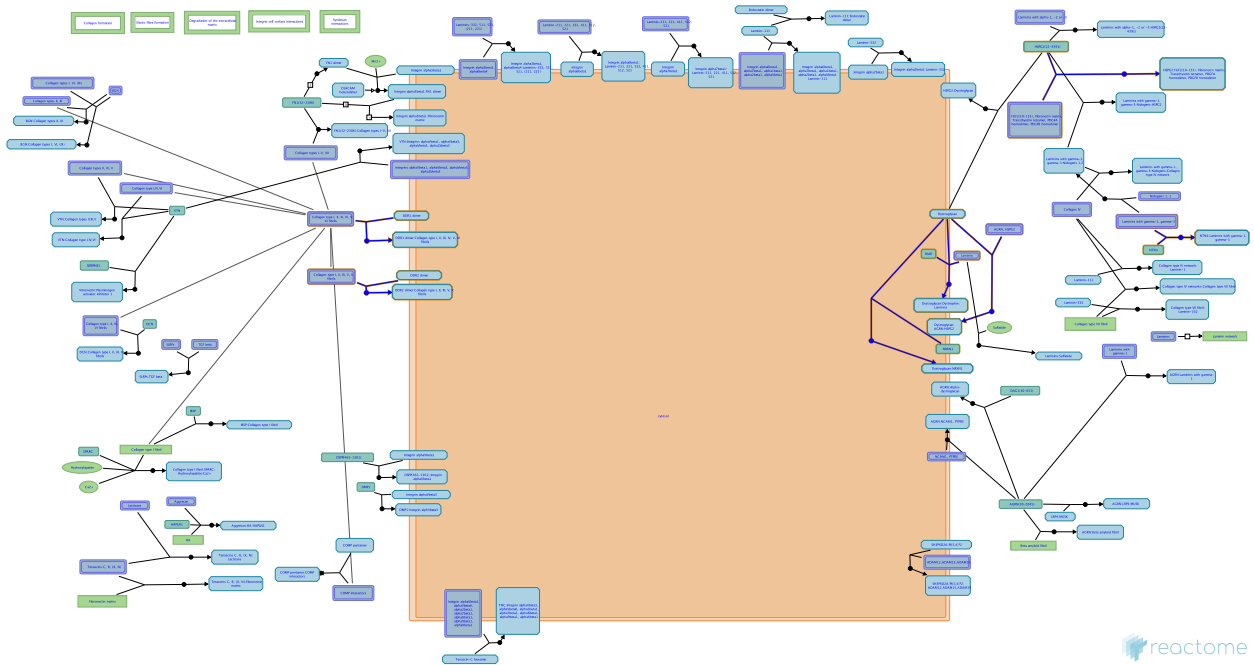


Non-integrin membrane-ECM interactions



Fuentes, J., Jupe, S., Ricard-Blum, S.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

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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.

