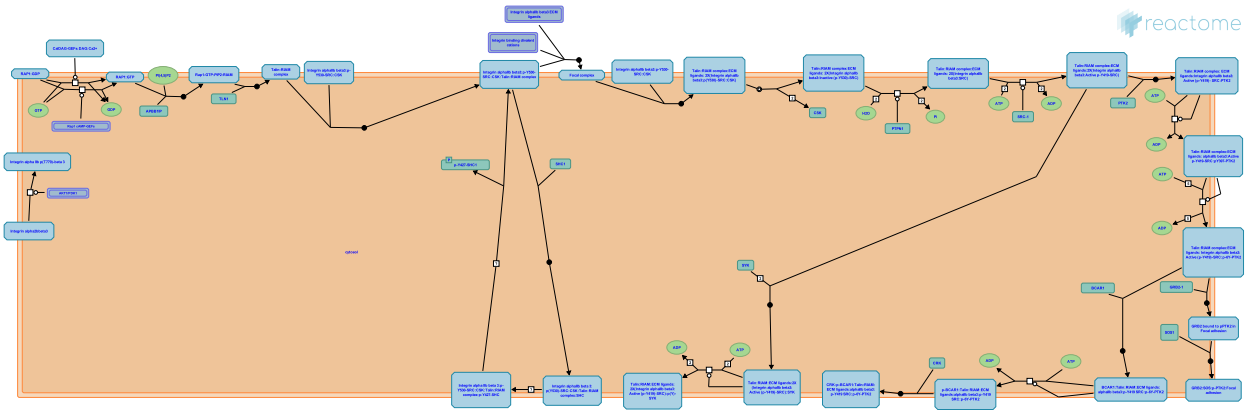
Editions

2004-08-13	Authored	de Bono, B.

Integrin signaling ↗

Location: Platelet Aggregation (Plug Formation)

Stable identifier: R-HSA-354192



Integrins are a major family of cell surface receptors that modulate cell adhesion, migration, proliferation and survival through interaction with the extracellular matrix (ECM) and the actin cytoskeleton. Integrins are type 1 transmembrane proteins that exist at the cell surface as heterodimers of alpha and beta subunits, of which there are 18 and 8 different isoforms, respectively, in human cells. In addition to their mechanical role in mediating contact between the ECM and the cytoskeleton, integrins also modulate intracellular signaling pathways governing cytoskeletal rearrangements and pro-survival and mitogenic signaling (reviewed in Hehlgans et al, 2007; Harburger and Calderwood, 2009; Ata and Antonescu, 2017).

In this pathway, we describe signaling through integrin alphaIIb beta3 as a representative example.

At the sites of vascular injury bioactive molecules such as thrombin, ADP, collagen, fibrinogen and thrombospondin are generated, secreted or exposed. These stimuli activate platelets, converting the major platelet integrin alphaIIbbeta3 from a resting state to an active conformation, in a process termed integrin priming or 'inside-out signalling'. Integrin activation refers to the change required to enhance ligand-binding activity. The activated alphaIIbbeta3 interacts with the fibrinogen and links platelets together in an aggregate to form a platelet plug. AlphaIIbbeta3 bound to fibrin generates more intracellular signals (outside-in signalling), causing further platelet activation and platelet-plug retraction.

In the resting state the alpha and beta tails are close together. This interaction keeps the membrane proximal regions in a bent conformation that maintains alphaIIbbeta3 in a low affinity state.

Integrin alphaIIbbeta3 is released from its inactive state by interaction with the protein talin. Talin interacts with the beta3 cytoplasmic domain and disrupts the salt bridge between the alpha and beta chains. This separation in the cytoplasmic regions triggers the conformational change in the extracellular domain that increases its affinity to fibrinogen.

Much of talin exists in an inactive cytosolic pool, and the Rap1 interacting adaptor molecule (RIAM) is implicated in talin activation and translocation to beta3 integrin cytoplasmic domain.

