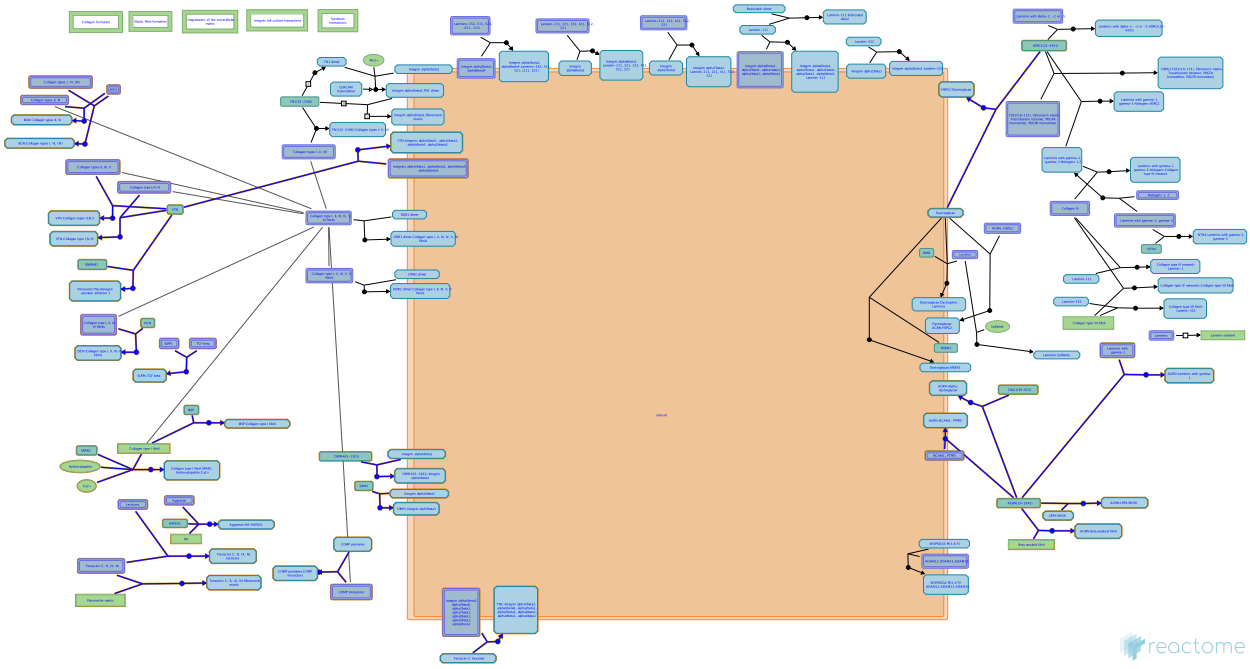
ECM proteoglycans



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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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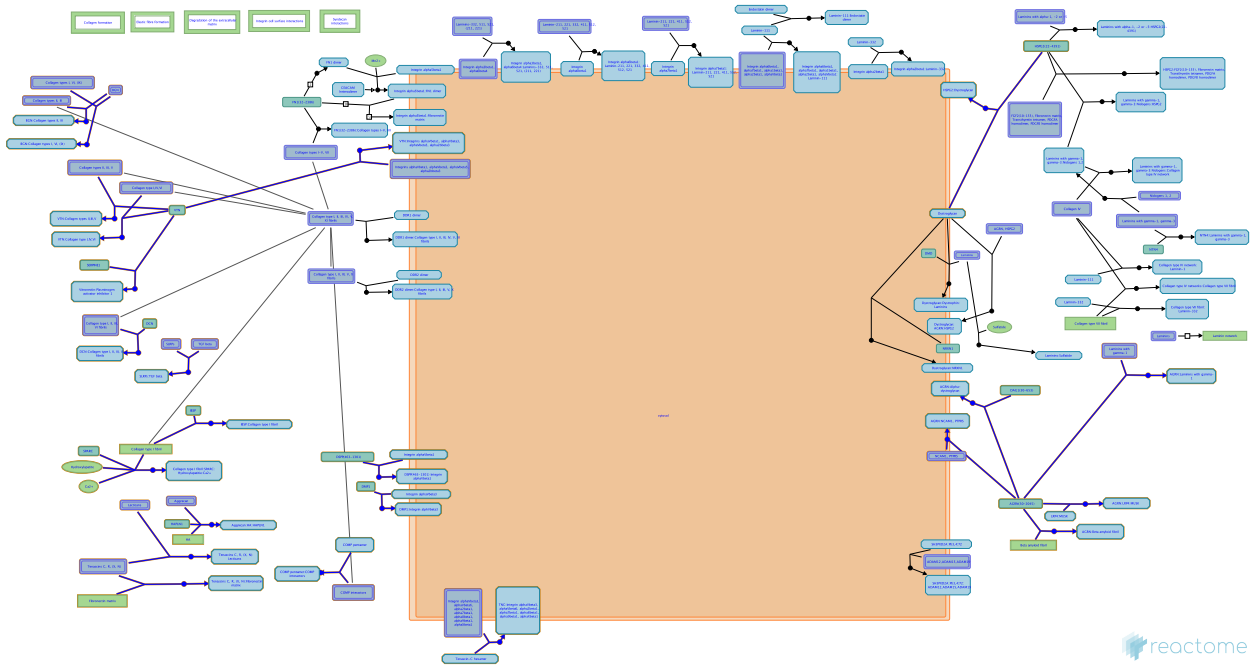
ECM proteoglycans ↗

Stable identifier: R-HSA-3000178



Proteoglycans are major components of the extracellular matrix. In cartilage the matrix constitutes more than 90% of tissue dry weight. Proteoglycans are proteins substituted with glycosaminoglycans (GAGs), linear polysaccharides consisting of a repeating disaccharide, generally of an acetylated amino sugar alternating

with a uronic acid. Most proteoglycans are located in the extracellular

space. Proteoglycans are highly diverse, both in terms of the core proteins and the subtypes of GAG chains, namely chondroitin sulfate (CS), keratan sulfate (KS), dermatan sulfate (DS) and heparan sulfate (HS). Hyaluronan is a non-sulfated GAG whose molecular weight runs into millions of Dalton; in articular cartilage, a single hyaluronan molecule can hold upto 100 aggrecan molecules and these aggregates are stabilized by a link protein.