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Literature references

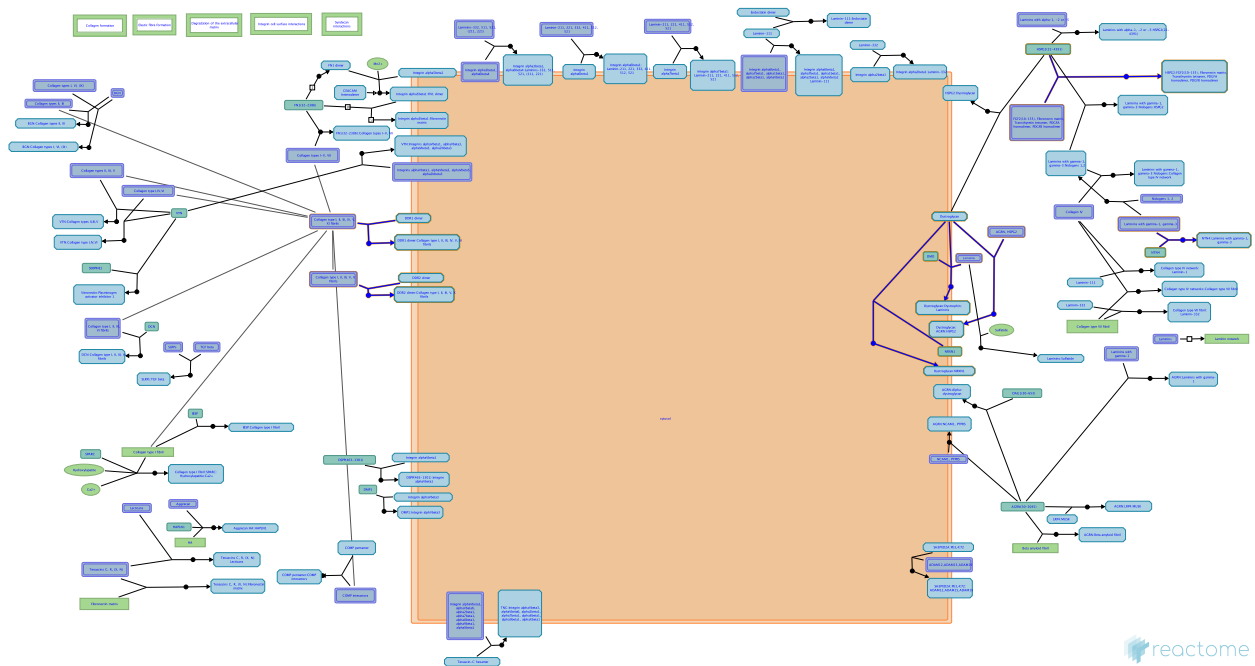
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Reactome database release: 77

This document contains 2 pathways and 7 reactions ([see Table of Contents](#))

Non-integrin membrane-ECM interactions ↗

Stable identifier: R-HSA-3000171



Several non-integrin membrane proteins interact with extracellular matrix proteins. Transmembrane proteoglycans may associate with integrins and growth factor receptors to influence their function, or they can signal independently, often influencing the actin cytoskeleton.

Literature references

Couchman, JR. (2010). Transmembrane signaling proteoglycans. *Annu. Rev. Cell Dev. Biol.*, 26, 89-114. ↗

Rosso, F., Giordano, A., Barbarisi, M., Barbarisi, A. (2004). From cell-ECM interactions to tissue engineering. *J. Cell. Physiol.*, 199, 174-80. ↗

Editions

2012-07-31	Authored	Jupe, S.
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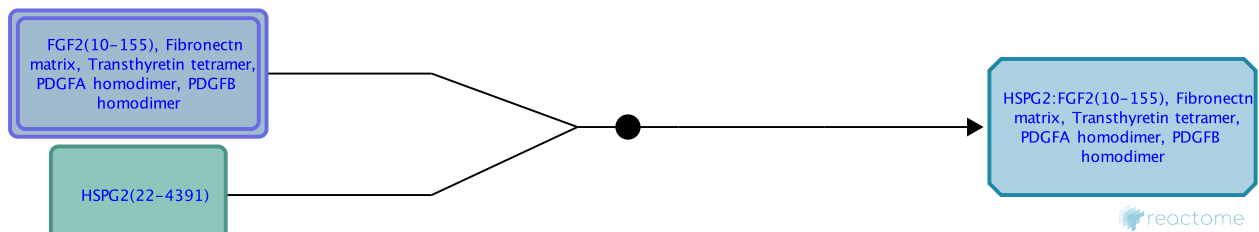
HSPG2 binds FGF2(10-155), Fibronectin matrix, Transthyretin tetramer, PDGFA homodimer, PDGFB homodimer ↗

