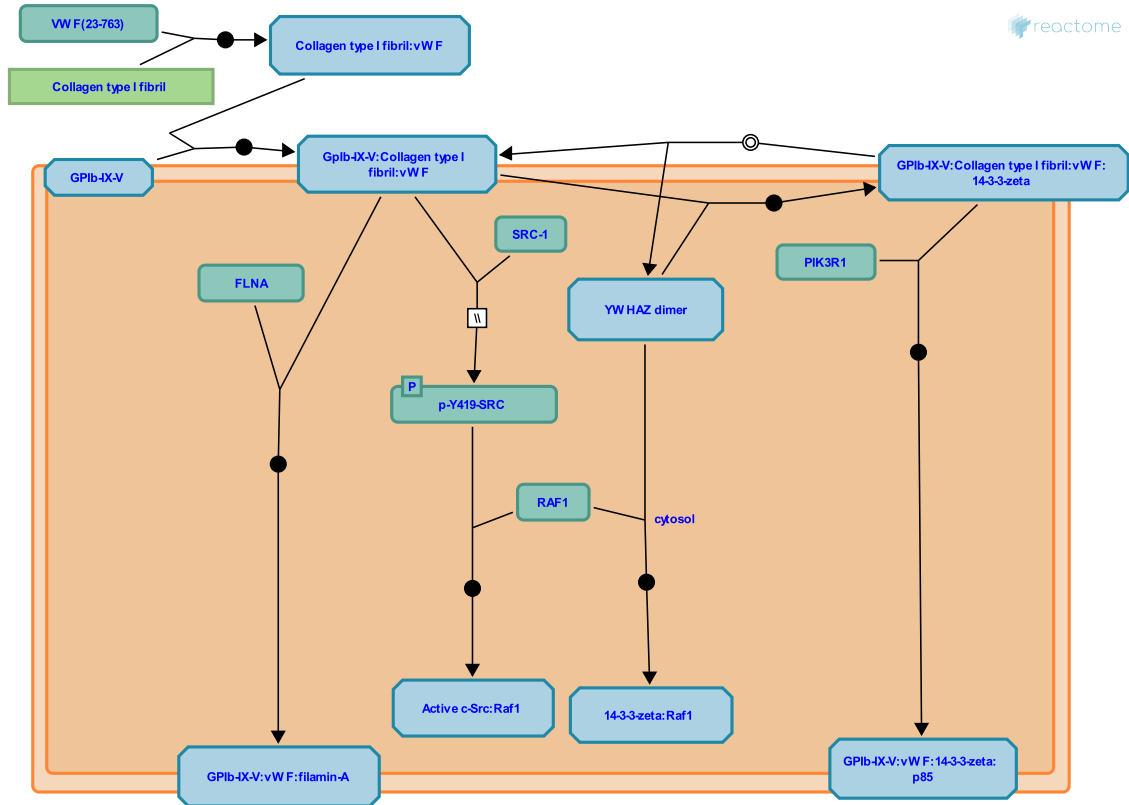


GP1b-IX-V activation signalling



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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](https://reactome.org/textbook).

30/04/2024

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.

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

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- 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. [↗](#)

