Integrin alphaIIb beta3 signaling

Akkerman, JW., Garapati, P V., Heemskerk, JW., Jupe, S., Shattil, SJ.

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03/07/2019
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


Reactome database release: 69

This document contains 3 pathways and 19 reactions (see Table of Contents)
Integrin alphaIIb beta3 signaling

Stable identifier: R-HSA-354192

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


Editions

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Activation of Rap1 by cytosolic GEFs

Location: Integrin alphaIIb beta3 signaling

Stable identifier: R-HSA-354173

Type: transition

Compartments: cytosol, plasma membrane

Signals from agonist receptors (such as GPVI) trigger the production of PIP3, DAG, cAMP and elevated Ca++ levels. This leads to the activation and translocation of active Rap1-GTP to the plasma membrane. Rap-GEFs stimulate the replacement of GDP for GTP, activating Rap1. Several Rap1 GEFs have been identified enabling Rap1 to respond to diverse stimuli. CalDAG-GEFs activate Rap1 in response to calcium and DAG, downstream of Phospholipase C. EPAC (exchange proteins directly activated by cAMP) GEFs are activated by binding cAMP.

Followed by: Translocation of RIAM to plasma membrane

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https://reactome.org
Activation of Rap1 by membrane-associated GEFs

**Location:** Integrin alphaIIb beta3 signaling

**Stable identifier:** R-HSA-939265

**Type:** transition

**Compartments:** cytosol, plasma membrane

Signals from agonist receptors (such as GPVI) trigger the production of PIP3, DAG, cAMP and elevated Ca++ levels. This leads to the activation and translocation of active Rap1-GTP to the plasma membrane. Rap-GEFs stimulate the replacement of GDP for GTP, activating Rap1. Several Rap1 GEFs have been identified enabling Rap1 to respond to diverse stimuli. CalDAG-GEFs activate Rap1 in response to calcium and DAG, downstream of Phospholipase C. EPAC (exchange proteins directly activated by cAMP) GEFs are activated by binding cAMP.

**Followed by:** Translocation of RIAM to plasma membrane

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Translocation of RIAM to plasma membrane

**Location:** Integrin alphaIIb beta3 signaling

**Stable identifier:** R-HSA-354060

**Type:** binding

**Compartments:** cytosol, plasma membrane

Upon the production of activated Rap1A at the plasma membrane, RIAM interacts with Rap1A-GTP with its N-ter RA domain, and with its C-ter PH domain it interacts with PIP2.

**Preceded by:** Activation of Rap1 by cytosolic GEFs, Activation of Rap1 by membrane-associated GEFs

**Followed by:** Activation of Talin

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Activation of Talin

Location: Integrin alphaIIb beta3 signaling

Stable identifier: R-HSA-354097

Type: binding

Compartments: cytosol, plasma membrane

Talin is one of the major cytoskeletal proteins involved in integrin activation and linking the resulting focal adhesion (FA) with cytoskeleton. Talin comprises an N-ter head region and a flexible rod domain. The head region has the FERM domain (subdivided into F1, F2 and F3 subdomains), which has the binding sites for beta integrin cytoplasmic regions and actin binding sites close to the C-terminal rod domain.

Talin exists in closed inactive conformation, where the head region interacts with the rod domain masking the integrin binding sites. At the plasma membrane the RIAM bound to active Rap1 recruits talin to form the integrin activation complex. This interaction exposes the integrin-binding site in talin F3 domain leading to integrin activation.

Preceded by: Translocation of RIAM to plasma membrane

Followed by: Integrin alphaIIb beta3 activation

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Integrin alphaIIb beta3 activation

Location: Integrin alphaIIb beta3 signaling

Stable identifier: R-HSA-354077

Type: binding

Compartments: plasma membrane

The interaction between talin and integrin alphaIIb beta3 breaks the putative salt bridge between the alphaIIb (R995) and beta3 (D723) integrin chains and induces conformational changes in their external domains increasing their affinity for fibrinogen and other ECM ligands. Breaking of this salt bridge is necessary but not sufficient for full activation.