Location: Non-integrin membrane-ECM interactions

Stable identifier: R-HSA-2396337

Type: binding

Compartments: extracellular region



Perlecan (HSPG2) is a modular proteoglycan primarily located in the basement membranes of vascular tissues. It is involved in several developmental processes, both during embryogenesis and in human diseases such as cancer and diabetes (Iozzo et al. 1994). HSPG2 can self-aggregate into dimeric or multimeric forms (Yurchenco et al. 1987) and is involved in heterotypic interactions with numerous extracellular macromolecules (Whitelock et al. 2008, Perlecan entry in MatrixDB). HSPG2's GAG chains mediate interactions with fibroblast growth factor-2 (Vigny et al. 1988, Knox et al. 2002), and nidogens (Entactins, represented elsewhere). The core protein binds fibronectin (Isemura et al. 1987, Heremans et al. 1990, Vladavsky et al. 1991), transthyretin (Smeland et al. 1997) and platelet-derived growth factor A and B homodimers (Göhring et al. 1998).

Literature references

Knox, S., Merry, C., Stringer, S., Melrose, J., Whitelock, J. (2002). Not all perlecans are created equal: interactions with fibroblast growth factor (FGF) 2 and FGF receptors. *J. Biol. Chem.*, 277, 14657-65. ↗

Editions

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Dystroglycan binds Laminins and Dystrophin ↗

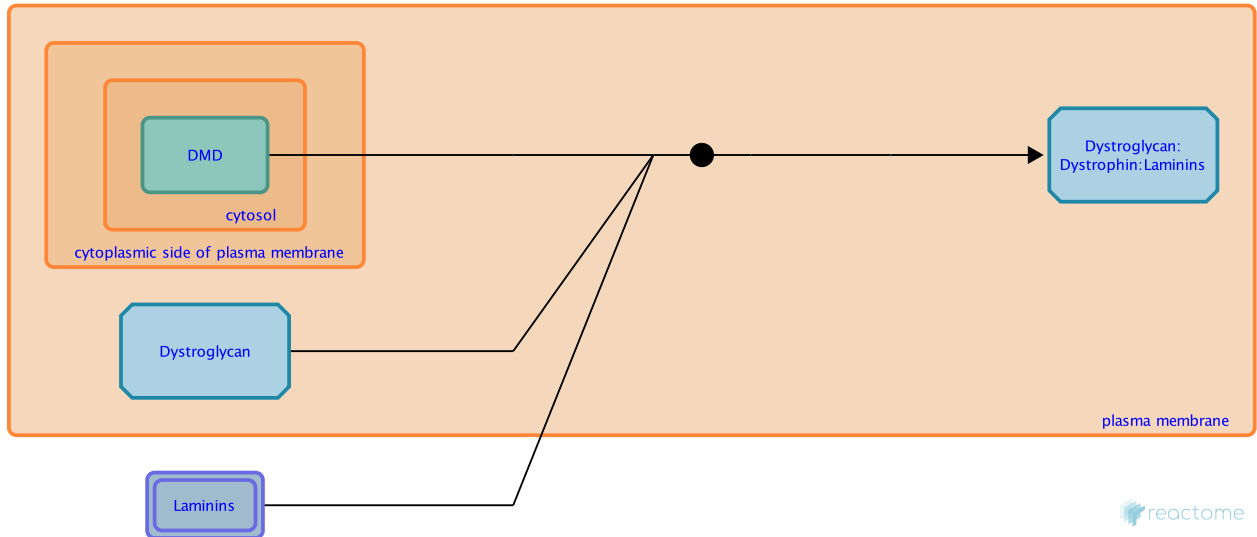
Location: [Non-integrin membrane-ECM interactions](#)

Stable identifier: R-HSA-2328129

Type: binding

Compartments: plasma membrane, cytosol, extracellular region

Inferred from: [Dystroglycan bind Laminins and Dystrophin \(Mus musculus\)](#)



