



## 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. [↗](#)

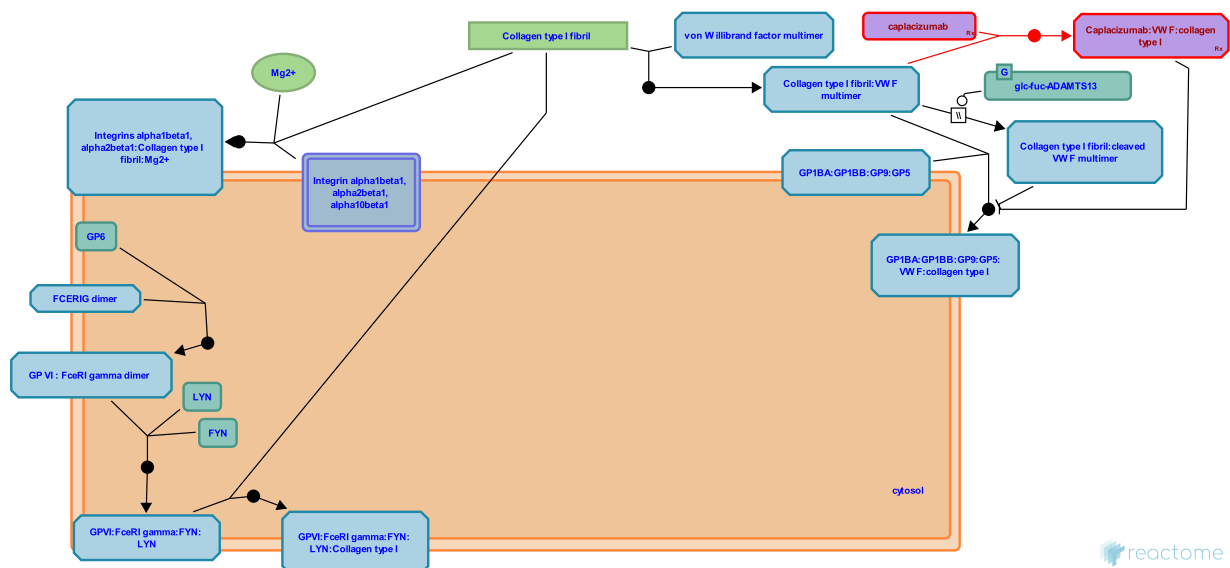
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology*, 14, e1005968. [↗](#)

Reactome database release: 88

This document contains 1 pathway and 8 reactions ([see Table of Contents](#))

## Platelet Adhesion to exposed collagen ↗

Stable identifier: R-HSA-75892



Initiation of platelet adhesion is the first step in the formation of the platelet plug. Circulating platelets are arrested and subsequently activated by exposed collagen and von Willebrand factor (VWF). It is not entirely clear which type of collagen is responsible for adhesion and activation; collagen types I and III are abundant in vascular epithelia but several other types including IV are present (Farndale RW 2006). Several collagen binding proteins are expressed on platelets, including integrin alpha2 beta1 ( $\alpha 2\beta 1$  or ITGA2:ITGB1), GPVI, and GPIV. ITGA2:ITGB1, known on leukocytes as VLA-2, is the major platelet collagen receptor (Kunicki TJ et al., 1988). ITGA2:ITGB1 ( $\alpha 2\beta 1$ ) requires  $Mg^{2+}$  to interact with collagen. The activation of ITGA2:ITGB1 ( $\alpha 2\beta 1$ ) is modulated by the activation of integrin alphaIIb beta3 ( $\alpha IIb\beta 3$  or ITGA2B:ITGB3), which functions as a platelet receptor for fibrinogen and VWF (van de Walle GR et al., 2007). The I domain of  $\alpha 2$  (ITGA2) subunit binds a collagen motif with the sequence Gly-Phe-Hyp-Gly-Glu-Arg (Emsley J et al., 2000). Binding of collagen to ITGA2:ITGB1 ( $\alpha 2\beta 1$ ) generates intracellular signals that contribute to platelet activation. These interactions facilitate the engagement of the lower-affinity collagen receptor, GPVI (Tsuji M et al., 1997), the key receptor involved in collagen-induced platelet activation. The GPVI receptor is a complex of the GPVI protein with a dimer of Fc epsilon R1 gamma (FceRI gamma). The Src family kinases Fyn and Lyn constitutively associate with the GPVI:FceRI gamma complex in platelets and initiate platelet activation through phosphorylation of the immunoreceptor tyrosine-based activation motif (ITAM) in FceRI gamma, leading to binding and activation of the tyrosine kinase Syk. Downstream of Syk, a series of adapter molecules and effectors lead to platelet activation. VWF circulates in plasma as a multimeric molecule that senses hydrodynamic shear forces in the bloodstream (Reininger AJ 2008; Mojzisch A & Brehm MA 2021). Upon vascular injury, circulating VWF binds to subendothelial collagen, which becomes exposed to the flowing blood (Bergmeier W & Hynes RO 2012; Colace TV & Diamond SL 2013). Upon binding to collagen, VWF becomes anchored to the damaged surface. Shear forces then induce conformational changes to mechanosensitive VWF causing the bound VWF to stretch and unfold (Li F et al., 2004; Schneider SW et al., 2007; Fu H et al., 2017). VWF unfolding leads to exposure of the A1 domain to allow binding to glycoprotein Ib  $\alpha$  (GPIb $\alpha$ , encoded by GP1BA), a subunit of the platelet surface GPIb:IX:V complex (Dumas JJ et al., 2004; Ju L et al., 2013). Shear-induced aggregation is achieved when VWF interacts both with exposed collagen and platelets to initiate platelet adhesion to vascular injury sites. The interaction between VWF and GPIb is regulated by shear force; an increase in the shear stress results in a corresponding increase in the affinity of VWF for GPIb.