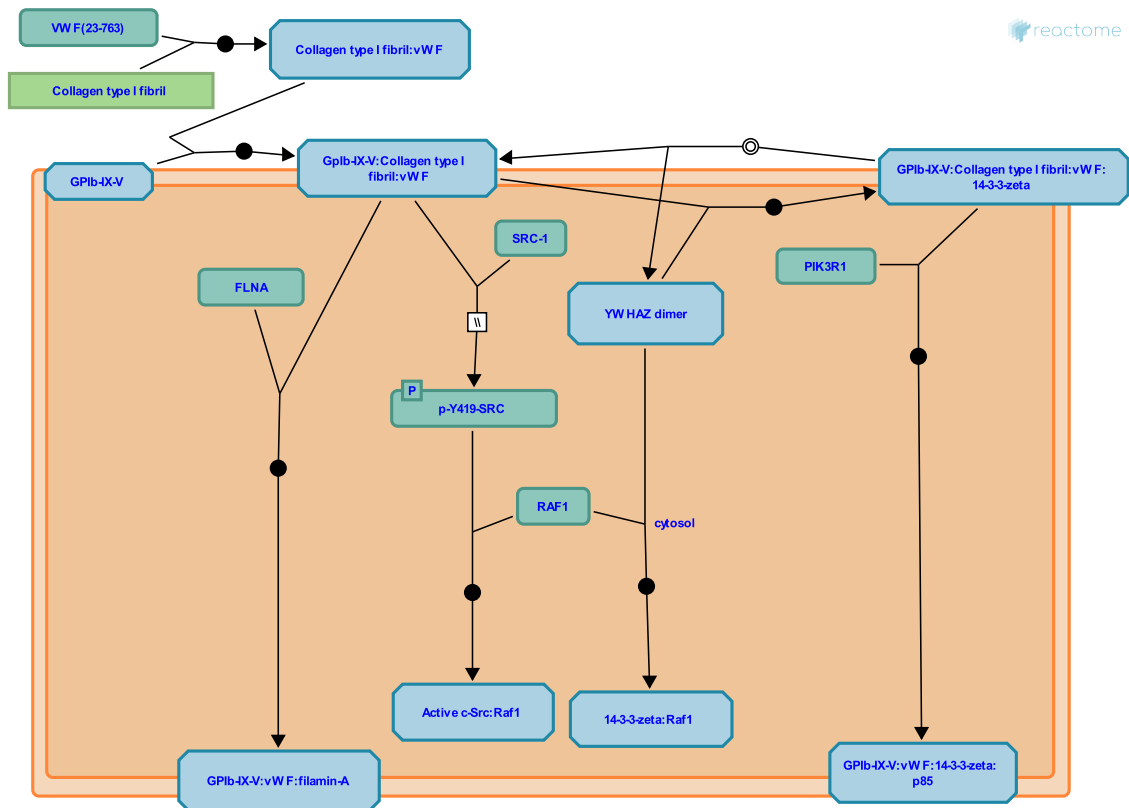
Reactome database release: 88

This document contains 1 pathway and 9 reactions ([see Table of Contents](#))

GP1b-IX-V activation signalling [↗](#)

Stable identifier: R-HSA-430116

Compartments: plasma membrane



The platelet GPIb complex (GP1b-IX-V) together with GPVI are primarily responsible for regulating the initial adhesion of platelets to the damaged blood vessel and platelet activation. The importance of GPIb is demonstrated by the bleeding problems in patients with Bernard-Soulier syndrome where this receptor is either absent or defective. GP1b-IX-V binds von Willebrand Factor (vWF) to resting platelets, particularly under conditions of high shear stress. This transient interaction is the first stage of the vascular repair process. Activation of GP1b-IX-V on exposure of the fibrous matrix following atherosclerotic plaque rupture, or in occluded arteries, is a major contributory factor leading to thrombus formation leading to heart attack or stroke. GpIb also binds thrombin (Yamamoto et al. 1986), at a site distinct from the site of vWF binding, acting as a docking site for thrombin which then activates Proteinase Activated Receptors leading to enhanced platelet activation (Dormann et al. 2000).

Literature references

Berndt, MC., Andrews, RK. (2004). Platelet physiology and thrombosis. *Thromb Res*, 114, 447-53. [↗](#)

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

Editions

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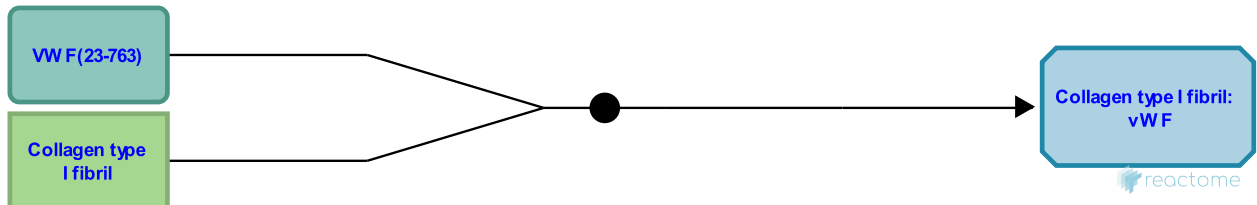
vWF binds to collagen ↗

Location: [GP1b-IX-V activation signalling](#)

Stable identifier: R-HSA-114671

Type: binding

Compartments: extracellular region



At the beginning of this reaction, 1 molecule of 'Collagen I', and 1 molecule of 'Von Willebrand factor precursor' are present. At the end of this reaction, 1 molecule of 'Collagen IV : vWF complex' is present.