Dystroglycan (DG) is a cell-surface laminin receptor. In skeletal muscle it is a central component of the dystrophin-glycoprotein (DGC) complex (Ervasti & Campbell 1991). Mutations in components of the DGC render muscle fibres more susceptible to damage and lead to various types of muscle disorder such as Duchenne muscular dystrophy and limb-girdle muscular dystrophies (Straub & Campbell, 1997, Cohn & Campbell 2000). DG is present as non-covalently associated alpha and beta subunits following cleavage at Ser654. The extracellular alpha subunit binds to laminin-2 (merosin) in the muscle basement membrane while the membrane-associated beta subunit binds dystrophin, which associates with the actin cytoskeleton (Ervasti & Campbell 1993, Yamada et al. 1994, Talts et al. 1999). Alpha-DG also binds the carboxy-terminal G domains of laminin alpha-1 (Gee et al. 1993, Zhou et al. 2012) and alpha-5 (Yu & Talts 2003). G domains are relatively well conserved in all five alpha-laminin chains, so DG is likely to bind all laminin heterotrimers.

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Dystroglycan binds AGRN and HSPG2 ↗

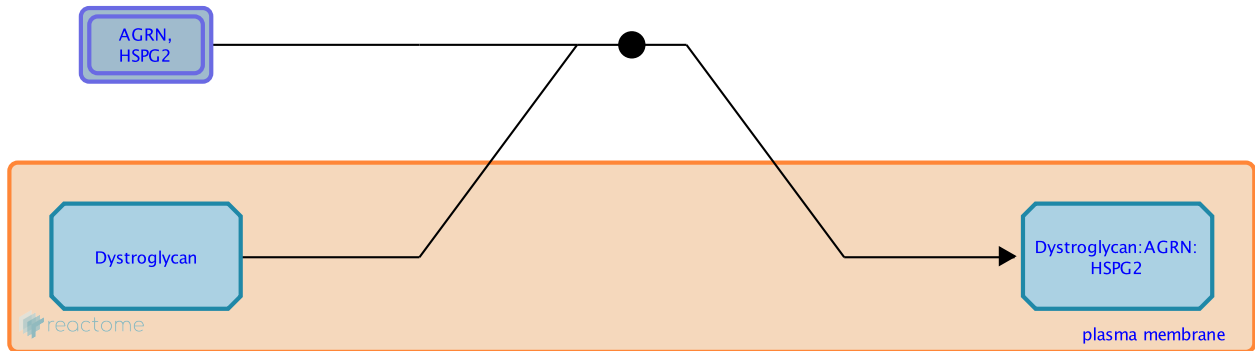
Location: [Non-integrin membrane-ECM interactions](#)

Stable identifier: R-HSA-2396113

Type: binding

Compartments: extracellular region, plasma membrane

Inferred from: [Dystroglycan binds Agrn and Hspg2 \(Mus musculus\)](#)



Alpha-dystroglycan (DG) binds G domain-like sequences in other extracellular matrix molecules such as AGRN (Agrin) (Gee et al. 1994, Campanelli et al. 1994, Sugiyama et al. 1994, Yamada et al. 1996, Gesemann et al. 1996) and HSPG2 (perlecan) (Peng et al. 1998, Talts et al. 1999). DG knockout mice exhibit severe disruption of basement membranes and embryonic stem cells fail to deposit laminin, suggesting a role for DG in laminin matrix formation (Henry & Campbell 1998). Conditional ablation of DG expression in cultured mammary epithelial cells disrupted laminin-111-induced polarity and beta-casein production, and abolished laminin binding and assembly on the cell surface. Dystroglycan re-expression restored these deficiencies (Weir et al. 2006).