## Literature references

- Tsuji, M., Arai, M., Ezumi, Y., Takayama, H. (1997). A novel association of Fc receptor gamma-chain with glycoprotein VI and their co-expression as a collagen receptor in human platelets. *J Biol Chem*, 272, 23528-31. ↗
- Moroi, M., Miura, Y., Takahashi, T., Jung, SM. (2002). Analysis of the interaction of platelet collagen receptor glycoprotein VI (GPVI) with collagen. A dimeric form of GPVI, but not the monomeric form, shows affinity to fibrous collagen. *J Biol Chem*, 277, 46197-204. ↗

## Editions

2004-08-13	Authored	de Bono, B.
2022-12-27	Revised	Shamovsky, V.
2023-11-07	Edited	Shamovsky, V.
2023-11-09	Reviewed	Gao, R.

# Collagen type I binds integrin alpha1beta1, alpha2beta1, alpha10beta1 ↗

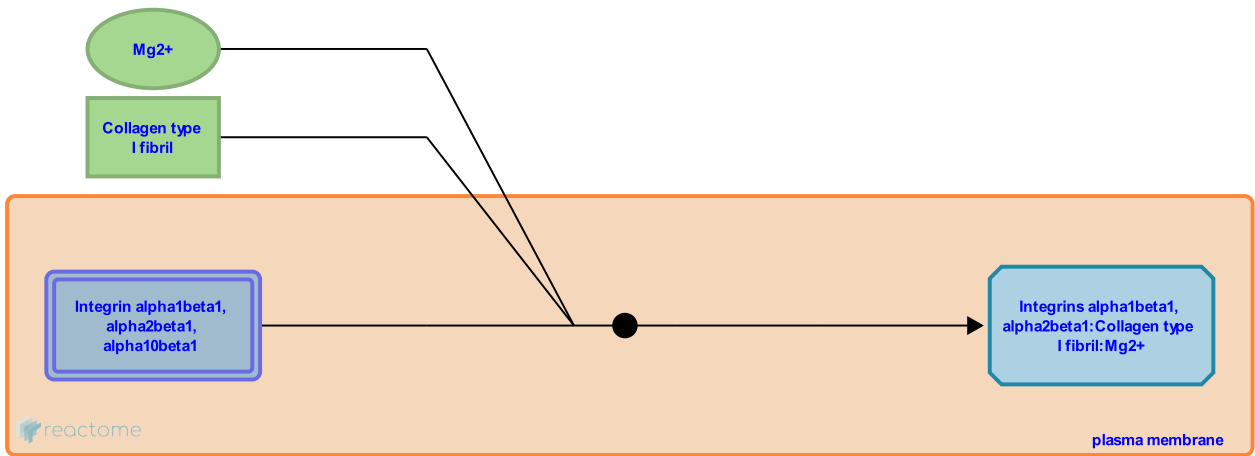
**Location:** [Platelet Adhesion to exposed collagen](#)

**Stable identifier:** R-HSA-114563

**Type:** binding

**Compartments:** plasma membrane, extracellular region

**Inferred from:** [Collagen type I binds integrin alpha1beta1, alpha2beta1, alpha10beta1 \(Homo sapiens\)](#)



Integrin alpha1beta1 binds to collagen type IV and VI with higher affinity than to types I-III, whereas alpha2beta1 has a higher affinity for collagen types I-III than for type IV. Integrin alpha10beta1 binds collagen types I, IV, and VI with similar affinities (Tulla et al. 2001). Integrin alpha11beta1 binds preferentially to the fibril-forming collagen types I and II, binding to type III is weaker and collagens IV and VI are poor ligands (Zhang et al. 2003).

Binding to collagen type I occurs at sites corresponding to the six-residue sequence G(F/L)OGER (Knight et al. 1998, 2000, Xu et al. 2000).

Integrin alpha2beta1 is the major platelet collagen receptor (Kunicki et al. 1988). It requires Mg2+ to interact with collagen and may require initiation mediated by the activation of Integrin alphaIIbBeta3 (van de Walle 2007).

## Editions

2008-05-07	Authored	Geiger, B., Horwitz, AR.
2008-05-07	Reviewed	Humphries, MJ., Yamada, KM., Hynes, R.
2013-08-13	Revised	Jupe, S.
2013-08-13	Reviewed	Ricard-Blum, S.