Followed by: [GP1b-IX-V binds to vWF:Collagen complex](#)

Literature references

Zimmerman, TS., Weiss, HJ., Sussman, IL., Turitto, VT. (1985). Factor VIII/von Willebrand factor in subendothelium mediates platelet adhesion. *Blood*, 65, 823-31. ↗

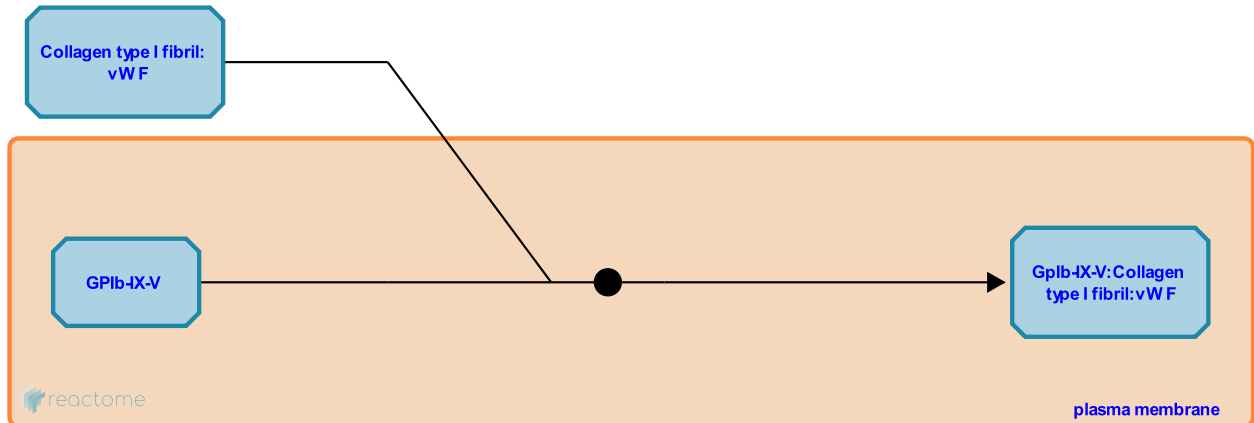
GPIb-IX-V binds to vWF:Collagen complex ↗

Location: [GPIb-IX-V activation signalling](#)

Stable identifier: R-HSA-114670

Type: binding

Compartments: plasma membrane, extracellular region



The initial tethering of platelets at sites of vascular injury is mediated by a receptor complex of glycoproteins 1b, IX and V (GPIb:IX:V - frequently referred to as the GPIb receptor). The GPIb component binds to von Willebrand factor (VWF) complexed with collagen exposed in vascular epithelium following injury. In conditions of high shear stress, when a blood vessel is partially blocked, VWF can bind to GPIb:V:IX in absence of collagen, a major factor in heart attack and stroke. GPIb:IX:V interaction with VWF:collagen potentiates the binding of platelet-associated integrin $\alpha IIb\beta 3$ to VWF and fibrinogen, triggering stable platelet adhesion and generation of further signals that lead to platelet aggregation.

Preceded by: [vWF binds to collagen](#)

Followed by: [GPIb signaling involves c-Src](#), [GPIb-IX-V binds filamin](#), [GPIb-IX-V binds 14-3-3-zeta](#)

Literature references

Schafer, AI., Handin, RI., Kroll, MH., Moake, JL., Harris, TS. (1991). von Willebrand factor binding to platelet GpIb initiates signals for platelet activation. *J Clin Invest*, 88, 1568-73. ↗