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Dystroglycan binds NRXN1 ↗

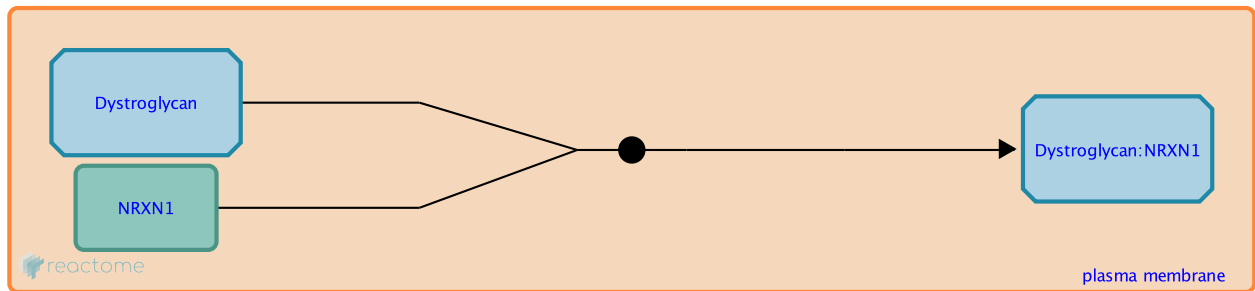
Location: [Non-integrin membrane-ECM interactions](#)

Stable identifier: R-HSA-2426263

Type: binding

Compartments: plasma membrane

Inferred from: [Dystroglycan binds Nrnx1 \(Rattus norvegicus\)](#)



Dystroglycan binds specifically to a subset of neurexin LNS domains in a tight interaction that requires the glycosylation of dystroglycan and is regulated by neurexin alternative splicing. Alpha-dystroglycan binds G domain-like sequences in neurexin-1-alpha (NRXN1) (Sugita et al. 2001).

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NTN4 binds laminins with gamma-1, gamma-3 ↗

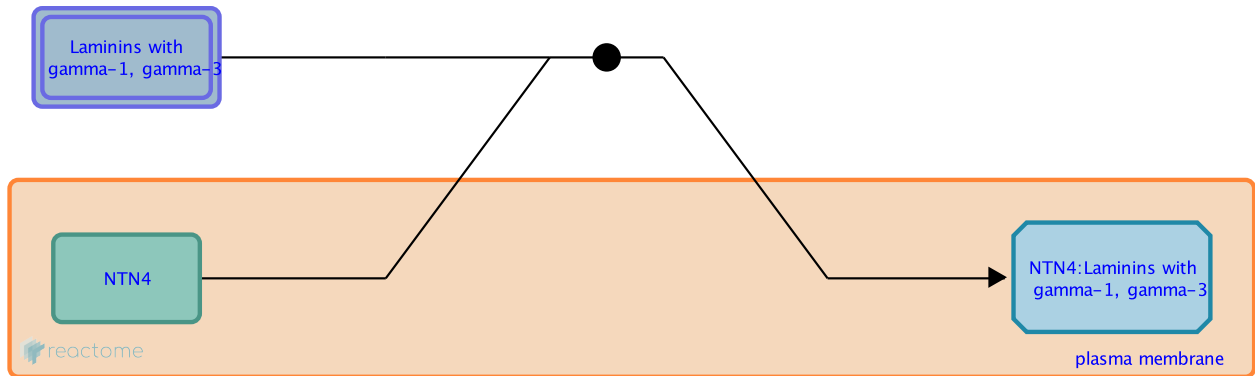
Location: [Non-integrin membrane-ECM interactions](#)

Stable identifier: R-HSA-2426355

Type: binding

Compartments: extracellular region, plasma membrane

Inferred from: [Ntn4 binds laminin-gamma-1 and -3 \(Mus musculus\)](#)



Netrins are a family of extracellular proteins that include axonal guidance factors. They have N-terminal domains that are homologous to the LN domains of laminins. Netrin-4 (NTN4), but not other forms of netrin, bind laminin gamma-1 and gamma-3 short arms in the basement membrane, suggesting a role in regulating basement membrane formation (Schneiders et al. 2007). NTN4 has been found associated in a functional complex with laminin gamma-1 chain and integrin alpha6beta1, suggesting a role in regulation of neurogenesis in the olfactory system (Staquicini et al. 2009).