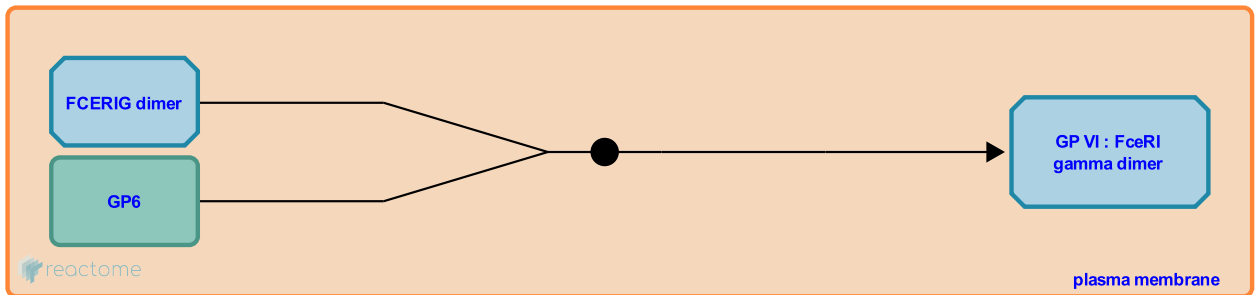
Interaction of GPVI and FceRI gamma ↗

Location: Platelet Adhesion to exposed collagen

Stable identifier: R-HSA-210282

Type: binding

Compartments: plasma membrane



Glycoprotein VI (GPVI) was identified as a collagen receptor from studies of patients with a GPVI deficiency. GPVI-deficient platelets lack collagen-induced aggregation and the ability to form thrombi on a collagen surface under flow conditions. GPVI complexes with the Fc epsilon R1 receptor gamma chain, with a possible stoichiometry of two GPVI molecules and one FceRI gamma-chain dimer (Jung & Moroi 2008). GPVI binding to FcR gamma is necessary for high affinity GPVI binding to collagen.

Followed by: GPVI binds Fyn and Lyn

Literature references

Farndale, R., Watson, SP., Gibbins, JM., Okuma, M., Barnes, M. (1997). Glycoprotein VI is the collagen receptor in platelets which underlies tyrosine phosphorylation of the Fc receptor gamma-chain. *FEBS Lett*, 413, 255-9. ↗

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

Editions

2008-02-06	Authored	de Bono, B.
2009-11-02	Reviewed	Jones, ML., Harper, MT.
2009-11-02	Edited	Jupe, S.
2009-11-02	Reviewed	Poole, AW.

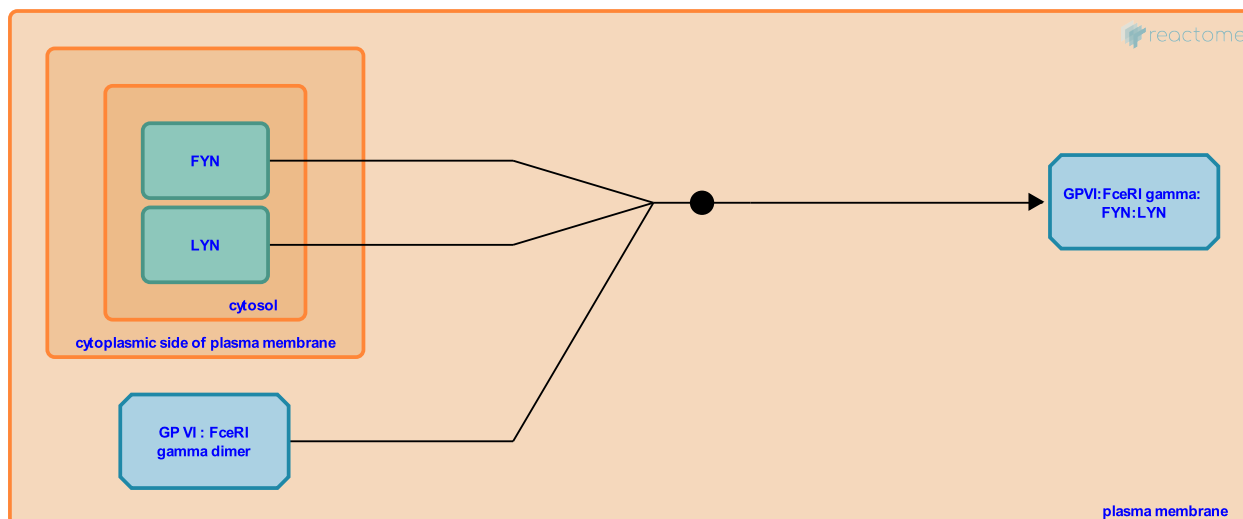
## GPVI binds Fyn and Lyn ↗

**Location:** [Platelet Adhesion to exposed collagen](#)

**Stable identifier:** R-HSA-432295

**Type:** binding

**Compartments:** plasma membrane, cytosol



Fyn and Lyn constitutively associate with GPVI-Fc epsilon R1 gamma in platelets. The proline-rich region of GPVI is required for this interaction.