Literature references

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SLRPs bind TGF Beta ↗

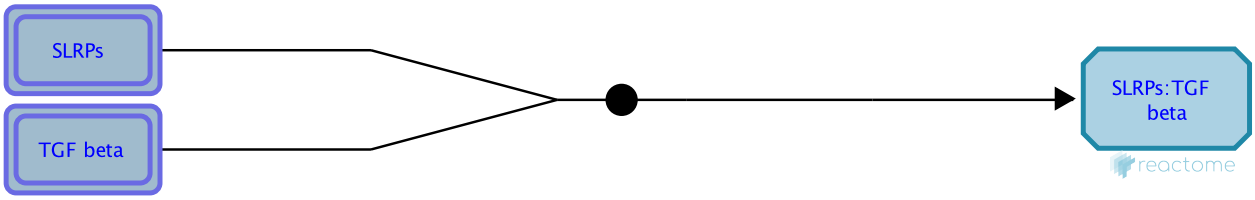
Location: ECM proteoglycans

Stable identifier: R-HSA-2327886

Type: binding

Compartments: extracellular region

Inferred from: SLRPs bind TGF beta (Homo sapiens)



Small leucine rich repeat proteoglycans (SLRPs) are a family of extracellular glycoproteins that includes decorin (DCN), biglycan (BGN), fibromodulin, lumican and asporin (Hedbom & Heinegard 1993, Ezura et al. 2000, Schaefer & Iozzo 2008, Iozzo & Schaefer 2010). DCN inhibits cellular proliferation in a TGF-Beta-dependent manner in Chinese hamster ovary (CHO) cells (Yamaguchi et al. 1990), arterial smooth muscle cells (Fischer et al. 2001), human hepatic stellate cells (Shi et al. 2006) and fibroblasts (Zhang et al. 2007). DCN, BGN and fibromodulin can all bind to TGF-Beta (Hildebrand 1994). Binding is mediated by the leucine rich repeat suggesting that all members of the SLRP family have TGF-beta binding capability (Schönherr et al. 1998). DCN has independent binding sites for collagen and TGF-Beta (Schönherr et al. 1998, Cabello-Verrugio et al. 2012). DCN binding is thought to sequester TGF-Beta extracellularly, thereby diminishing its biological activity (Markmann et al. 2000). DCN treatment has beneficial effects in fibrotic disorders involving TGF-Beta overproduction (Border et al. 1992; Kolb et al. 2001, Baghy et al. 2012). BGN attenuates the proliferative actions of TGF-beta1 on fibroblasts (Kobayashi et al. 2003). DCN and BGN appear to mediate crosstalk between Toll-like receptors (TLRs), NOD-like receptors (NLRs) and transforming growth factor Beta (TGFBeta) receptors (reviewed in Moreth et al. 2012).

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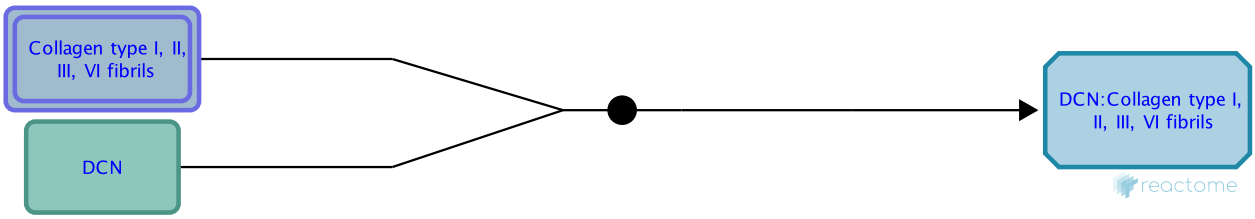
DCN binds collagen I, II, III, VI fibrils ↗

Location: ECM proteoglycans

Stable identifier: R-HSA-2327909

Type: binding

Compartments: extracellular region



Decorin (DCN) belongs to the small leucine-rich repeat proteoglycan family (SLRPs) which also includes biglycan, fibromodulin (Hedlund et al. 1994 - binding to collagen II), lumican and asporin (Hedbom & Heinegard 1993, Ezura et al. 2000). Fibromodulin and lumican bind the same site while the binding site for decorin is distinct (Hedbom & Heinegard 1993). All appear to be involved in collagen fibril formation and matrix assembly (Ameye & Young 2002, Kalamajski & Oldberg 2010). DCN consists of a core protein of approximately 40 kDa attached to a single chondroitin or dermatan sulfate glycosaminoglycan (GAG) chain. It interacts with collagen types I, II (Vogel et al. 1984), III (Witos et al. 2011), V (Whinna et al. 1993), VI (Bidanset et al. 1992) and XIV (Ehnis et al. 1997). It binds collagen I and II near the N-terminus, placing it at the 'd' band gap in the fibril structure (Kalamajski et al. 2007). The binding site for DCN on collagen XIV is in the NH2-terminal fibronectin type III repeat. In addition, an auxiliary binding site located COOH-terminally to this fibronectin type III repeat interacts with the glycosaminoglycan component of DCN.

DCN binding regulates fibrillogenesis (Vogel et al. 1984, Orgel et al. 2006). One molecule of DCN interacts with four to six collagen molecules. The interaction is between collagen and the core protein, not the GAG chain, and is more likely to involve the monomeric, not dimeric form (Orgel et al. 2009). Fibronectin (Winnemoller et al. 1991) and thrombospondin-1 (Winnemoller et al. 1992) are also DCN interactors. DCN acts as a sink for all three isoforms of TGF-Beta, binding them when already bound to collagen (Markmann et al. 2000). Degradation of DCN by matrix metalloproteinases MMP-2, -3 or -7 results in release of TGF-beta (Imai et al. 1997). In addition, DCN binds to EGFR (Iozzo et al. 1999) causing prolonged down-regulation of EGFR-mediated mobilization of intracellular calcium (Csordás et al. 2000).

Literature references

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Vogel, KG., Paulsson, M., Heinegård, D. (1984). Specific inhibition of type I and type II collagen fibrillogenesis by the small proteoglycan of tendon. *Biochem. J., 223*, 587-97. ↗

Witos, J., Saint-Guirons, J., Meinander, K., D'Ulivo, L., Riekkola, ML. (2011). Collagen I and III and their decorin modified surfaces studied by atomic force microscopy and the elucidation of their affinity toward positive apolipoprotein B-100 residue by quartz crystal microbalance. *Analyst, 136*, 3777-82. ↗

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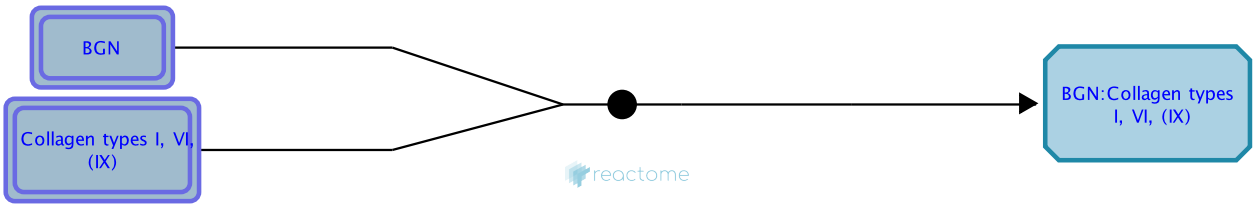
BGN binds Collagen types I, VI, (IX) ↗

Location: ECM proteoglycans

Stable identifier: R-HSA-2466106

Type: binding

Compartments: extracellular region



Biglycan is a member of the small leucine-rich repeat proteoglycan family (SLRPs) which also includes decorin, fibromodulin (Hedlund et al. 1994 - binding to collagen II), lumican and asporin (Hedbom & Heinegard 1993, Ezura et al. 2000). All appear to be involved in collagen fibril formation and matrix assembly (Ameye & Young 2002).