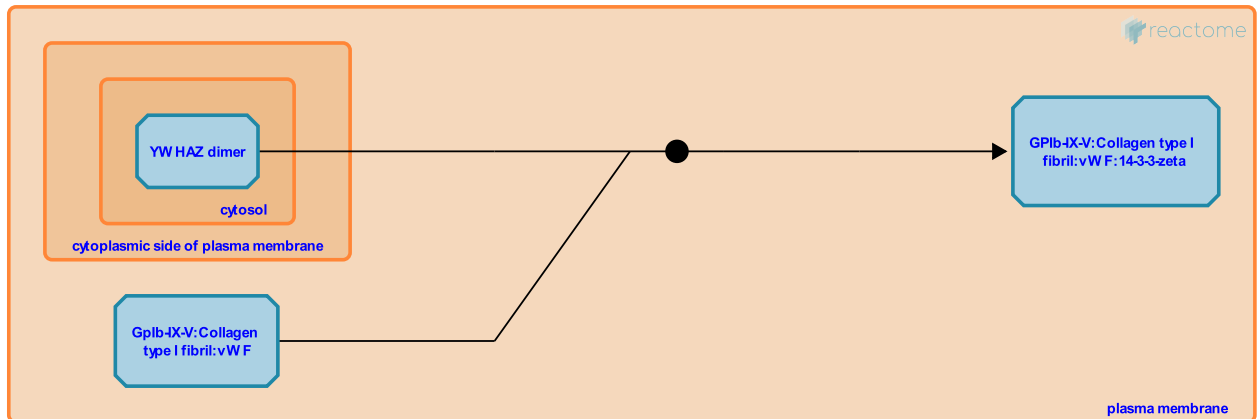
GP1b-IX-V binds 14-3-3-zeta [↗](#)

Location: [GP1b-IX-V activation signalling](#)

Stable identifier: R-HSA-430076

Type: binding

Compartments: plasma membrane, cytosol



The Gp1b-IX-V complex binds to 14-3-3-zeta, a scaffolding protein. The highly conserved cytoplasmic domain of Gp1b alpha binds directly to dimeric 14-3-3 zeta adapter protein. Binding also involves regions of GpV, and is enhanced by phosphorylation of GP1b at Ser-609 or Ser-166 of Gp1b alpha and beta respectively. For Gp1b beta this phosphorylation is PKA-dependent.

Preceded by: [GPIb-IX-V binds to vWF:Collagen complex](#)

Followed by: [GPIb-IX-V binding to 14-3-3 zeta is reduced by shear stress](#), [GPIb-IX-V:13-3-3-zeta complexes with p85 PI3K](#), [14-3-3-zeta binds Raf1](#)

Literature references

- Du, X., Berndt, MC., Ginsberg, MH., Harris, SJ., Tetaz, TJ. (1994). Association of a phospholipase A2 (14-3-3 protein) with the platelet glycoprotein Ib-IX complex. *J Biol Chem*, 269, 18287-90. [↗](#)
- Du, X., Fox, JE., Pei, S. (1996). Identification of a binding sequence for the 14-3-3 protein within the cytoplasmic domain of the adhesion receptor, platelet glycoprotein Ib alpha. *J Biol Chem*, 271, 7362-7. [↗](#)
- Christodoulides, N., Reséndiz, JC., Kroll, MH., Berndt, MC., Feng, S. (2000). Cytoplasmic domains of GpIbalpha and GpIbbeta regulate 14-3-3zeta binding to GpIb/IX/V. *Blood*, 95, 551-7. [↗](#)
- Berndt, MC., Andrews, RK., Harris, SJ., McNally, T. (1998). Binding of purified 14-3-3 zeta signaling protein to discrete amino acid sequences within the cytoplasmic domain of the platelet membrane glycoprotein Ib-IX-V complex. *Biochemistry*, 37, 638-47. [↗](#)

