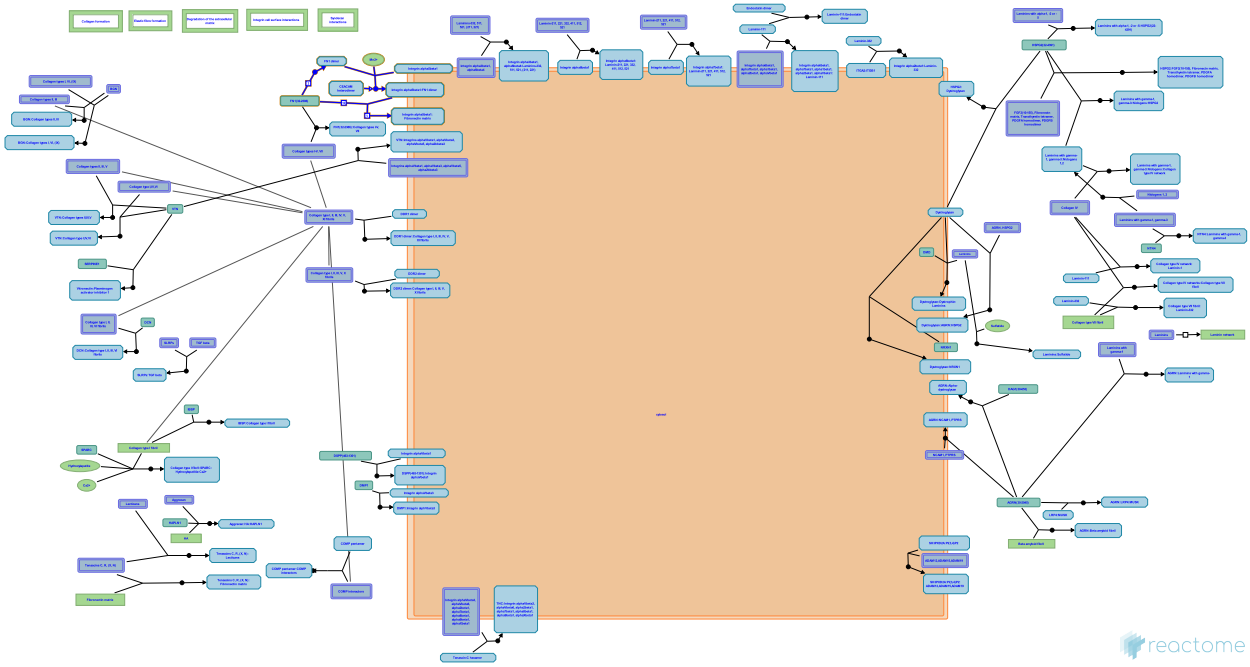
Fibronectin matrix formation



Humphries, MJ., Hynes, R., Jupe, S., Ouwehand, WH., Reinhardt, DP., Yamada, KM., Zwaginga, JJ.

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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.
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

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. ↗

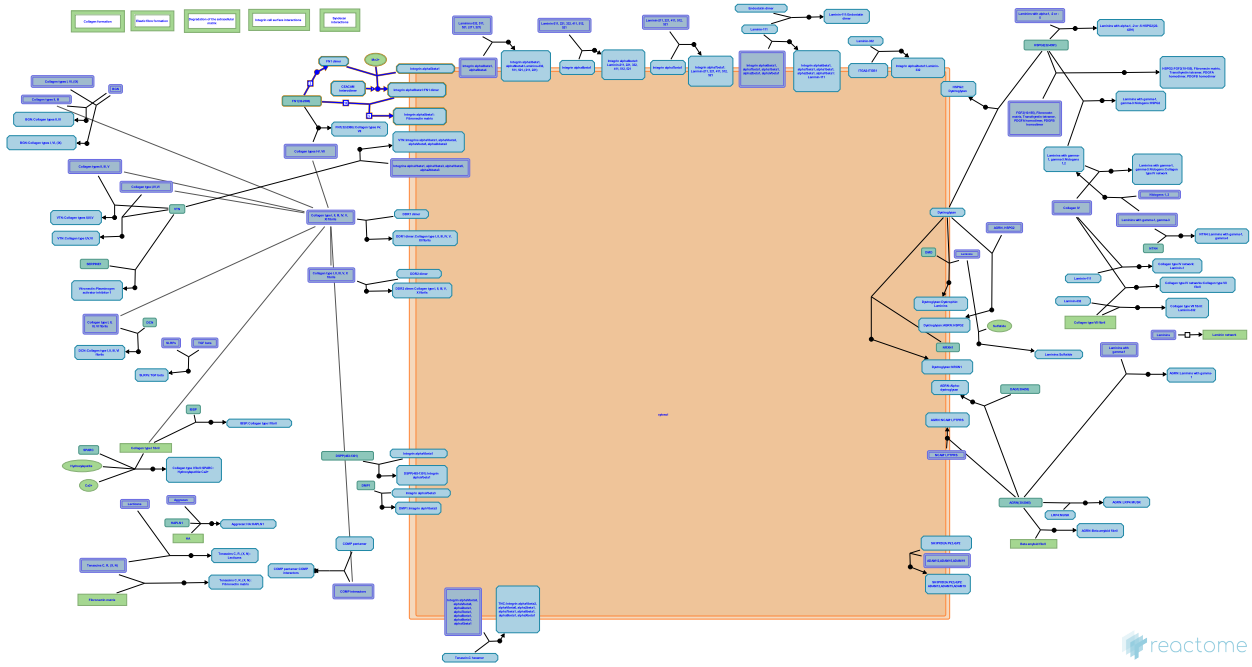
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Fibronectin matrix formation ↗