**Preceded by:** [Interaction of GPVI and FcεRI gamma](#)

**Followed by:** [Binding of GPVI:Fc Epsilon R1 gamma receptor complex with collagen](#)

## Literature references

Suzuki-Inoue, K., Moroi, M., Bori-Sanz, T., Inoue, O., Berndt, MC., Watson, SP. et al. (2002). Association of Fyn and Lyn with the proline-rich domain of glycoprotein VI regulates intracellular signaling. *J Biol Chem*, 277, 21561-6. ↗

## Editions

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

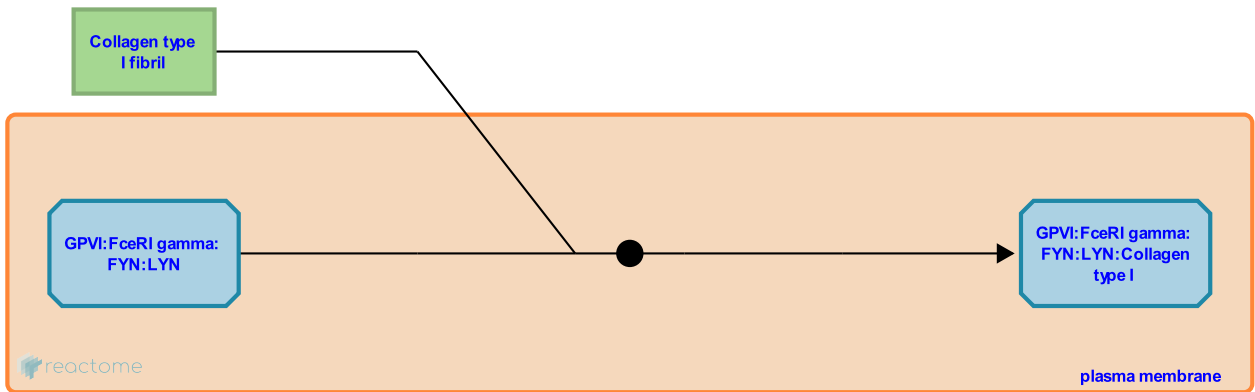
# Binding of GPVI:Fc Epsilon R1 gamma receptor complex with collagen ↗

**Location:** [Platelet Adhesion to exposed collagen](#)

**Stable identifier:** R-HSA-114577

**Type:** binding

**Compartments:** plasma membrane, extracellular region



GPVI receptor has little affinity for soluble forms of collagen but binds collagen fibrils. Recent structural models indicate that each GPVI receptor complex could bind up to 3 collagen fibrils (Jung & Moroi 2008). The Src family kinases Fyn and Lyn constitutively associate with the GPVI-Fc epsilon R1 gamma complex in platelets and initiate platelet activation through phosphorylation of the immunoreceptor tyrosine-based activation motif (ITAM) in the Fc epsilon R1 gamma chain, leading to binding and activation of the tyrosine kinase Syk. Downstream of Syk, a series of adapter molecules and effectors lead to platelet activation.

**Preceded by:** [GPVI binds Fyn and Lyn](#)

## Literature references

Tsuji, M., Arai, M., Ezumi, Y., Takayama, H. (1997). A novel association of Fc receptor gamma-chain with glycoprotein VI and their co-expression as a collagen receptor in human platelets. *J Biol Chem*, 272, 23528-31. ↗

## Editions

2007-11-12	Authored	Ouwehand, WH.
2009-11-02	Reviewed	Jones, ML., Harper, MT.
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2009-11-02	Reviewed	Poole, AW.



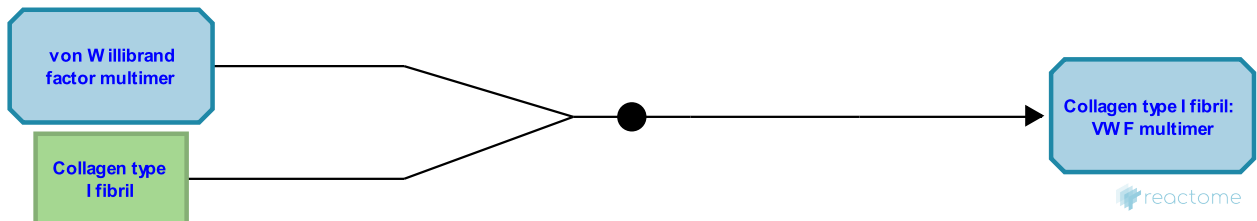
## VWF multimer binds to collagen type I ↗