Biglycan binds collagen types I (Schönherr et al. 1995), II (Bovine, using pig byglycan - Vynios et al. 2001, Bovine, using bovine biglycan - Douglas et al. 2008), III (Bovine, using bovine biglycan - Douglas et al. 2008), VI (Wiberg et al. 2001, 2002, human) and IX (Chen et al. 2006 - species source of collagen/biglycan unknown).

Literature references

Schönherr, E., Witsch-Prehm, P., Harrach, B., Robenek, H., Rauterberg, J., Kresse, H. (1995). Interaction of biglycan with type I collagen. *J. Biol. Chem., 270*, 2776-83. ↗

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BGN binds Collagen types II, III ↗

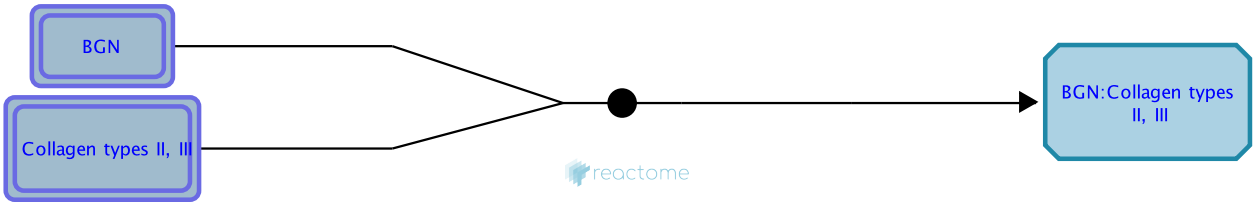
Location: ECM proteoglycans

Stable identifier: R-HSA-2466238

Type: binding

Compartments: extracellular region

Inferred from: BGN binds Collagen types II, III, IV (Bos taurus)



Biglycan (BGN) is a member of the small leucine-rich repeat proteoglycan family (SLRPs) which also includes decorin, fibromodulin (Hedlund et al. 1994 - binding to collagen II), lumican and asporin (Hedbom & Heinegard 1993, Ezura et al. 2000). All appear to be involved in collagen fibril formation and matrix assembly (Ameye & Young 2002).

BGN-deficient mice exhibit larger and irregular fibrils leading to thin dermis and reduced bone mass (Corsi et al. 2002, Xu et al. 1998). BGN binds collagen types I (Schönherr et al. 1995), II (Bovine, using pig BGN - Vynios et al. 2001, Bovine, using bovine BGN - Douglas et al. 2008), III (Bovine, using bovine BGN - Douglas et al. 2008), VI (Wiberg et al. 2001) and IX (Chen et al. 2006 - species source of collagen/BGN unknown).

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VTN binds collagens I, IV and VI ↗

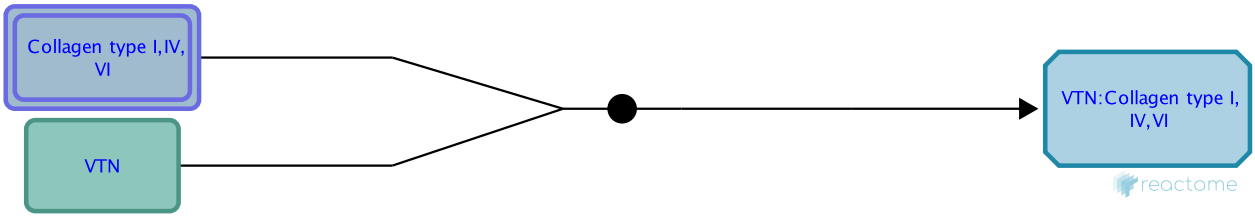
Location: ECM proteoglycans

Stable identifier: R-HSA-2465883

Type: binding

Compartments: extracellular region

Inferred from: VTN binds collagen I, IV and VI (Homo sapiens)



Vitronectin (VTN) is a major plasma glycoprotein of 75 kDa, circulating at approximately 0.2 mg/ml in humans. It interacts with collagen types I, II, III, IV, V, and VI (Gebb et al. 1986). Deglycosylation enhances VTN binding to collagen and is associated with VTN multimerization (Uchibori-Iwaki et al. 2000, Sano et al. 2007).

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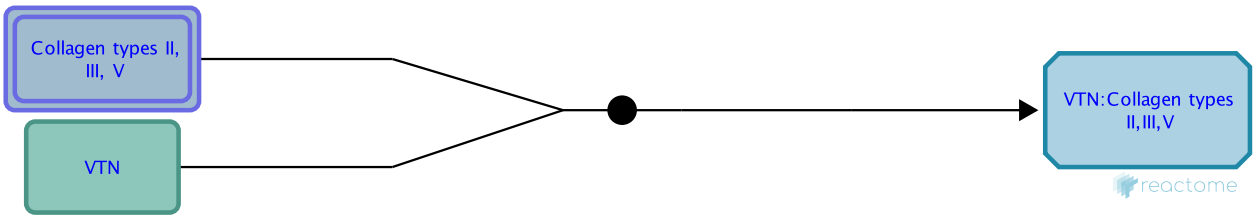
VTN binds collagens II, III and V ↗

Location: ECM proteoglycans

Stable identifier: R-HSA-2396370

Type: binding

Compartments: extracellular region



Vitronectin (VTN) is a major plasma glycoprotein of 75 kDa, circulating at approximately 0.2 mg/ml in humans. It interacts with collagen types I, II, III, IV, V, and VI (Gebb et al. 1986). Deglycosylation enhances VTN binding to collagen and is associated with VTN multimerization (Uchibori-Iwaki et al. 2000, Sano et al. 2007).