The Talin F3 subdomain of the FERM domain has a phosphotyrosine binding (PTB) domain fold. This domain interacts with the membrane-proximal (MP) region within the integrin beta3 chain. The primary function of this interaction is to provide an initial strong linkage between talin and integrin and this interaction holds the key to the molecular recognition required for activation. In platelets SRC kinase and its negative regulator CSK associates constitutively with integrin alphaIIbbeta3. SRC is involved in alphaIIbbeta3 dependent activation of SYK, and both SRC and SYK are required to initiate cytoskeletal events responsible for platelet spreading on fibrinogen.

Preceded by: Activation of Talin

Followed by: Interaction of integrin alphaIIb beta3 with Fibrinogen, Activated integrin alphaIIb beta3 binds SHC1

Literature references


Editions

2008-06-16 Authored, Edited Garapati, P V.
2008-09-16 Reviewed Shattil, SJ.
The overall shape of integrins is that of a globular 'head' supported by two rod like legs. The ligand-binding pocket is formed by the combination of A-domain or beta-1 domain on the beta3 subunit and the putative beta-propeller fold on the alphaIIb subunit in the head regions. The binding of ligand to integrin is also dependent on divalent cations (usually Mn++ or Mg++ or Ca++). A conserved motif, the metal ion-dependent adhesion site (MIDAS) is located in the alpha and the beta chains that coordinate the divalent cation at the top of the domain.

Active integrin alphaIIb beta3 interacts with a variety of plasma proteins such as fibrinogen, vWF, thrombin, thrombospondin, and fibronectin. The ability of alphaIIbbeta3 to bind fibrinogen plays a crucial role in platelet aggregation and hemostasis. Most of these matrix proteins have integrin binding sites of 3-6 amino acids length, of which the best known are the 'RGD' and 'KGD' motifs. The alpha and beta integrin subunits are both required for ligand binding.

**Preceded by:** Integrin alphaIIb beta3 activation

**Followed by:** Clustering of Integrin alphaIIb beta3 complexes

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The fibrinogen-bound integrin alphaIIb beta3 clusters platelets together to form a platelet plug and generates intracellular signals (outside-in) causing further platelet activation and platelet plug retraction.

Intracellular integrin alphaIIb beta3 clustering brings SRCs bound to integrin beta3 chains into proximity. SRC associates constitutively with integrin alphaIIb beta3. In unstimulated cells this SRC is inactive, auto-inhibited by an internal interaction between phosphorylated Y530 and the SH2 domain. CSK is selective for the Y530 residue and prevents access to SRC of PTP1B, a protein tyrosine phosphatase that is capable of de-phosphorylating Y530.

**Precended by:** Interaction of integrin alphaIIb beta3 with Fibrinogen

**Followed by:** Release of CSK from SRC

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Release of CSK from SRC

Location: Integrin alphaIIb beta3 signaling

Stable identifier: R-HSA-377644

Type: dissociation

Compartments: cytosol, plasma membrane

CSK bound to integrin alphaIIb beta3 negatively regulates SRC by phosphorylating the Tyr-530. Platelet adhesion to fibrinogen causes the disassociation of CSK from alphaIIb beta3 complex.

Preceded by: Clustering of Integrin alphaIIb beta3 complexes

Followed by: Dephosphorylation of inactive SRC by PTPB1

Literature references


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Dephosphorylation of inactive SRC by PTPB1

Location: Integrin alphaIIb beta3 signaling

Stable identifier: R-HSA-377643

Type: transition

Compartments: cytosol, plasma membrane

The integrin alphaIIb beta3:Inactive SRC complex recruits PTP1B protein tyrosine phosphatase resulting in the dephosphorylation of SRC tyrosine 530. The phosphorylated tail of SRC tail interacts with the SH2 domain thereby repressing kinase activity; removal of phosphorylation activates SRC kinase activity.