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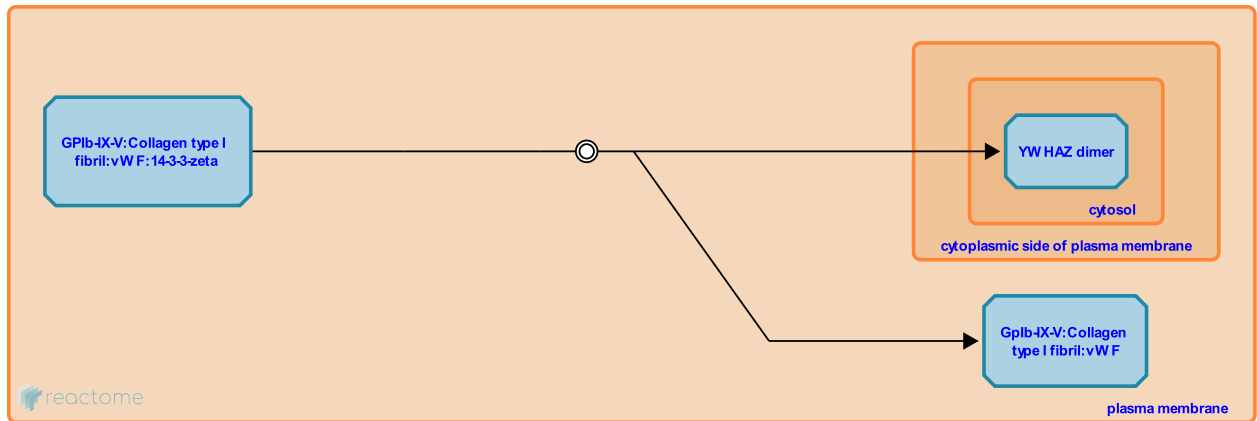
GPIb-IX-V binding to 14-3-3 zeta is reduced by shear stress ↗

Location: [GPIb-IX-V activation signalling](#)

Stable identifier: R-HSA-430073

Type: dissociation

Compartments: plasma membrane, cytosol



High shear stress, or immobilization of VWF under high shear conditions induce VWF binding to GPIb-IX-V. This activation mechanism is believed to involve shear-stress induced conformational changes in vWF.

Preceded by: [GPIb-IX-V binds 14-3-3-zeta](#)

Literature references

Araki, Y., Kawano, K., Handa, M., Anbo, H., Ikeda, Y., Kamata, T. et al. (1991). The role of von Willebrand factor and fibrinogen in platelet aggregation under varying shear stress. *J Clin Invest*, 87, 1234-40. ↗

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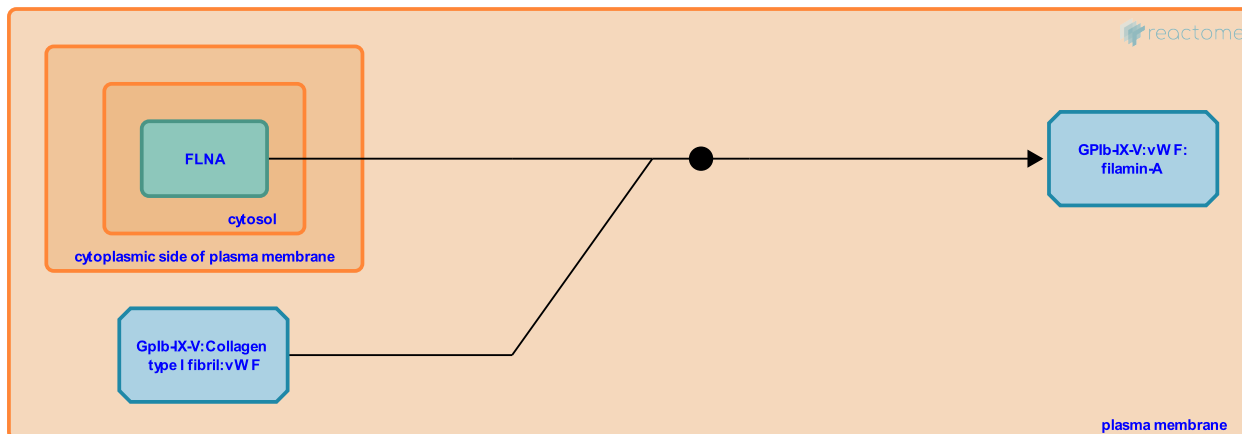
GP1b-IX-V binds filamin [↗](#)

Location: [GP1b-IX-V activation signalling](#)

Stable identifier: R-HSA-430096

Type: binding

Compartments: plasma membrane, cytosol



GP1b-IX-V interacts with filamin-1; within the cytoplasmic domain of GP1b alpha amino acids 557-568 and 569-579 are critical for this association. GPIb-filamin-1 association links the receptor complex to the membrane skeleton and has been proposed to regulate the ability of GPIb-IX-V to adhere to vWf under conditions of high shear.