Literature references

Gebb, C., Hayman, EG., Engvall, E., Ruoslahti, E. (1986). Interaction of vitronectin with collagen. *J. Biol. Chem., 261*, 16698-703. ↗

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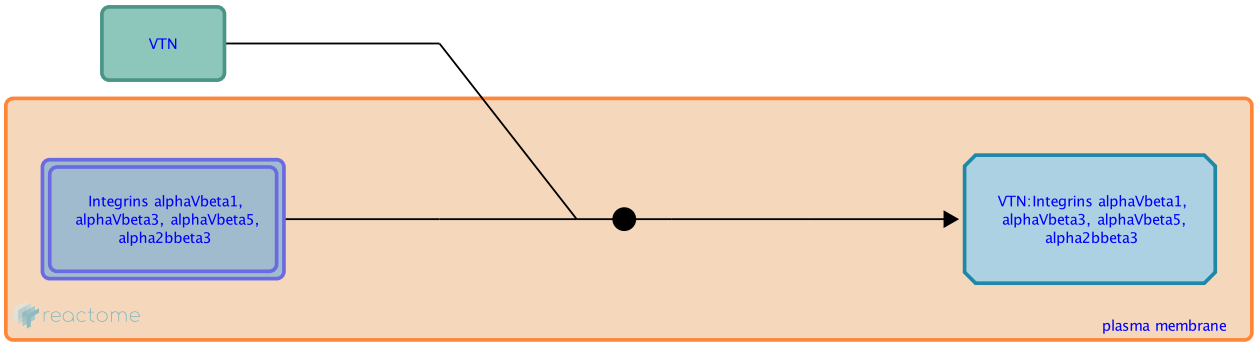
VTN binds integrins alphaVbeta1, alphaVbeta3, alpha3beta5, alphaIIBbeta3 ↗

Location: ECM proteoglycans

Stable identifier: R-HSA-2426471

Type: binding

Compartments: plasma membrane, extracellular region



Integrin alphaVbeta3 is sometimes referred to as the 'vitronectin receptor'. Vitronectin interacts with integrins alphaVbeta1 (Marshall et al. 1995), alphaVbeta3 (Pytela et al. 1985, Boettiger et al. 2001), alphaVbeta5 (Panetti & McKeown-Longo 1993) and alpha2b beta3 (Pytela et al. 1986) through Arg-Gly-Asp (RGD) cell binding sequences.

Endothelial cells lining the microvascular wall form a semi-permeable barrier to the movement of blood components. The attachment of endothelial cells to the extracellular matrix (ECM) is largely mediated by transmembrane integrins which recognize short sequence motifs such as Arg-Gly-Asp (RGD) in many ECM proteins.

Integrin alpha5beta1 and alphaVbeta3 bind to the ECM proteins fibronectin and vitronectin respectively. Both are critical for the establishment and stabilization of endothelial monolayers (Cheng & Kramer 1989). Synthetic peptides that compete with ECM proteins for the integrins or antibodies directed against alpha5beta1 and alphaVbeta3 cause endothelial cell detachment (Hayman et al. 1985, Pierschbacher & Ruoslahti 1987).

Literature references

Marshall, JF., Rutherford, DC., McCartney, AC., Mitjans, F., Goodman, SL., Hart, IR. (1995). Alpha v beta 1 is a receptor for vitronectin and fibrinogen, and acts with alpha 5 beta 1 to mediate spreading on fibronectin. *J Cell Sci, 108*, 1227-38. ↗

Pytela, R., Pierschbacher, MD., Ruoslahti, E. (1985). A 125/115-kDa cell surface receptor specific for vitronectin interacts with the arginine-glycine-aspartic acid adhesion sequence derived from fibronectin. *Proc. Natl. Acad. Sci. U.S.A., 82*, 5766-70. ↗

Panetti, TS., McKeown-Longo, PJ. (1993). The alpha v beta 5 integrin receptor regulates receptor-mediated endocytosis of vitronectin. *J. Biol. Chem., 268*, 11492-5. ↗

Pytela, R., Pierschbacher, MD., Ginsberg, MH., Plow, EF., Ruoslahti, E. (1986). Platelet membrane glycoprotein IIb/IIIa: member of a family of Arg-Gly-Asp--specific adhesion receptors. *Science, 231*, 1559-62. ↗

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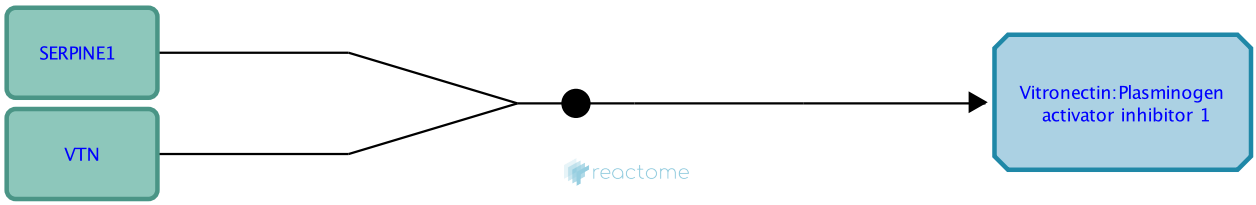
VTN binds Plasminogen activator inhibitor- 1 ↗

Location: ECM proteoglycans

Stable identifier: R-HSA-2396079

Type: binding

Compartments: extracellular region



The somatomedin B domain of vitronectin (VTN) binds to and stabilizes plasminogen activator inhibitor-1 (PAI1) (Declerck et al. 1988). PAI1 is the principal physiological inhibitor of both tissue (tPA) and urokinase (uPA) plasminogen activators and a key regulator of the fibrinolytic system; the stabilization of PAI1 by VTN thereby regulates proteolysis of fibrin (Zhou et al. 2003). Elevated PAI1 activity is associated with coronary thrombosis (Hamsten et al. 1987) and poor prognosis in many cancers.

Literature references

Kost, C., Stüber, W., Ehrlich, HJ., Pannekoek, H., Preissner, KT. (1992). Mapping of binding sites for heparin, plasminogen activator inhibitor-1, and plasminogen to vitronectin's heparin-binding region reveals a novel vitronectin-dependent feedback mechanism for the control of plasmin formation. *J. Biol. Chem., 267*, 12098-105. ↗

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AGRN binds Alpha-dystroglycan ↗

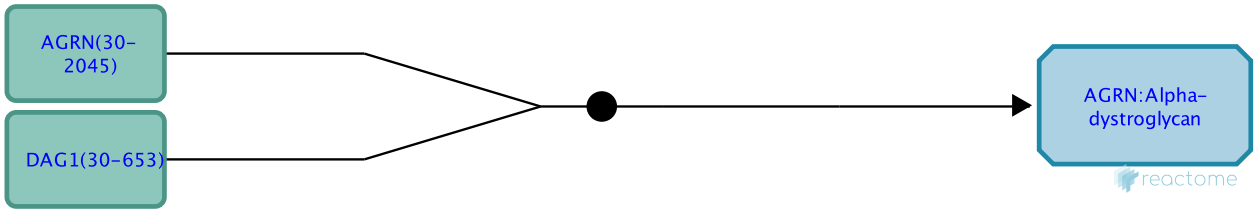
Location: ECM proteoglycans

Stable identifier: R-HSA-2467716

Type: binding

Compartments: extracellular region

Inferred from: Agrin binds alpha-dystroglycan (Gallus gallus)