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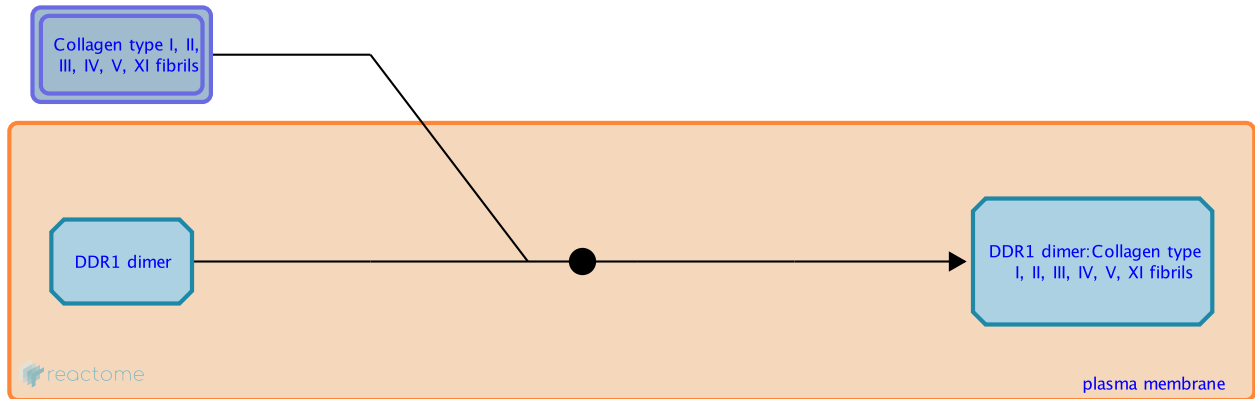
DDR1 binds collagen type I, II, III, IV, V, XI fibrils ↗

Location: [Non-integrin membrane-ECM interactions](#)

Stable identifier: R-HSA-2327738

Type: binding

Compartments: plasma membrane, extracellular region



Discoidin domain receptors (DDRs) are a subfamily of receptor tyrosine kinases, the only members known to respond to an ECM component. DDR1 binds several of the major fibrillar collagens (types I, II, III, and V) and the non-fibrillar collagen IV (Shrivastava et al. 1997, Vogel et al. 1997, Hou et al. 2001). DDR proteins bind collagen as dimers (Leitinger 2003, 2011). DDR1 is mostly found in epithelial cells and leukocytes. It control developmental processes and regulates cell adhesion, migration, proliferation, and remodelling of the extracellular matrix by controlling the expression and activity of matrix metalloproteinases (Leitinger & Hohenester 2007).

Literature references

Shrivastava, A., Radziejewski, C., Campbell, E., Kovac, L., McGlynn, M., Ryan, TE. et al. (1997). An orphan receptor tyrosine kinase family whose members serve as nonintegrin collagen receptors. *Mol. Cell*, 1, 25-34. ↗

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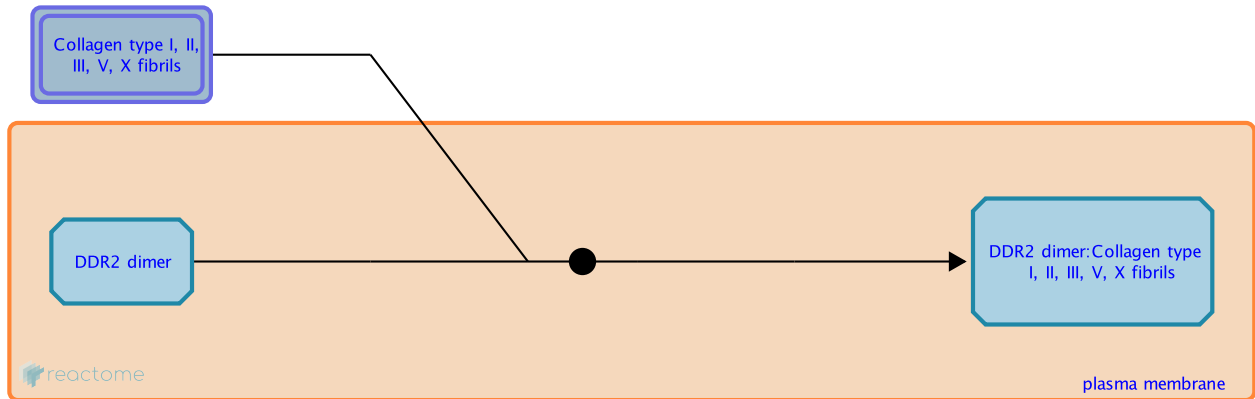
DDR2 binds collagen type I, II, III, V, X fibrils ↗

