Platelet Adhesion to exposed collagen

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21/03/2020
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


Reactome database release: 72

This document contains 1 pathway and 6 reactions (see Table of Contents)
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 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 2006). Several collagen binding proteins are expressed on platelets, including integrin alpha2 beta1, GPVI, and GPIV. Integrin alpha2 beta1, known on leukocytes as VLA-2, 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 alphaIIb beta3 (van de Walle 2007). Binding occurs via the alpha2 subunit I domain to a collagen motif with the sequence Gly-Phe-Hyp-Gly-Glu-Arg (Emsley 2000). Binding of collagen to alpha2 beta1 generates intracellular signals that contribute to platelet activation. These facilitate the engagement of the lower-affinity collagen receptor, GPVI (Keely 1996), 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:FceRIgamma 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 protein is a polymeric structure of variable size. It is secreted in two directions, by the endothelium basolaterally and into the bloodstream. Shear-induced aggregation is achieved when vWF binds via its A1 domain to GPIb (part of GPIb-IX-V), and via its A3 domain mediating collagen binding to the subendothelium. 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**


**Editions**

2004-08-13 Authored de Bono, B.
Collagen type I binds integrin alpha1beta1, alpha2beta1, alpha10beta1

**Location:** Platelet Adhesion to exposed collagen

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

**Type:** binding

**Compartments:** extracellular region, plasma membrane

**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)GER (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**

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Interaction of GPVI and FcεRI 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 FcεRI 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


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GPVI binds Fyn and Lyn

Location: Platelet Adhesion to exposed collagen

Stable identifier: R-HSA-432295

Type: binding

Compartments: cytosol, plasma membrane

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 FceRI gamma

Followed by: Binding of GPVI:Fc Epsilon R1 gamma receptor complex with collagen

Literature references


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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: extracellular region, plasma membrane

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-FceRIgamma complex in platelets and initiate platelet activation through phosphorylation of the immunoreceptor tyrosine-based activation motif (ITAM) in the FceRIgamma 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


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vWF binds to collagen

Location: Platelet Adhesion to exposed collagen

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

Literature references

GPIb-IX-V binds to vWF:Collagen complex

**Location:** Platelet Adhesion to exposed collagen

**Stable identifier:** R-HSA-114670

**Type:** binding

**Compartments:** extracellular region, plasma membrane

The initial tethering of platelets at sites of vascular injury is mediated by a receptor complex of glycoproteins 1b, IX and V (GP1b-IX-V - frequently referred to as the GPIb receptor). The GP1b 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 GP1b:V:IX in the absence of collagen, a major factor in heart attack and stroke. GPIb-IX-V interaction with vWF:collagen potentiates the ability of alphaIIb betaIII integrin to bind vWF and fibrinogen, triggering stable platelet adhesion and generation of further signals that lead to aggregation.

**Preceded by:** vWF binds to collagen

**Literature references**

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