Agrin (AGRN) is a multidomain heparan sulfate proteoglycan found in basement membranes, named for its ability to promote aggregation of AChR clusters on the muscle surface directly beneath the nerve terminal (Nitkin et al. 1987). It is a critical organizer of postsynaptic differentiation at the skeletal neuromuscular junction; synaptogenesis is profoundly disrupted in its absence (Gautam et al. 1996, Daniels 2012). Two alternate N-termini exist with differential expression, tissue localization and function. The secreted and predominant longer LN form (Burgess et al. 2000) starts with a secretion signal sequence and a laminin-binding domain (Denzer et al. 1995, Kammerer et al. 1999); the shorter SN form associates with the plasma membrane (Burgess et al. 2000, Neumann et al. 2001). Following the SN or LN regions are 8 follistatin repeats, known to bind growth factors and inhibit proteases in other proteins. The central region has two repeats homologous to domain III of laminin. The C-terminal portion, which is responsible for the molecule's known signaling functions, contains four EGF repeats and three LG (G) domains homologous to those found in laminin alpha chains, neurexins and slits (Timpl et al. 2000).

The LG domains of AGRN bind alpha-dystroglycan (Yamada et al. 1996, Gee et al. 1994, Bowen et al. 1996, Campanelli et al. 1996, Gesemann et al. 1996, Hopf & Hoch 1996).

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AGRN binds LRP4:MUSK ↗

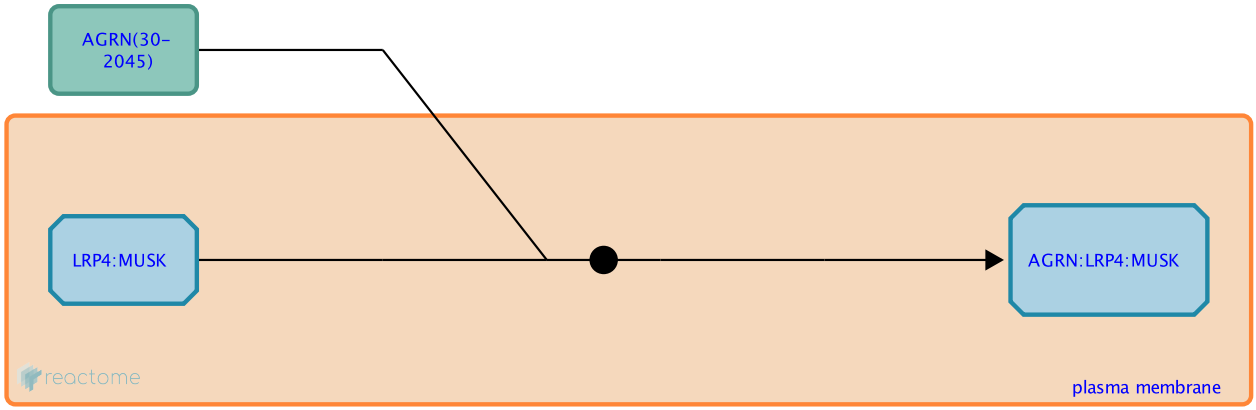
Location: ECM proteoglycans

Stable identifier: R-HSA-2467633

Type: binding

Compartments: plasma membrane, extracellular region

Inferred from: Agrin binds Lrp4:Musk (Mus musculus)



Agrin (AGRN) is a large multidomain heparan sulfate proteoglycan found in basement membranes, named for its ability to promote aggregation of AChR clusters on the muscle surface directly beneath the nerve terminal (Nitkin et al. 1987). It is a critical organizer of postsynaptic differentiation at the skeletal neuromuscular junction; synaptogenesis is profoundly disrupted in its absence (Gautam et al. 1996). Two alternate N termini exist with differential expression, tissue localization and function. The predominant longer LN form (Burgess et al. 2000) starts with a secretion signal sequence and a laminin-binding domain (Denzer et al. 1995, Kammerer et al. 1999); the shorter SN form associates with the plasma membrane (Burgess et al. 2000, Neumann et al. 2001). Following the SN or LN regions are 8 follistatin repeats, known to bind growth factors and inhibit proteases in other proteins. The central region has two repeats homologous to domain III of laminin. The C-terminal portion, which is responsible for the molecule's known signaling functions, contains four EGF repeats and three LG (G) domains homologous to those found in laminin alpha chains, neurexins and slits (Timpl et al. 2000).

AGRN binds a complex of the tyrosine kinase receptor MuSK, which is responsible for mediating agrin's ability to cluster AChR (Glass et al. 1996, Sanes & Lichtman 2001, Burden et al. 2003) and the coreceptor LRP4 (Kim et al. 2008, Zhang et al. 2008, Zong et al. 2012).

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AGRN binds Laminins with gamma-1 subunit ↗

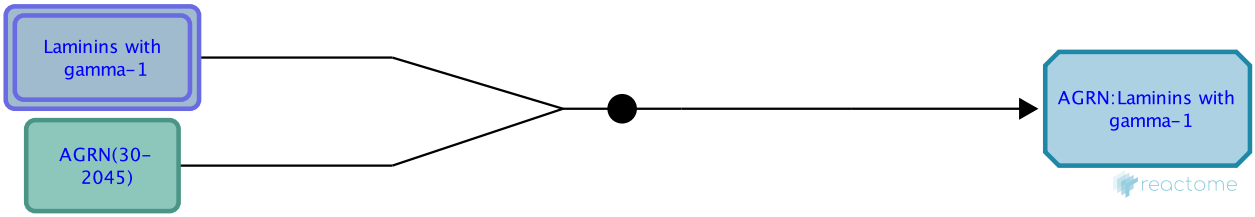
Location: ECM proteoglycans

Stable identifier: R-HSA-2396124

Type: binding

Compartments: extracellular region

Inferred from: AGRN binds laminins (Mus musculus)



Agrin (AGRN) is a large (>400 kDa) multi-domain heparan sulfate proteoglycan found in basement membranes. It is a critical organizer of postsynaptic differentiation at the skeletal neuromuscular junction; synaptogenesis is profoundly disrupted in its absence (Gautam et al. 1996). Two alternate N-termini exist with differential expression, tissue localization and function. The predominant longer LN form (Burgess et al. 2000) starts with a secretion signal sequence and a laminin-binding domain (Denzer et al. 1995, Kammerer et al. 1999); the shorter SN form associates with the plasma membrane (Burgess et al. 2000, Neumann et al. 2001). Following the SN or LN regions are 8 follistatin repeats, known to bind growth factors and inhibit proteases in other proteins. The central region has two repeats homologous to domain III of laminin. The C-terminal portion, which is responsible for the molecule's known signalling functions, contains four EGF repeats and three LG (G) domains homologous to those found in laminin alpha chains, neurexins and slits (Timpl et al. 2000).