**Location:** [Platelet Adhesion to exposed collagen](#)

**Stable identifier:** R-HSA-9822539

**Type:** binding

**Compartments:** extracellular region



Von Willebrand factor (VWF) is an essential component in platelet-endothelium and platelet-platelet interactions. VWF circulates in plasma as a multimeric molecule that senses hydrodynamic shear forces in the bloodstream (Reininger AJ 2008; Mojzisch A & Brehm MA 2021). Upon vascular injury, circulating VWF binds to subendothelial collagen which becomes exposed to the flowing blood (Bergmeier W & Hynes RO 2012; Colace TV & Diamond SL 2013). Structural and biochemical analysis have revealed that collagen types I and III bind to the A3 domain of VWF (Lankhof H et al., 1996; Huizinga EG et al., 1997; Romijn RA et al., 2003; Nishida N et al., 2003; Brondijk THC et al., 2012). Collagen types IV and VI interact with the A1 domain of VWF (Hoylaerts MF et al., 1997; Mazzucato M et al., 1999; Flood VH et al., 2015). Impaired binding of VWF to collagen in patients with von Willebrand disease (VWD) type 2M (Flood VH et al., 2012; Favaloro EJ 2017; 2020) is caused by missense mutations within the collagen-binding domains of VWF (Morales LD et al., 2006; Posch S et al., 2018). It is worth noting that the A1 domain of VWF, which is essential for the interaction with collagen type IV and VI, can compensate for a defective collagen binding caused by mutations in the A3 domain (Bonnefoy A et al., 2006; Posch S et al., 2018). Upon binding to collagen, VWF becomes anchored to the damaged surface. Shear forces then induce conformational changes to mechanosensitive VWF causing the bound VWF to stretch and unfold (Li F et al., 2004; Schneider SW et al., 2007; Fu H et al., 2017). VWF unfolding leads to exposure of the A1 domain to allow binding to glycoprotein Ib  $\alpha$  (GPIb $\alpha$ , encoded by GP1BA), a subunit of the platelet surface GPIb-IX-V complex (Dumas JJ et al., 2004; Ju L et al., 2013). Thus, VWF interacts both with exposed collagen and platelets to initiate platelet adhesion to vascular injury sites. Under normal physiological conditions, VWF circulates in a folded, inactive form, which does not interact with platelets due to autoinhibitory regulation (Aponte-Santamaria C et al., 2015; Butera D et al., 2018; Arce NA et al., 2021; Zhao YC et al., 2022).

This Reactome event shows interaction between VWF multimer and fibrillar collagen type I, which is one of the most abundant collagens in the human body (Shekhonin BV et al., 1987; Naomi R et al., 2021).

**Followed by:** [GPIb:IX:V binds to VWF multimer:collagen](#), [ADAMTS13 cleaves VWF multimer](#)

### Literature references

- Bracke, M., Vink, T., Schiphorst, ME., van Hoeij, M., de Groot, PG., Wu, YP. et al. (1996). A3 domain is essential for interaction of von Willebrand factor with collagen type III. *Thromb Haemost*, 75, 950-8. ↗
- Takahashi, H., Shimada, I., Terasawa, H., Shimba, N., Nishida, N., Sakakura, M. et al. (2003). Collagen-binding mode of vWF-A3 domain determined by a transferred cross-saturation experiment. *Nat Struct Biol*, 10, 53-8. ↗
- Diamond, SL., Colace, TV. (2013). Direct observation of von Willebrand factor elongation and fiber formation on collagen during acute whole blood exposure to pathological flow. *Arterioscler Thromb Vasc Biol*, 33, 105-13. ↗
- Nuyts, K., Hoylaerts, MF., Yamamoto, H., Vermynen, J., Deckmyn, H., Vreys, I. (1997). von Willebrand factor binds to native collagen VI primarily via its A1 domain. *Biochem J*, 324, 185-91. ↗
- Lenting, PJ., Bouma, B., Huizinga, EG., Sixma, JJ., Schiphorst, ME., Westein, E. et al. (2003). Mapping the collagen-binding site in the von Willebrand factor-A3 domain. *J Biol Chem*, 278, 15035-9. ↗

Editions

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2023-11-07	Edited	Shamovsky, V.

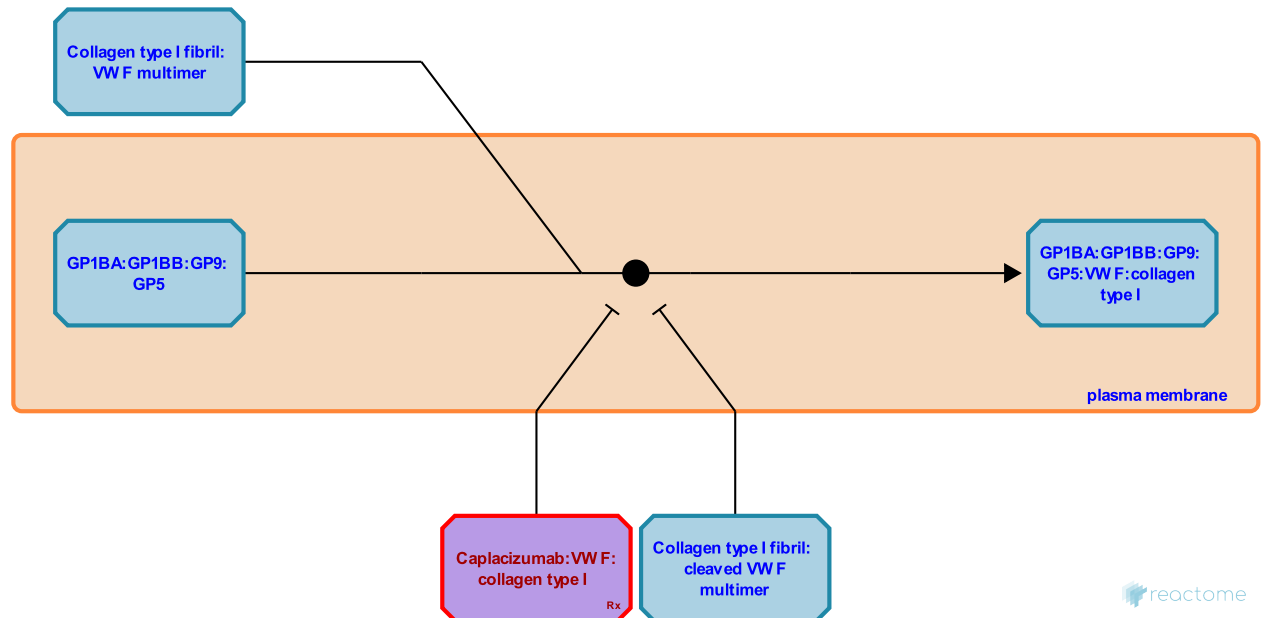
## GPIb:IX:V binds to VWF multimer:collagen ↗