Location: [Non-integrin membrane-ECM interactions](#)

Stable identifier: R-HSA-2465890

Type: binding

Compartments: plasma membrane, extracellular region



Discoidin domain receptors (DDR2) are a subfamily of receptor tyrosine kinases, the only members known to respond to an ECM component. DDR2 binds the major fibrillar collagens types I, II, III, and V) and the non-fibrillar collagen X (Shrivastava et al. 1997, Vogel et al. 1997, Leitinger & Kwan 2006). DDR proteins bind collagen as dimers (Leitinger 2003, 2011). DDR2 is confined to mesenchymal cells where it controls developmental processes and regulates cell adhesion, migration, proliferation, and remodelling of the extracellular matrix by controlling the expression and activity of matrix metalloproteinases (Leitinger & Hohenester 2007).

Literature references

Shrivastava, A., Radziejewski, C., Campbell, E., Kovac, L., McGlynn, M., Ryan, TE. et al. (1997). An orphan receptor tyrosine kinase family whose members serve as nonintegrin collagen receptors. *Mol. Cell*, 1, 25-34. ↗

Leitinger, B., Kwan, AP. (2006). The discoidin domain receptor DDR2 is a receptor for type X collagen. *Matrix Biol.*, 25, 355-64. ↗

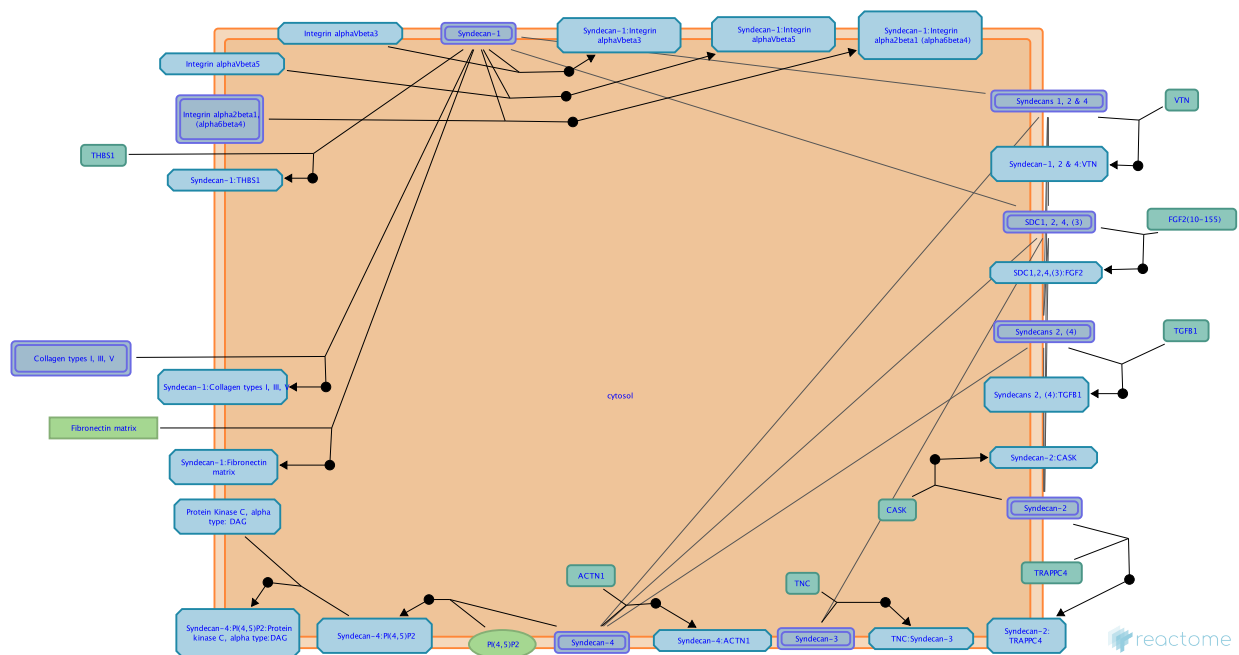
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Syndecan interactions [↗](#)