The N-terminus of the LN form of AGRN binds to the laminin gamma1 subunit (Denzer et al. 1997, Kammerer et al. 1999, Mascarenhas et al. 2003). This may indirectly bind AGRN to integrins on the cell surface (Bezakova & Ruegg 2003).

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AGRN binds NCAM1, PTPRS ↗

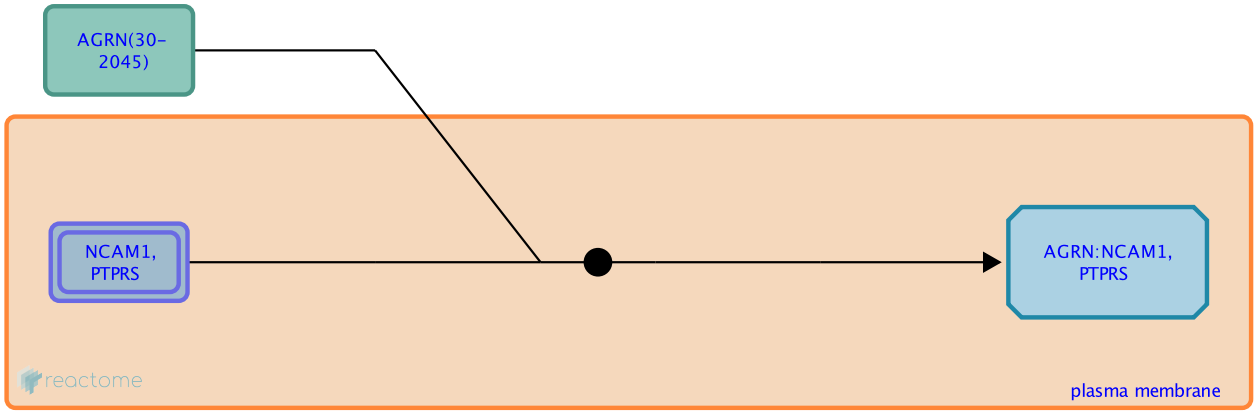
Location: ECM proteoglycans

Stable identifier: R-HSA-2467659

Type: binding

Compartments: plasma membrane, extracellular region

Inferred from: AGRN binds NCAM1, PTPRS (Gallus gallus)



Several agrin (AGRN) ligands require the presence of heparan-sulfate sidechains and are probably mediated by them. Membrane-associated AGRN ligands include the neural cell adhesion molecule NCAM1 (Burg et al. 1995, Tsen et al. 1995, Cole & Halfter 1996 - represented in REACT_19071) and receptor protein tyrosine phosphatase sigma (PTPRS) (Aricescu et al. 2002).

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2013-05-22	Reviewed	Ricard-Blum, S.

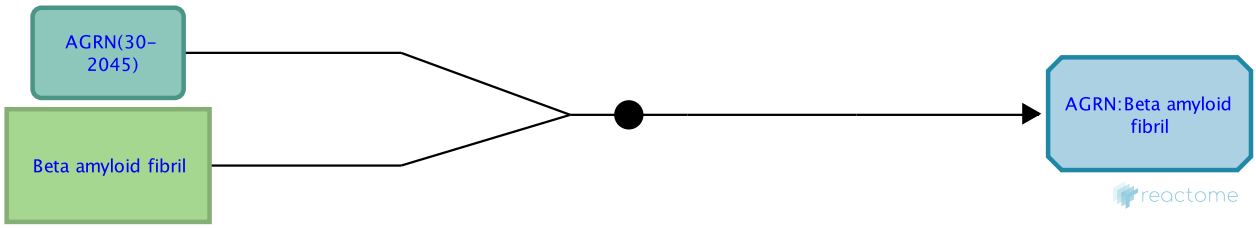
AGRN binds Beta amyloid fibril via GAG chains ↗

Location: ECM proteoglycans

Stable identifier: R-HSA-2467665

Type: binding

Compartments: extracellular region



Several agrin (AGRN) ligands require the presence of heparan-sulfate GAG sidechains and probably represent interactions with them. Extracellular ligands include Beta-amyloid (Donahue et al. 1999, Cotman et al. 2000). Other ligands (unconfirmed in humans) include alpha-synuclein fibrils (chicken - Liu et al. 2005), HB-GAM/pleiotropin (Dagget et al. 1996), thrombospondin and FGF2 (Cotman et al. 1999).

Literature references

Cotman, SL., Halfter, W., Cole, GJ. (2000). Agrin binds to beta-amyloid (Abeta), accelerates abeta fibril formation, and is localized to Abeta deposits in Alzheimer's disease brain. *Mol. Cell. Neurosci., 15*, 183-98. ↗

Donahue, JE., Berzin, TM., Rafii, MS., Glass, DJ., Yancopoulos, GD., Fallon, JR. et al. (1999). Agrin in Alzheimer's disease: altered solubility and abnormal distribution within microvasculature and brain parenchyma. *Proc. Natl. Acad. Sci. U.S.A., 96*, 6468-72. ↗

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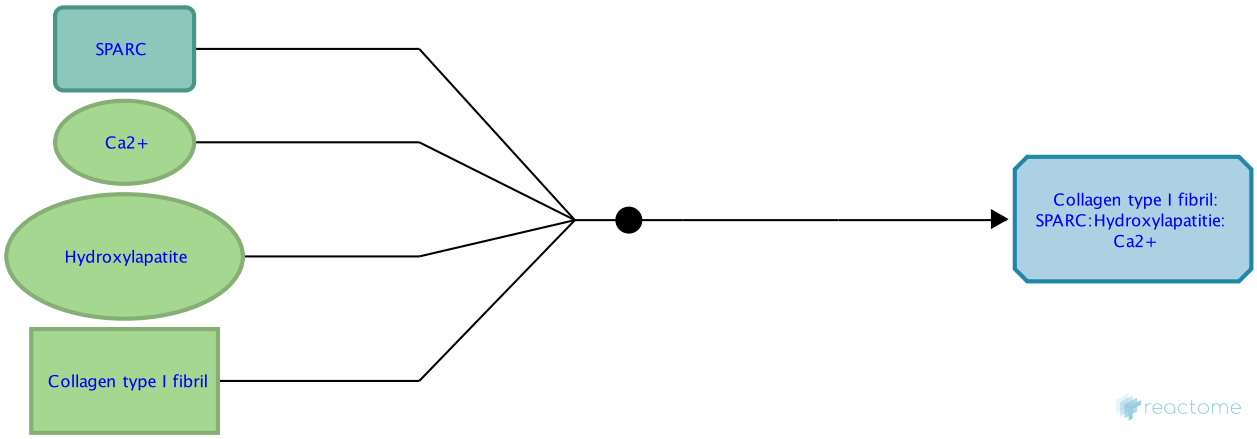
SPARC binds Collagen type I fibril, hydroxylapatite and Ca2+ ↗