Preceded by: Release of CSK from SRC

Followed by: Autophosphorylation of SRC

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**Autophosphorylation of SRC**

**Location:** Integrin alphaIIb beta3 signaling

**Stable identifier:** R-HSA-377640

**Type:** transition

**Compartments:** cytosol, plasma membrane

Clustering of Integrin alphaIIb beta3 complexes results in the trans auto-phosphorylation of SRC tyrosine residue 419 (often referred to as 418 in the literature, as the initiating methionine is cleaved in the mature peptide) in SRC's kinase activation loop.

**Preceded by:** Dephosphorylation of inactive SRC by PTPB1

**Followed by:** SYK binds to integrin alphaIIb beta3, Translocation of PTK2 to Focal complexes

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Translocation of PTK2 to Focal complexes

Location: Integrin alphaIIb beta3 signaling

Stable identifier: R-HSA-354066

Type: binding

Compartments: cytosol, plasma membrane

As integrins do not have an intrinsic catalytic activity, the signals initiated by the ECM-integrin interactions are transduced into cells through the integrin bound protein-tyrosine kinases. PTK2 (protein-tyrosine kinase 2, also known as Focal adhesion kinase 1; FADK1, FAK) is one of the protein tyrosine kinases that plays a prominent role in integrin signaling. PTK2 has been implicated in controlling cell motility and transmitting a cell survival signal from ECM.

PTK2 is recruited to sites of integrin clustering by directly binding to integrin associated c-Src.

Preceded by: Autophosphorylation of SRC

Followed by: Autophosphorylation of PTK2 at Y397

Literature references


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**Autophosphorylation of PTK2 at Y397**

**Location:** Integrin alphaIIb beta3 signaling

**Stable identifier:** R-HSA-354073

**Type:** transition

**Compartments:** cytosol, plasma membrane

The co-localization of PTK2/FAK with integrins in focal adhesions and the actin cytoskeleton is essential for the activation and phosphorylation of PTK2/FAK.

PTK2/FAK has six tyrosine phosphorylation sites and tyrosine 397 is the main auto-phosphorylation site present upstream of the kinase domain.

**Preceded by:** Translocation of PTK2 to Focal complexes

**Followed by:** Phosphorylation of pPTK2 by SRC

**Literature references**


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**Phosphorylation of pPTK2 by SRC**

**Location:** Integrin alphaIIb beta3 signaling

**Stable identifier:** R-HSA-354124

**Type:** transition

**Compartments:** cytosol, plasma membrane

The recruitment of FADK1 to active SRC leads to the efficient tyrosine phosphorylation of multiple additional sites on FADK1. SRC trans-phosphorylates FADK1 within the kinase domain activation loop (Y576 and Y577) and within the FADK1 C-terminal domain (Y861 and Y925).

**Preceded by:** Autophosphorylation of PTK2 at Y397

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Integrin signaling is linked to the MAP kinase pathway by recruiting Grb2 to the FADK1/SRC activation complex.

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p130Cas linkage to MAPK signaling for integrins

Location: Integrin alphaIIb beta3 signaling

Stable identifier: R-HSA-372708

Integrin signaling is linked to the MAP kinase pathway by recruiting p130cas and Crk to the FAK/Src activation complex.

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**Integrin alpha IIb beta3 T779 phosphorylation blocks SHC binding**

**Location:** Integrin alphaIIb beta3 signaling

**Stable identifier:** R-HSA-432110

**Type:** transition

**Compartments:** plasma membrane

The binding of SHC to integrin alpha IIb beta 3 is blocked by phosphorylation of beta 3 at Thr-779, or by substitution of this residue for Asp. PDK1 and Akt1/PKB-alpha both specifically target Thr-779 in in vitro assays.