Stable identifier: R-HSA-1566977

Compartments: extracellular region



Fibronectin (FN1) is found in the extracellular matrix (ECM) of all cells as linear and branched networks that surround and connect neighbouring cells (Singh et al. 2010). Prior to matrix formation FN1 exists as a protein dimer. Often the two peptide chains represent differentially-spliced variants. The chains are linked by a pair of C-terminal disulfide bonds which are essential for subsequent multimerization (Schwarzbaur 1991). FN1 monomers have a molecular weight of 230-270 kDa depending on alternative splicing and contain three types of repeating unit, I, II, and III. I and II are stabilized by intra-chain disulfide bonds. The absence of disulfide bonds in type III modules allows them to partially unfold under applied force (Erickson 2002). Three regions of variable splicing occur along the length of the FN1 monomer (Mao & Schwarzbauer 2005). One or both of the 'extra' type III modules EIIIA and EIIIB may be present in cellular FN1, but never in plasma FN1. A variable (V) region exists between the 14th and 15th type III module. This contains the binding site for alpha4 beta1 and alpha4beta7 integrins. It is present in most cellular FN1, occasionally in plasma FN1. The modules are arranged into several functional and protein-binding domains. There are four FN1-binding domains (Mao & Schwarzbauer 2005). One of these domains (I1-5), referred to as the 'assembly domain', is required for the initiation of FN1 matrix assembly. Modules III9-10 correspond to the 'cell-binding domain' of FN1. The Arg-Gly-Asp (RGD) integrin binding sequence located in III10 is the primary site of FN1 to cell attachment, mediated predominantly by alpha5 beta1 and alphaV beta3 integrins. The 'synergy site' in III9 modulates FN1's association with alpha5 beta1 integrins. FN1 also contains interaction domains for fibrin (I1-5, I10-12), collagen (I6-9, II1-2), fibulin-1 (III13-14), heparin, syndecan (III12-14) and fibrillin-1 (I6-9) (Mao & Schwartzbauer 2005, Sabatier et al. 2009).

FN1 dimer binding to alpha5beta1 integrin stimulates self-association. Binding is thought to lead to a conformational change in FN1 that triggers the addition of further FN1 dimers (Singh et al. 2010). I1-5 functions as a unit that is the primary FN1 matrix assembly domain (Sottile et al. 1991) but other units are likely to be involved (Singh et al. 2010), the process is not fully understood.

Several ECM proteins appear to require the FN1 matrix for their own assembly. Fibrillin-1 containing microfibrils are formed when fibrillin-1 multimers bind to the FN1 matrix (Sabatier et al. 2009). FN1 polymerization promotes the deposition of type I and type III collagen (Sottile and Hocking 2002, Velling et al. 2002). Inhibition of FN1 polymerization increases its turnover and a concomitant loss of collagen types I and III from the ECM (Sottile and Hocking 2002, Sottile et al. 2007). FN1 is regulated by matrix metalloproteinases, particularly MMP14 (Shi & Sottile 2011).

Literature references

Singh, P., Schwarzbauer, JE., Carraher, C. (2010). Assembly of fibronectin extracellular matrix. *Annu. Rev. Cell Dev. Biol., 26*, 397-419. ↗

Editions

2011-07-12	Authored, Edited	Jupe, S.
2013-02-08	Reviewed	Reinhardt, DP.