Preceded by: [GPIb-IX-V binds to vWF:Collagen complex](#)

Literature references

Pidard, D., Montgomery, RR., Okita, JR., Newman, PJ., Kunicki, TJ. (1985). On the association of glycoprotein Ib and actin-binding protein in human platelets. *J Cell Biol*, 100, 317-21. [↗](#)

Domagala, T., Mistry, N., Lanza, F., Cranmer, SL., Jackson, SP., Pikovski, I. et al. (2002). Interaction between platelet glycoprotein Ibalpha and filamin-1 is essential for glycoprotein Ib/IX receptor anchorage at high shear. *J Biol Chem*, 277, 2151-9. [↗](#)

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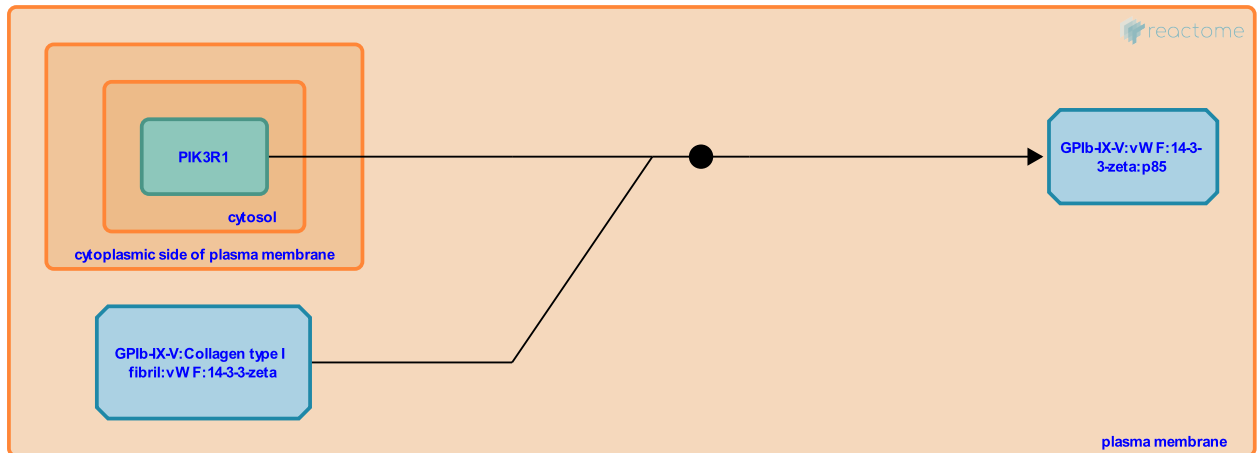
GP1b-IX-V:13-3-3-zeta complexes with p85 PI3K [↗](#)

Location: [GP1b-IX-V activation signalling](#)

Stable identifier: R-HSA-443402

Type: binding

Compartments: plasma membrane, cytosol



Resting platelets contain a heterotrimeric complex of GPIb-IX-V, 14-3-3-zeta and the p85 subunit of PI-3K. While GPIb-IX-V has no apparent binding sites for PI3K so the interaction with p85 is likely to be mediated by 14-3-3-zeta.

Preceded by: [GP1b-IX-V binds 14-3-3-zeta](#)

Literature references

Berndt, MC., Munday, AD., Mitchell, CA. (2000). Phosphoinositide 3-kinase forms a complex with platelet membrane glycoprotein Ib-IX-V complex and 14-3-3zeta. *Blood*, 96, 577-84. [↗](#)