**Location:** [Platelet Adhesion to exposed collagen](#)

**Stable identifier:** R-HSA-9823065

**Type:** binding

**Compartments:** plasma membrane, extracellular region



The initial tethering of platelets at sites of vascular injury is mediated by the platelet receptor complex of glycoproteins Ib $\alpha$ , IX and V (GPIb $\alpha$ :IX:V, frequently referred to as the GPIb receptor). GPIb $\alpha$ , encoded by the GP1BA gene, binds to von Willebrand factor (VWF), which is complexed with collagen exposed in vascular epithelium following injury (Mody NA & King MR 2008). Shear-induced interaction between VWF and collagen leads to exposure of the A1 domain of VWF to allow binding to GPIb $\alpha$  (Dumas JJ et al., 2004; Ju L et al., 2013). Thus, the damaged vessel wall and platelets interactions are facilitated by VWF multimer, which under normal physiological flow conditions circulates in a folded, inactive form, which does not interact with platelets due to autoinhibitory regulation (Aponte-Santamaria C et al., 2015; Butera D et al., 2018; Arce NA et al., 2021; Zhao YC et al., 2022). However, under conditions of high shear stress, when a blood vessel is partially blocked, VWF can bind to GPIb $\alpha$ :V:IX in the absence of collagen causing thrombotic diseases like heart attack and stroke (reviewed by Mehta R et al., 2019; Kozlov S et al., 2022).

This Reactome event describes GPIb $\alpha$ :IX:V interaction with VWF:collagen that potentiates the binding of platelet-associated integrin  $\alpha$ IIb $\beta$ 3 to VWF and fibrinogen, triggering stable platelet adhesion to damaged vessels and platelet activation, which results in platelet aggregation (Dumas JJ et al., 2004; Ju L et al., 2013).

ADAMTS13 downregulates VWF procoagulant activity by cleaving the peptide bond between Tyr1605 and Met1606 within the A2 domain of VWF (Crawley JTB et al., 2011).

Caplacizumab (CABLIVI®, also known as ALX-0081), is a bivalent humanized antibody fragment consisting of a single variable domain that binds the A1 domain of VWF with high affinity (Lee HT et al., 2021). Caplacizumab inhibits binding between VWF and GPIb $\alpha$ .

**Preceded by:** [VWF multimer binds to collagen type I](#)

## 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. ↗

Somers, WS., McDonagh, T., Stahl, ML., Sullivan, F., Dumas, JJ., Kumar, R. et al. (2004). Crystal structure of the wild-type von Willebrand factor A1-glycoprotein Iba $\alpha$  complex reveals conformation differences with a complex bearing von Willebrand disease mutations. *J Biol Chem*, 279, 23327-34. [↗](#)

Ju, L., Zhu, C., Cruz, MA., Dong, JF. (2013). The N-terminal flanking region of the A1 domain regulates the force-dependent binding of von Willebrand factor to platelet glycoprotein Iba. *J Biol Chem*, 288, 32289-32301. [↗](#)

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2022-12-25	Authored	Shamovsky, V.
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2023-11-07	Edited	Shamovsky, V.