Literature references

Hehlgans, S., Haase, M., Cordes, N. (2007). Signalling via integrins: implications for cell survival and anticancer strategies. *Biochim Biophys Acta, 1775*, 163-80. ↗

Harburger, DS., Calderwood, DA. (2009). Integrin signalling at a glance. *J. Cell. Sci., 122*, 159-63. ↗

Ata, R., Antonescu, CN. (2017). Integrins and Cell Metabolism: An Intimate Relationship Impacting Cancer. *Int J Mol Sci, 18*. ↗

Watson, SP., Auger, JM., McCarty, OJ., Pearce, AC. (2005). GPVI and integrin alphaIIb beta3 signaling in platelets. *J Thromb Haemost, 3*, 1752-62. ↗

Kasirer-Friede, A., Kahn, ML., Shattil, SJ. (2007). Platelet integrins and immunoreceptors. *Immunol Rev, 218*, 247-64. ↗

Editions

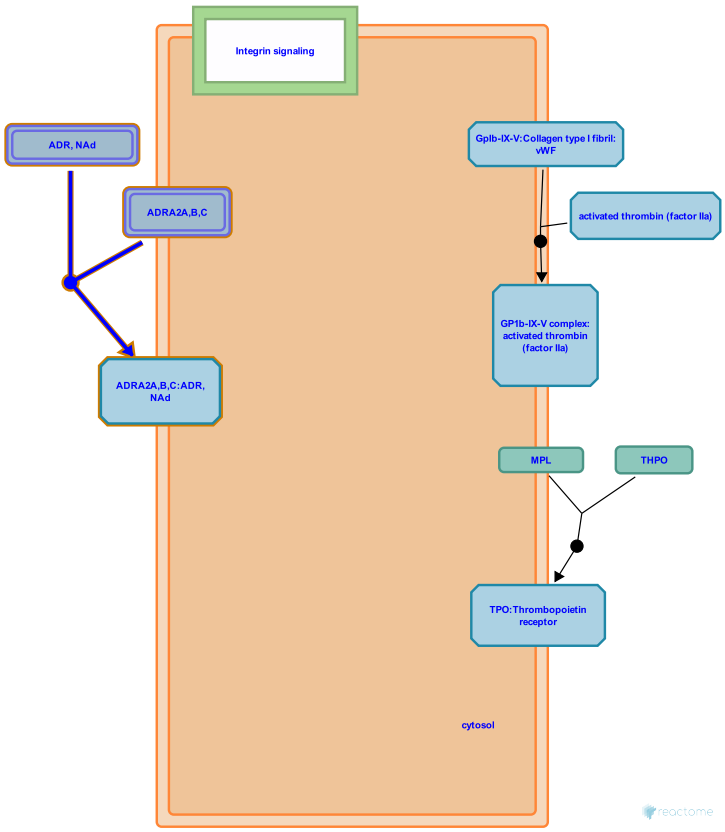
2008-06-16	Authored, Edited	Garapati, P V.
2008-09-16	Reviewed	Shattil, SJ.
2011-02-13	Revised	Garapati, P V.

Adrenaline signalling through Alpha-2 adrenergic receptor ↗

Location: Platelet Aggregation (Plug Formation)

Stable identifier: R-HSA-392023

Compartments: plasma membrane



Adrenaline (epinephrine) signalling via the alpha-2 adrenergic receptor has many effects including inhibition of insulin release in pancreas, iinduction of glucagon release from pancreas, contraction of sphincters of the gastrointestinal tract, negative feedback processes in neuronal synapses and stimulation of platelet aggregation. This receptor preferentially couples to members of the Gi class of heterotrimeric G-proteins, leading to inhibition af adenylate cyclase and thereby decreased cAMP levels.

Literature references

Kobilka, BK., Matsui, H., Kobilka, TS., Yang-Feng, TL., Francke, U., Caron, MG. et al. (1987). Cloning, sequencing, and expression of the gene coding for the human platelet alpha 2-adrenergic receptor. *Science, 238*, 650-6. ↗

Editions

2009-02-26	Authored	Jupe, S.
2009-09-04	Reviewed	Akkerman, JW.
2009-09-10	Edited	Jupe, S.

Thrombin binding to GP1b:IX:V ↗

Location: Platelet Aggregation (Plug Formation)

Stable identifier: R-HSA-429529

Type: binding

Compartments: extracellular region, plasma membrane