Editions

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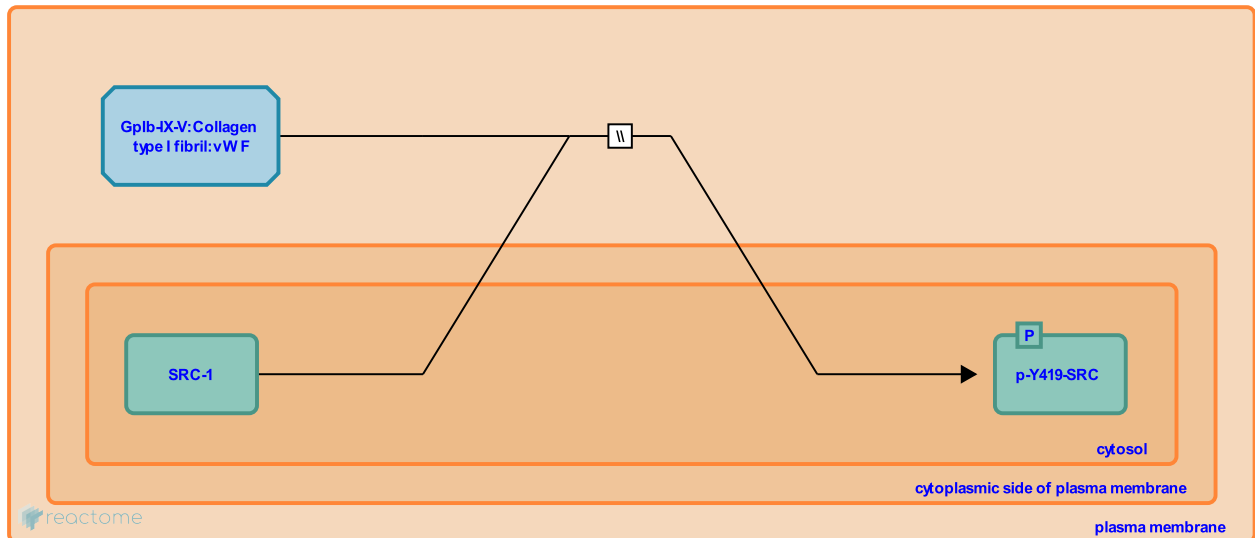
GP1b signaling involves c-Src ↗

Location: [GP1b-IX-V activation signalling](#)

Stable identifier: R-HSA-443418

Type: omitted

Compartments: plasma membrane



Src and its downstream signaling molecule PLC gamma 2 are implicated in GPIb-IX-V (GPIbR) signalling. GPIbR-mediated platelet activation correlates with cytoskeletal association of Src, activation of PI3K and the appearance of multiple tyrosine-phosphorylated proteins (Jackson et al. 1994). von Willebrand Factor (vWF) and the vWF modulator botrocetin induce tyrosine phosphorylation of FcεRIγ, Syk, LAT and PLCγ2. Src kinase inhibition markedly suppresses these events (Wu et al. 2001). Src and Lyn form a complex with FcεRIγ and Syk upon GPIbR/vWF interaction (Wu et al. 2003). FcγRIIIa was tyrosine phosphorylated upon vWF and ristocetin-induced-platelet activation, followed by Syk and PLCγ2 activation. A selective Src kinase inhibitor inhibited these events (Torti et al. 1994).

Though a considerable body of evidence suggests Src as a signaling molecule downstream of GPIbR the mechanism that connects Src to GPIbR is not clear. There are obvious similarities with the GPIV signal transduction pathway but also important differences: Src appears to be recruited to GPIbR upon platelet activation, while Lyn and Fyn constitutively associate with GPVI; GPVI activation induces a robust level of inositol phosphate production and PLCγ2 activity, while GPIbR activation PLCγ2 activation is modest and the tyrosine phosphorylation sites of PLCγ2 are distinct from those of GPVI stimulation (Suzuki-Inoue et al. 2004). GPVI signalling requires the FcεRIγ chain while mouse knockouts suggest it is not required for GPIbR signalling (Kaiser-Friede et al. 2004).

Studies on GPIbα transgenic mice suggested that GPIbR activates AlphaIIbBeta3 Integrin through Src and PLC gamma2 activation (Kaiser-Friede et al. 2004). An alternative suggested mechanism is indirect association via 14-3-3-zeta and the p85 subunit of PI3K; the p85 subunit of PI3K constitutively associates with GPIbR so upon vWF/GPIb-IX-V interaction can bind Src via its SH3 domain (Wu et al. 2003).

Although many studies support a role for Src signaling in vWF/GPIb induced platelet activation, Src-independent platelet activation has been reported for platelets spreading on surfaces coated with echicetin, a GPIb-cross-linking component of snake venom (Navdaev & Clemetson, 2002).