**Followed by:** Activated integrin alphaIIb beta3 binds SHC1

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Activated integrin alphaIIb beta3 binds SHC1

**Location:** Integrin alphaIIb beta3 signaling

**Stable identifier:** R-HSA-432096

**Type:** binding

**Compartments:** cytosol, plasma membrane

The beta 3 integrin cytoplasmic tail binds SH2-containing protein (SHC), an adapter in Ras signaling. Phosphorylation of Y785 may be necessary for binding; phosphorylation of T779 inhibits SHC binding. Mice expressing a mutated beta 3 where Y773 and Y785 have been mutated to F exhibit rebleeding from tail wounds and subtle defects in clot retraction and platelet aggregation.

**Preceded by:** Integrin alpha IIb beta3 T779 phosphorylation blocks SHC binding, Integrin alphaIIb beta3 activation

**Followed by:** SHC1 bound to integrin alphaIIb beta3 is phosphorylated somehow

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**SHC1 bound to integrin alphaIIb beta3 is phosphorylated somehow**

**Location:** Integrin alphaIIb beta3 signaling

**Stable identifier:** R-HSA-443905

**Type:** uncertain

**Compartments:** plasma membrane

In a mechanism that is presumed to be analogous to signaling of SHC downstream of the insulin and TrkA receptors, SHC becomes phosphorylated and dissociates from the integrin alphaIIb beta3 complex.

**Preceded by:** Activated integrin alphaIIb beta3 binds SHC1

**Followed by:** SHC1 dissociates from integrin alphaIIb beta3

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**SHC1 dissociates from integrin alphaIIb beta3**

**Location:** Integrin alphaIIb beta3 signaling

**Stable identifier:** R-HSA-443910

**Type:** uncertain

**Compartments:** plasma membrane

In a mechanism that is presumed to be analogous to signaling of SHC downstream of the insulin and TrkA receptors, SHC becomes phosphorylated and dissociates from the integrin alphaIIb beta3 complex.

**Preceded by:** SHC1 bound to integrin alphaIIb beta3 is phosphorylated somehow

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**SYK binds to integrin alphaIIb beta3**

**Location:** Integrin alphaIIb beta3 signaling

**Stable identifier:** R-HSA-429415

**Type:** binding

**Compartments:** cytosol, plasma membrane

Integrin alphaIIb beta3 'outside-in' signalling involves multiple proteins including SRC, SYK, SLP-76 and PLCgamma2. SRC is constitutively associated with the C-terminal tail of integrin beta 3. SYK is recruited to the beta3 tail and subsequently activated by SRC.

**Preceded by:** Autophosphorylation of SRC

**Followed by:** SYK activation by SRC

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**SYK activation by SRC**

**Location:** Integrin alphaIIb beta3 signaling  

**Stable identifier:** R-HSA-429441  

**Type:** transition  

**Compartments:** cytosol, plasma membrane

SYK activation in integrin signalling is associated with increased tyrosine phosphorylation. SYK activation and phosphorylation of SYK targets can be blocked by SRC inhibitors or expression of dominant negative SRC mutants.

**Preceded by:** SYK binds to integrin alphaIIb beta3

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- Integrin alphaIIb beta3 signaling
  - Activation of Rap1 by cytosolic GEFs
  - Activation of Rap1 by membrane-associated GEFs
  - Translocation of RIAM to plasma membrane
  - Activation of Talin

- Integrin alphaIIb beta3 activation
  - Interaction of integrin alphaIIb beta3 with Fibrinogen
  - Clustering of Integrin alphaIIb beta3 complexes

- Release of CSK from SRC

- Dephosphorylation of inactive SRC by PTPB1

- Autophosphorylation of SRC

- Translocation of PTK2 to Focal complexes

- Autophosphorylation of PTK2 at Y397

- Phosphorylation of pPTK2 by SRC

- GRB2:SOS provides linkage to MAPK signaling for Integrins

- p130Cas linkage to MAPK signaling for integrins

- Integrin alpha IIb beta3 T779 phosphorylation blocks SHC binding

- Activated integrin alphaIIb beta3 binds SHC1

- SHC1 bound to integrin alphaIIb beta3 is phosphorylated somehow

- SHC1 dissociates from integrin alphaIIb beta3

- SYK binds to integrin alphaIIb beta3

- SYK activation by SRC