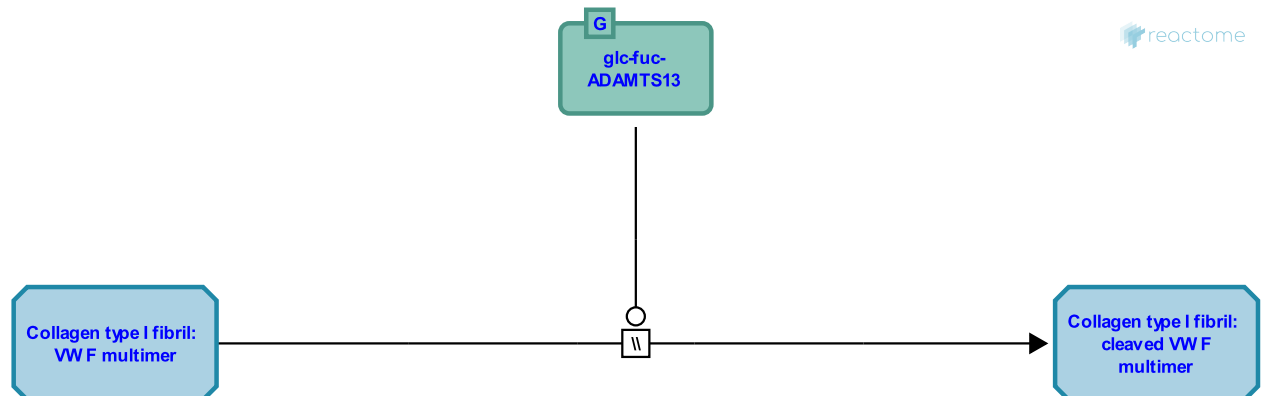
## ADAMTS13 cleaves VWF multimer ↗

**Location:** Platelet Adhesion to exposed collagen

**Stable identifier:** R-HSA-9822532

**Type:** omitted

**Compartments:** extracellular region



Von Willebrand factor (VWF) is synthesized by endothelial cells and megakaryocytes, and released as a multimeric glycoprotein into the peripheral blood stream. Ultra large VWF multimers are formed in the Golgi apparatus. In circulation, VWF senses a vessel injury and induces platelet adhesion to vascular injury sites (Reininger AJ 2008; Mojzisch A & Brehm MA 2021). VWF also functions as a carrier protein for factor VIII (FVIII), stabilizing FVIII, which otherwise has a very short half-life in the bloodstream (Kaufman RJ et al., 1997). VWF activity is dependent on its extent of multimerization, as larger VWF structures are more thrombogenic and display higher platelet tethering capacity at sites of a vascular injury. Under normal physiological conditions, ultra large VWF multimers are cleaved into smaller units by a disintegrin and metalloproteinase with thrombospondin type 1 repeats 13 (ADAMTS13) in a shear-dependent manner (Shim K et al., 2008; Zhang X et al., 2009). ADAMTS13 downregulates VWF procoagulant activity by cleaving the peptide bond between Tyr1605 and Met1606 within the A2 domain of VWF (Furlan M et al., 1996; Tsai HM 1996; Crawley JTB et al., 2011). ADAMTS13 is primarily expressed by hepatic stellate cells in the liver and is secreted into the bloodstream as an active enzyme (Zhou W et al., 2005) which circulates in its inactive (closed) conformation (South K et al., 2014; Petri A et al., 2019; Geist N et al., 2022). The closed conformation of ADAMTS13 is maintained by the interaction between the C-terminal CUB1-2 domains and the spacer domain of ADAMTS13 (South K et al., 2014; Kim HJ et al., 2021; reviewed in Ercig B et al., 2021). Structural and biochemical studies have revealed that ADAMTS13 becomes proteolytically active upon binding to its substrate, VWF (Crawley JTB et al., 2011; South K et al., 2014; Petri A et al., 2019; Geist N et al., 2022). The cleavage of VWF by ADAMTS13 is thought to occur on the surface of endothelial cells during secretion of VWF or at sites of vascular damage where VWF binds to exposed collagen and forms VWF-platelet strings (Dong JF et al., 2003; Shim K et al., 2008; Turner N et al., 2008). Cleavage of VWF multimer has also been detected in circulating blood (Majerus EM et al., 2005). Deficiency or dysfunction of ADAMTS13 has been linked to various bleeding disorders such as thrombotic thrombocytopenic purpura (TTP) (Zheng XL 2015; Sukumar S et al. 2021).

ADAMTS13 binding to VWF is controlled by the conformational changes in the mechanosensitive VWF multimer, which undergoes shear stress-induced transition from a folded, inactive conformation to an unfolded, elongated VWF multimers. In the inactive state, VWF is stabilized by autoinhibitory interdomain interactions that mask binding sites for platelets and ADAMTS13 within the A1 and A2 domain of VWF, respectively (Aponte-Santamaría C et al., 2015; Arce NA et al., 2021; Bonazza K et al., 2022; Zhao YC et al., 2022). In addition, the stability of the VWF A2 domain is maintained by the Ca<sup>2+</sup> ion-binding site (CBS) and the vicinal disulfide bond formed by Cys1669-Cys1670 within the A2 domain (Xu AJ & Springer TA 2012; Lynch CJ et al., 2014). These structural features prevent ADAMTS13-mediated cleavage of VWF (Xu AJ & Springer TA 2012; Lynch CJ et al., 2014; Aponte-Santamaría C et al., 2015; Arce NA et al., 2021; Bonazza K et al., 2022; Zhao YC et al., 2022). Shear-induced destabilization of the A2 domain of VWF results in exposing Tyr1605-Met1606 to ADAMTS13 (Zhang X et al., 2009; Baldauf C et al., 2009; Crawley JTB et al., 2011; Petri A et al., 2019). The ADAMTS13:VWF interaction involves multiple contact sites (Gao W et al., 2008; de Groot R et al., 2015; South K et al., 2017; Kretz CA et al., 2018; Petri A et al., 2019; Geist N et al., 2022; reviewed by Crawley JTB et al., 2011; DeYoung V et al., 2022). Surface plasmon resonance and equilibrium binding assays showed binding between CUB1-2 domains of ADAMTS13 and the D4-CK domain of VWR suggesting a release of the spacer domain (South K et al., 2017). Kinetic analyses of substrate proteolysis revealed that the unfolded A2 domain of VWF is recognized by exosites within the cysteine-rich and spacer domains of ADAMTS13, which conjugate VWF and ADAMTS13 in close

proximity to each other (Petri A et al., 2019). Then, interaction of the disintegrin-like domain of ADAMTS13 with VWF allosterically activates the adjacent metalloprotease domain of ADAMTS13 (Petri A et al., 2019). Structural insights further confirm the allosteric activation of ADAMTS13 induced by the multi-step VWF binding (Petri A et al., 2019; Geist N et al., 2022).