Preceded by: [GPIb-IX-V binds to vWF:Collagen complex](#)

Followed by: [c-Src binds Raf1](#)

Literature references

Asazuma, N., Suzuki-Inoue, K., Berndt, MC., Ozaki, Y. (2005). Platelet GPIb-IX-V-dependent signaling. *J Thromb Haemost*, 3, 1745-51. ↗

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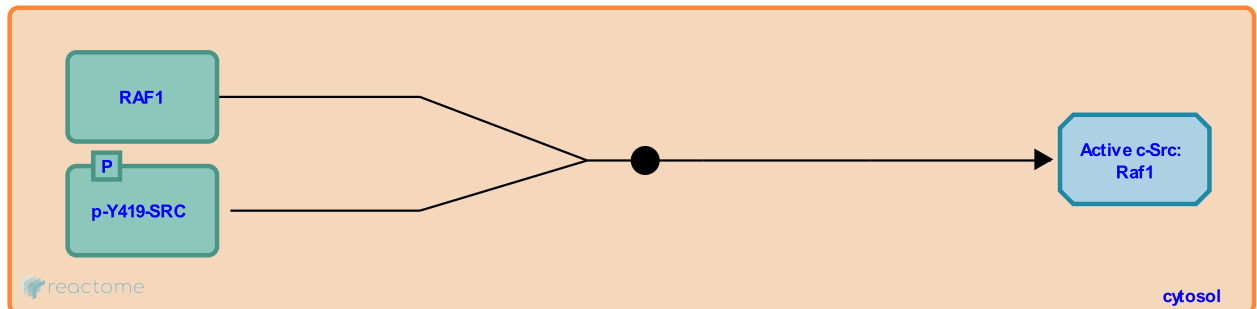
c-Src binds Raf1 [↗](#)

Location: [GP1b-IX-V activation signalling](#)

Stable identifier: R-HSA-443439

Type: binding

Compartments: cytosol



c-Src binds to Raf1, the interaction involves the SH2 and SH3 domains of c-Src and requires serine phosphorylation of Raf1. Coexpression of Raf1 and c-Src in Sf9 cells results in c-Src/Raf-1 complexes, tyrosine phosphorylation of Raf-1, and stimulation of Raf-1 kinase activity. Tyr-340 and Tyr-341 were found to be the major tyrosine phosphorylation sites of Raf1 when coexpressed with activated tyrosine kinases. However, the significance of tyrosine phosphorylation under physiological conditions remains unclear, as tyrosine phosphorylation of endogenous Raf-1 following activation has been disputed and may be limited to cells of hematopoietic origin.

Preceded by: [GP1b signaling involves c-Src](#)

Literature references

Cleghon, V., Morrison, DK. (1994). Raf-1 interacts with Fyn and Src in a non-phosphotyrosine-dependent manner. *J Biol Chem*, 269, 17749-55. [↗](#)

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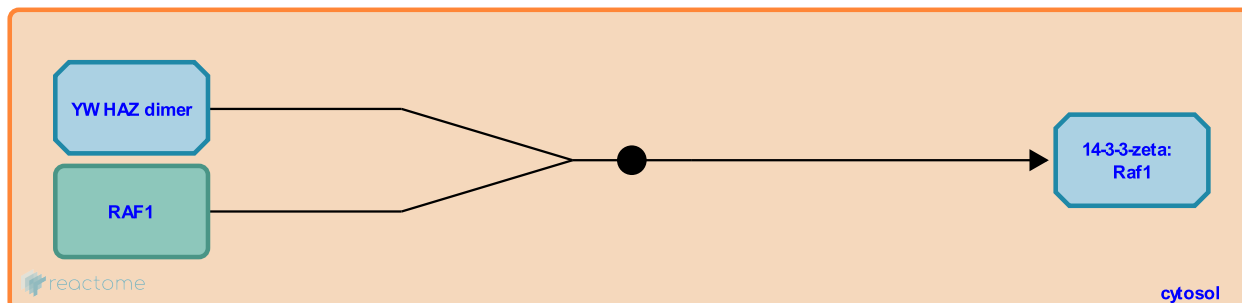
14-3-3-zeta binds Raf1 [↗](#)

Location: [GP1b-IX-V activation signalling](#)

Stable identifier: R-HSA-443831

Type: binding

Compartments: cytosol



14-3-3 family proteins can bind Raf1 and have been suggested to activate Raf1, but this has been refuted.

Preceded by: [GP1b-IX-V binds 14-3-3-zeta](#)

Literature references

Muslin, AJ., Kikuchi, A., Gross, RW., Martin, JA., Williams, LT., MacNicol, AM. et al. (1994). Activation of Raf-1 by 14-3-3 proteins. *Nature*, 371, 612-4. [↗](#)

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