Location: ECM proteoglycans

Stable identifier: R-HSA-2424243

Type: binding

Compartments: extracellular region



Secreted protein acidic and rich in cysteine (SPARC), also known as osteonectin or BM-40, binds Collagen type I, hydroxyapatite and Ca2+, suggesting a role in the mineralization of bone and cartilage (Termine et al. 1981). It is expressed by osteoblasts, odontoblasts, and many other cell types (Romanowski et al. 1990, Mundlos et al. 1992, Papagerakis et al. 2002). SPARC expression has been used to follow the progression of osteoblast cytodifferentiation.

Literature references

Romanowski, R., Jundt, G., Termine, JD., von der Mark, K., Schulz, A. (1990). Immunoelectron microscopy of osteonectin and type I collagen in osteoblasts and bone matrix. *Calcif. Tissue Int., 46*, 353-60. ↗

Editions

2013-01-10	Authored	Jupe, S.
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2013-05-22	Reviewed	Ricard-Blum, S.

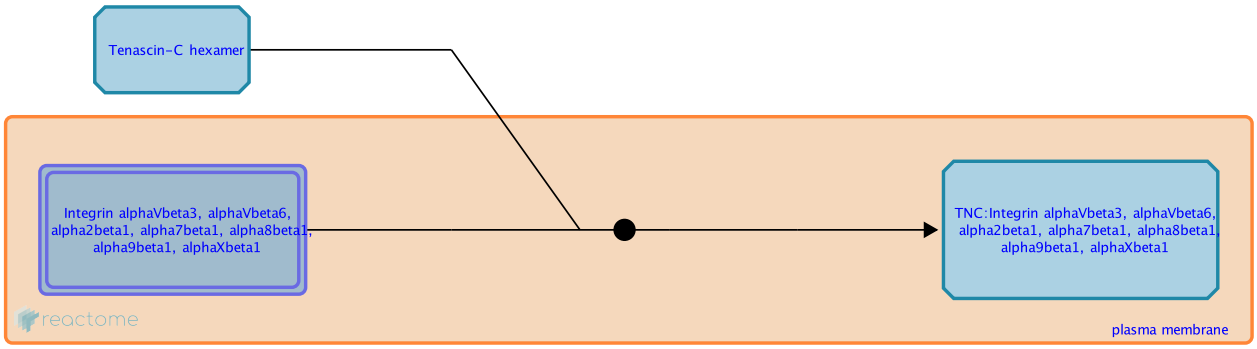
TNC binds Integrin alphaVbeta3, alphaVbeta6, alpha2beta1, alpha7beta1, alpha8beta1, alpha9beta1, alphaXbeta1 ↗

Location: ECM proteoglycans

Stable identifier: R-HSA-2681667

Type: binding

Compartments: plasma membrane, extracellular region



Tenascins are a family of 4 oligomeric extracellular glycoproteins, tenascin (TN) C, R, X, and W. In rotary shadowing images TNC is seen as a symmetrical structure called a hexabrachion (Erickson & Iglesias 1984). This hexamer is formed from initial trimers (Kammerer et al. 1988). All members of the family are believed able to form trimers but only C, R and W have the extra cysteine required for form hexamers. All have amino-terminal heptad repeats, epidermal growth factor (EGF)-like repeats, fibronectin type III domain repeats, and a carboxyl-terminal fibrinogen-like globular domain (Hsia & Schwartzbauer 2005). TNC was the first family member to be discovered and is the best characterised (Midwood et al. 2011). Its subunits vary greatly in size (between 190 and 330 kDa of the tenascin-C monomer) due to glycosylation and splicing isoforms (Joester & Faissner 1999). During embryonic development TNC is expressed in neural, skeletal, and vascular tissues. In adults it is detectable only in tendon and tissues undergoing remodeling processes such as wound repair and neovascularization, or in pathological processes such as inflammation and tumorigenesis (Midwood & Orend, 2009).

TNC binds several integrins including alpha2beta1 (Sriramararo et al. 1993), alphaVbeta6 (Yokosaki et al. 1996), alphaVbeta3 (Sriramararo et al. 1993, Yokosaki et al. 1996), alpha9beta1 (Yokosaki et al. 1996), alphaXbeta1 (Probstmeier & Peshva 1999), alpha8beta1 (Schnapp 1995) and alpha7beta1 (Mercado et al. 2004).

Literature references

Sriramarao, P., Mendler, M., Bourdon, MA. (1993). Endothelial cell attachment and spreading on human tenascin is mediated by alpha 2 beta 1 and alpha v beta 3 integrins. *J. Cell. Sci., 105*, 1001-12. ↗

Yokosaki, Y., Monis, H., Chen, J., Sheppard, D. (1996). Differential effects of the integrins alpha9beta1, alphavbeta3, and alphavbeta6 on cell proliferative responses to tenascin. Roles of the beta subunit extracellular and cytoplasmic domains. *J Biol Chem, 271*, 24144-50. ↗

Probstmeier, R., Pesheva, P. (1999). Tenascin-C inhibits beta1 integrin-dependent cell adhesion and neurite outgrowth on fibronectin by a disialoganglioside-mediated signaling mechanism. *Glycobiology, 9*, 101-14. ↗

Schnapp, LM., Hatch, N., Ramos, DM., Klimanskaya, IV., Sheppard, D., Pytela, R. (1995). The human integrin alpha 8 beta 1 functions as a receptor for tenascin, fibronectin, and vitronectin. *J Biol Chem, 270*, 23196-202. ↗

Mercado, ML., Nur-e-Kamal, A., Liu, HY., Gross, SR., Movahed, R., Meiners, S. (2004). Neurite outgrowth by the alternatively spliced region of human tenascin-C is mediated by neuronal alpha7beta1 integrin. *J. Neurosci., 24*, 238-47. ↗