Location: Non-integrin membrane-ECM interactions

Stable identifier: R-HSA-3000170



Syndecans are type I transmembrane proteins, with an N-terminal ectodomain that contains several consensus sequences for glycosaminoglycan (GAG) attachment and a short C-terminal cytoplasmic domain. Syndecan-1 and -3 GAG attachment sites occur in two distinct clusters, one near the N-terminus and the other near the membrane-attachment site, separated by a proline and threonine-rich 'spacer'. Syndecan ectodomain sequences are poorly conserved in the family and between species, but the transmembrane and cytoplasmic domains are highly conserved. Syndecan-1 and -3 form a subfamily. Syndecan core proteins form dimers (Choi et al. 2007) and at least syndecan-3 and -4 form oligomers (Asundi & Carey 1995, Shin et al. 2012). Syndecan-1 is the major syndecan of epithelial cells including vascular endothelium. Syndecan-2 is present mostly in mesenchymal, neuronal and smooth muscle cells. Syndecan-3 is the major syndecan of the nervous system, while syndecan-4 is ubiquitously expressed but at lower levels than the other syndecans (refs in Alexopoulou et al. 2007). The core syndecan protein has three to five heparan sulfate or chondroitin sulfate chains, which interact with a variety of ligands including fibroblast growth factors, vascular endothelial growth factor, transforming growth factor-beta, fibronectin, collagen, vitronectin and several integrins. Syndecans may act as integrin coreceptors. Interactions between fibronectin and syndecans are modulated by tenascin-C.

Syndecans bind a wide variety of soluble and insoluble ligands, including extracellular matrix components, cell adhesion molecules, growth factors, cytokines, and proteinases. As the cleaved ectodomains of syndecans retain the ability to bind ligands, ectodomain shedding is a mechanism for releasing soluble effectors that may compete for ligands with their cell-bound counterparts (Kainulainen et al. 1998). Shed ectodomains are found in inflammatory fluids (Subramanian et al. 1997) and may induce the proliferation of cancer cells (Maeda et al. 2004).

Literature references

Alexopoulou, AN., Multhaupt, HA., Couchman, JR. (2007). Syndecans in wound healing, inflammation and vascular biology. *Int. J. Biochem. Cell Biol.*, 39, 505-28. [↗](#)

Tkachenko, E., Rhodes, JM., Simons, M. (2005). Syndecans: new kids on the signaling block. *Circ. Res.*, 96, 488-500. [↗](#)

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Table of Contents

Introduction	1
⚡ Non-integrin membrane-ECM interactions	2
↳ HSPG2 binds FGF2(10-155), Fibronectin matrix, Transthyretin tetramer, PDGFA homodimer, PDGFB homodimer	3
↳ Dystroglycan binds Laminins and Dystrophin	4
↳ Dystroglycan binds AGRN and HSPG2	5
↳ Dystroglycan binds NRXN1	6
↳ NTN4 binds laminins with gamma-1, gamma-3	7
↳ DDR1 binds collagen type I, II, III, IV, V, XI fibrils	8
↳ DDR2 binds collagen type I, II, III, V, X fibrils	9
⚡ Syndecan interactions	10
Table of Contents	12