This Reactome event shows ADAMTS13-mediated cleavage of VWF between Tyr1605-Met1606.

**Preceded by:** [VWF multimer binds to collagen type I](#)

**Literature references**

Vanhoorelbeke, K., Li, C., Petri, A., Vandenbulcke, A., Emsley, J., Xu, Y. et al. (2019). Crystal structure and substrate-induced activation of ADAMTS13. *Nat Commun*, 10, 3781. [↗](#)

Sadler, JE., Wiswall, E., Shim, K., Tuley, EA., Anderson, PJ. (2008). Platelet-VWF complexes are preferred substrates of ADAMTS13 under fluid shear stress. *Blood*, 111, 651-7. [↗](#)

Springer, TA., Zhang, X., Wong, WP., Zhang, CZ., Halvorsen, K. (2009). Mechanoenzymatic cleavage of the ultralarge vascular protein von Willebrand factor. *Science*, 324, 1330-4. [↗](#)

Brehm, MA., Posch, S., Aponte-Santamaría, C., Obser, T., Bronowska, AK., Huck, V. et al. (2015). Force-sensitive autoinhibition of the von Willebrand factor is mediated by interdomain interactions. *Biophys J*, 108, 2312-21. [↗](#)

Lane, DA., Freitas, MO., South, K. (2017). A model for the conformational activation of the structurally quiescent metalloprotease ADAMTS13 by von Willebrand factor. *J Biol Chem*, 292, 5760-5769. [↗](#)

**Editions**

2022-12-25	Authored	Shamovsky, V.
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2023-11-07	Edited	Shamovsky, V.

## Caplacizumab binds VWF ↗

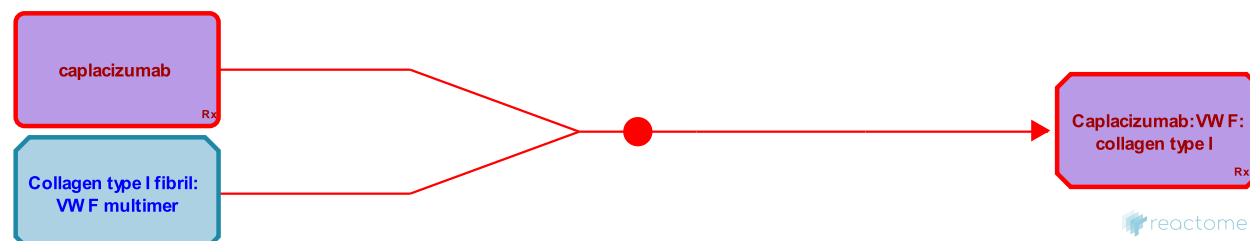
**Location:** [Platelet Adhesion to exposed collagen](#)

**Stable identifier:** R-HSA-9822734

**Type:** binding

**Compartments:** extracellular region

**Diseases:** autoimmune thrombocytopenic purpura



Caplacizumab (CABLIVI®, also known as ALX-0081) is a bivalent humanized antibody fragment consisting of a single variable domain (also called nanobody) that targets von Willebrand factor (VWF) (Ulrichs H et al., 2011; van Loon JE et al., 2011). Caplacizumab binds the A1 domain of VWF with high affinity (Ulrichs H et al., 2011; Lee HT et al., 2021). This interaction inhibits binding between VWF and the platelet glycoprotein Ib (GPIb) receptor complex preventing VWF-mediated tethering of platelets to the damaged vessel wall. Structural insights into the mechanism of action suggest that caplacizumab acts by stabilizing an inactive conformation of VWF, which does not interact with platelets, rather than competing with GPIb (Lee HT et al., 2021). Caplacizumab is the Food and Drug Administration (FDA) approved drug to treat thrombotic thrombocytopenic purpura (TTP), a clinical condition associated with immune-mediated deficiency of VWF-cleaving protease ADAMTS13 (Lämmle B 2016; Scully M et al., 2019; Hollifield AL et al., 2020; Peyvandi F et al., 2021).

## Literature references

de Groot, PG., Ulrichs, H., van Vliet, HH., de Maat, MP., van Loon, JE., Simoons, ML. et al. (2011). The in vitro effect of the new antithrombotic drug candidate ALX-0081 on blood samples of patients undergoing percutaneous coronary intervention. *Thromb Haemost*, 106, 165-71. ↗

Hollifield, AL., Moore, DC., Arnall, JR. (2020). Caplacizumab: an anti-von Willebrand factor antibody for the treatment of thrombotic thrombocytopenic purpura. *Am J Health Syst Pharm*, 77, 1201-1207. ↗

Verschueren, K., Roodt, J., Silence, K., Holz, JB., Stanssens, P., Casteels, P. et al. (2011). Antithrombotic drug candidate ALX-0081 shows superior preclinical efficacy and safety compared with currently marketed antiplatelet drugs. *Blood*, 118, 757-65. ↗

Gu, N., Jeong, TJ., Lee, HT., Kim, Y., Heo, YS., Park, UB. et al. (2021). High-resolution structure of the vWF A1 domain in complex with caplacizumab, the first nanobody-based medicine for treating acquired TTP. *Biochem Biophys Res Commun*, 567, 49-55. ↗

## Editions

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