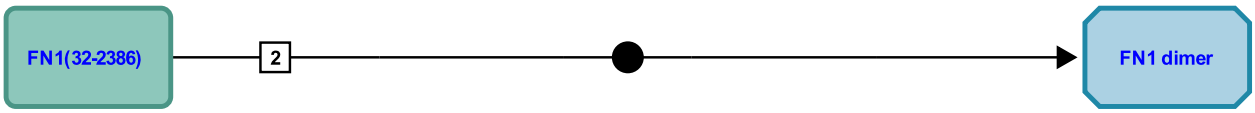
FN1 dimerizes ↗

Location: Fibronectin matrix formation

Stable identifier: R-HSA-2545196

Type: binding

Compartments: extracellular region



Prior to matrix formation, fibronectin (FN1) exists as a protein dimer. Often the two peptide chains are differentially-spliced variants. The chains are linked by a pair of C-terminal disulfide bonds which are essential for subsequent multimerization (Schwarzbaur 1991). FN1 monomers have a molecular weight of 230-270 kDa depending on the alternative splicing and contain three types of repeating domains, type I, II, and III. Type I and II domains are stabilized by intra-chain disulfide bonds. FN1 dimer binding to alpha5beta1 integrin stimulates self-association.

Followed by: Integrin alpha5beta1 binds FN1 dimer

Literature references

Schwarzbauer, JE. (1991). Identification of the fibronectin sequences required for assembly of a fibrillar matrix. *J. Cell Biol., 113*, 1463-73. ↗

Editions

2011-07-12	Authored, Edited	Jupe, S.
2013-02-08	Reviewed	Reinhardt, DP.

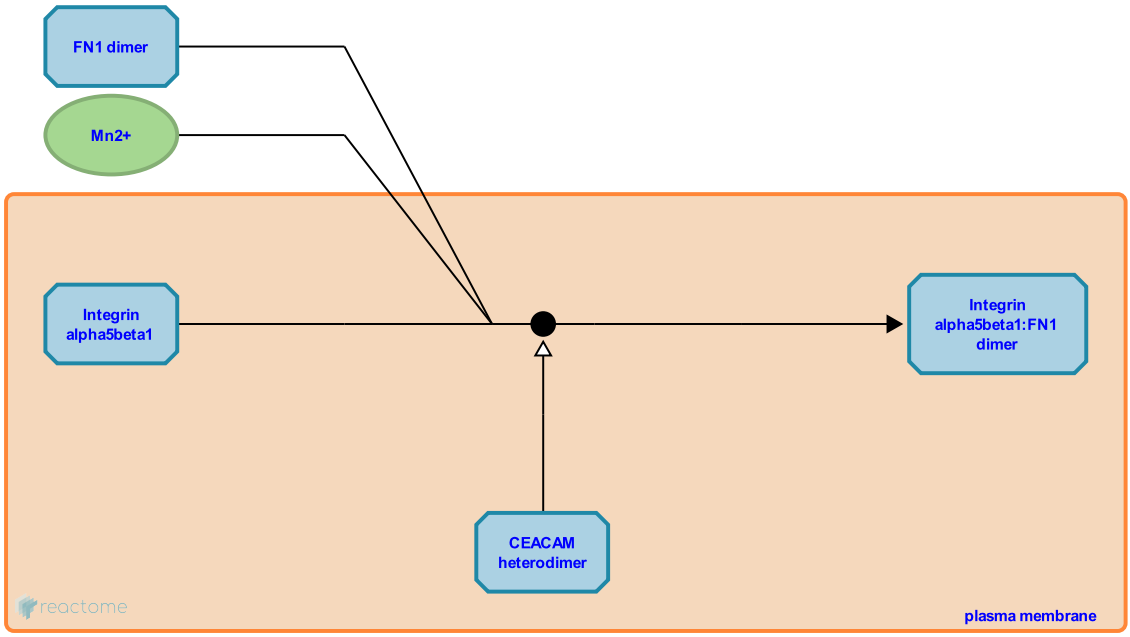
Integrin alpha5beta1 binds FN1 dimer ↗

Location: Fibronectin matrix formation

Stable identifier: R-HSA-202723

Type: binding

Compartments: plasma membrane, extracellular region



Alpha5beta1 integrin was the first integrin shown to bind fibronectin (FN1). Unlike other FN1-binding integrins it is a specialist at this task. In solution FN1 occurs as a dimer. Binding to alpha5beta1 integrin stimulates FN1 self-association; blocking the RGD-cell binding domain of FN1 blocks fibril formation (Fogerty et al. 1990). FN1 binding is believed to induce integrin clustering, which promotes FN1-FN1 interactions. Integrin clustering is mediated by association between integrins and intracellular actin stress fibers (Calderwood et al. 2000). Binding of integrins to each of the monomers in the FN1 dimer pair is thought to trigger a conformational change in FN1 that exposes 'cryptic' FN1 binding sites that allow additional fibronectin dimers to bind without the requirement for pre-association with integrins (Singh et al. 2010). This non-covalent interaction may involve interactions with fibrillin (Ohashi & Erickson 2009). I1-5 functions as a unit that is the primary FN matrix assembly domain (Sottile et al. 1991) but other units are likely to be involved (Singh et al. 2010). Other integrins able to bind FN1 include alphaIIbBeta3, which is highly expressed on platelets where it predominantly binds fibrinogen leading to thrombus formation but also binds FN1 (Savage et al. 1996). Alpha4beta1 mediates cell-cell contacts and cell-matrix contacts through the ligands VCAM-1 and FN1, respectively (Humphries et al. 1995). Integrins alpha3beta1, alpha4beta7, alphaVbeta1, 3 (Johansson et al. 1997), 6 (Busk et al. 1992) and alpha8beta1 (Muller et al. 1995, Farias et al. 2005) are all able to bind FN1.

Tenacious binding of free fibronectin to cells leads to enhanced fibronectin matrix assembly and the formation of a polymerized fibronectin "cocoon" around the cells. This process is enhanced in the presence of CEACAM molecules.

Preceded by: FN1 dimerizes

Followed by: FN1 aggregation

Literature references

Schnapp, LM., Lu, M., Farias, E., Li, X. (2005). Integrin alpha8beta1-fibronectin interactions promote cell survival via PI3 kinase pathway. *Biochem Biophys Res Commun, 329*, 305-11. ↗

Fassler, R., Brakebusch, C. (2005). beta 1 integrin function in vivo: adhesion, migration and more. *Cancer Metastasis Rev, 24*, 403-11. ↗

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Bauer, JS., Juliano, RL., Ruoslahti, E., Morla, AO., Vuori, K., Zhang, Z. (1993). The alpha v beta 1 integrin functions as a fibronectin receptor but does not support fibronectin matrix assembly and cell migration on fibronectin. *J Cell Biol, 122*, 235-42. ↗

Editions

2007-11-12	Authored	Ouwehand, WH.
2007-11-12	Reviewed	Zwaginga, JJ.
2008-05-07	Reviewed	Humphries, MJ., Yamada, KM., Hynes, R.
2010-01-21	Edited	Jupe, S.
2013-02-08	Reviewed	Reinhardt, DP.
2013-08-13	Revised	Jupe, S.

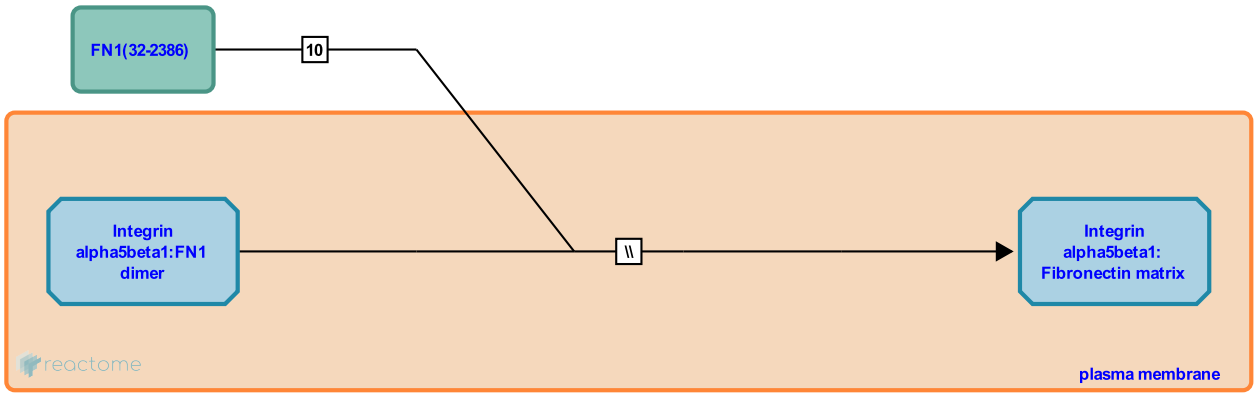
FN1 aggregation ↗

Location: Fibronectin matrix formation

Stable identifier: R-HSA-2327746

Type: omitted

Compartments: plasma membrane



The binding of integrins to each of the monomers in the FN1 dimer pair is thought to trigger a conformational change in FN1 that allows additional FN1 dimers to bind without pre-association with integrins (Singh et al. 2010). Domain I1-5 functions as the primary unit of FN1 matrix assembly (Sottile et al. 1991) but the process is not fully characterised and other FN1 units are likely to be involved (Singh et al. 2010). In this reaction an arbitrary 10 FN1 monomers are represented as being incorporated into the FN1 polymeric matrix.

Preceded by: Integrin alpha5beta1 binds FN1 dimer

Literature references

Singh, P., Schwarzbauer, JE., Carraher, C. (2010). Assembly of fibronectin extracellular matrix. *Annu. Rev. Cell Dev. Biol., 26*, 397-419. ↗

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Editions

2011-07-12	Authored, Edited	Jupe, S.
2013-02-08	Reviewed	Reinhardt, DP.

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