Editions

2013-01-10	Authored	Jupe, S.
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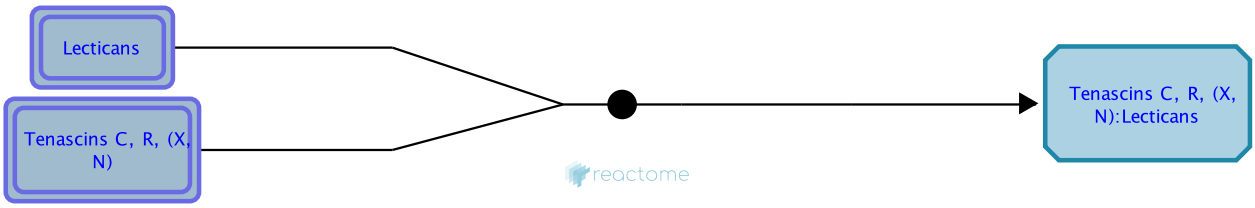
Tenascins C, R, (X, N) bind lecticans ↗

Location: ECM proteoglycans

Stable identifier: R-HSA-2424246

Type: binding

Compartments: extracellular region



Tenascins are a family of 4 oligomeric extracellular glycoproteins, tenascin (TN) C, R, X, and N (also called W). In rotary shadowing images TNC is seen as a symmetrical structure called a hexabrachion (Erickson & Iglesias 1984). This hexamer is formed from initial trimers (Kammerer et al. 1988). All members of the family are believed able to form trimers but only C, R and W have the extra cysteine required for form hexamers. All have amino-terminal heptad repeats, epidermal growth factor (EGF)-like repeats, fibronectin type III domain repeats, and a carboxyl-terminal fibrinogen-like globular domain (Hsia & Schwartzbauer 2005). TNC was the first family member to be discovered and is the best characterised. Its subunits vary greatly in size (between 190 and 330 kDa of the tenascin-C monomer) due to glycosylation and splicing isoforms (Joester & Faissner 1999). During embryonic development TNC is expressed in neural, skeletal, and vascular tissues. In adults it is detectable only in tendon and tissues undergoing remodeling processes such as wound repair and neovascularization, or in pathological processes such as inflammation and tumorigenesis (Midwood & Orend 2009). TNR forms dimers and trimers (Norenberg et al. 1992) and is expressed only in the developing and adult central nervous system. TNC and TNR-null mice (single and double knock-outs) have surprisingly normal gross phenotypes, but exhibit behavioural and wound healing abnormalities (Mackie & Tucker 1999, Montag-Sallaz & Montag 2003). TNX is the largest member of the family and is widely expressed during development, but in adults is limited to musculoskeletal, cardiac, and dermal tissue. It can form trimers, though it lacks the amino-terminal cysteine residues involved in hexamer formation. It is clearly associated with a variant of a heritable connective tissue disorder known as Ehler-Danlos Syndrome, which is associated with fibrillar collagen defects (Burch et al. 1997, Mao et al. 2002). TNY is thought to be an avian orthologue of TNX (Chiquet-Ehrismann 2004). TNN, first identified in zebrafish (Weber et al. 1998), is the least well characterized member of the tenascin family. It forms hexamers (Degen et al. 2007) and is expressed in developing skeletal tissue and neural crest cells, a pattern that partially overlaps with TNC.

TNC and TNR bind to members of the lectican family, a class of extracellular chondroitin sulfate proteoglycans consisting of aggrecan, versican, brevican and neurocan. TNC binds aggrecan (Lundell et al. 2004), versican (Tsujii et al. 2006) and neurocan (Milev et al. 1994, Grumet et al. 1994, Rauch et al. 1997). TNR binds aggrecan (Aspberg et al. 1997, Lundell et al. 2004), versican (Aspberg et al. 1995, 1997), brevican Aspberg et al. 1997, Hagihara et al. 1999) and neurocan (Aspberg et al. 1997).

Literature references

Lundell, A., Olin, AI., Mörgelin, M., al-Karadaghi, S., Aspberg, A., Logan, DT. (2004). Structural basis for interactions between tenascins and lectican C-type lectin domains: evidence for a crosslinking role for tenascins. *Structure, 12* , 1495-506. ↗

Tsujii, M., Hirata, H., Yoshida, T., Imanaka-Yoshida, K., Morita, A., Uchida, A. (2006). Involvement of tenascin-C and PG-M/versican in flexor tenosynovial pathology of idiopathic carpal tunnel syndrome. *Histol. Histopathol., 21*, 511-8. ↗

Rauch, U., Clement, A., Retzler, C., Fröhlich, L., Fässler, R., Göhring, W. et al. (1997). Mapping of a defined neurocan binding site to distinct domains of tenascin-C. *J. Biol. Chem., 272*, 26905-12. ↗

Aspberg, A., Miura, R., Bourdoulous, S., Shimonaka, M., Heinegârd, D., Schachner, M. et al. (1997). The C-type lectin domains of lecticans, a family of aggregating chondroitin sulfate proteoglycans, bind tenascin-R by protein-protein interactions independent of carbohydrate moiety. *Proc. Natl. Acad. Sci. U.S.A., 94*, 10116-21. ↗

Editions

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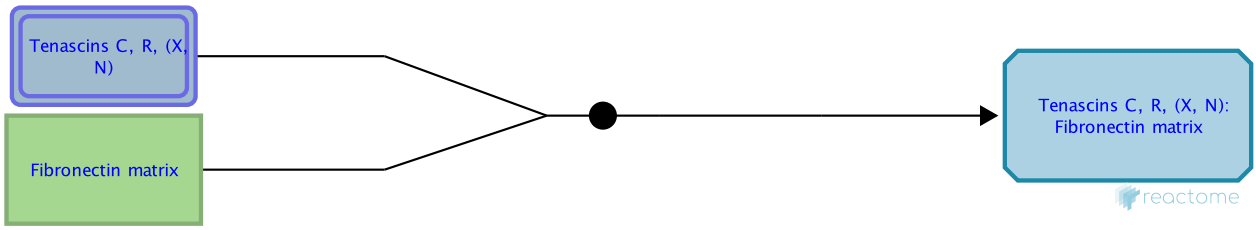
Tenascins C, R, (X, N) bind fibronectin matrix ↗

Location: ECM proteoglycans

Stable identifier: R-HSA-2681681

Type: binding

Compartments: extracellular region



Tenascins are a family of 4 oligomeric extracellular glycoproteins, tenascin (TN) C, R, X, and N (also called W). In rotary shadowing images TNC is seen as a symmetrical structure called a hexabrachion (Erickson & Iglesias 1984). This hexamer is formed from initial trimers (Kammerer et al. 1988). All members of the family are believed able to form trimers but only C, R and N have the extra cysteine required for form hexamers. All have amino-terminal heptad repeats, epidermal growth factor (EGF)-like repeats, fibronectin type III domain repeats, and a carboxyl-terminal fibrinogen-like globular domain (Hsia & Schwartzbauer 2005). TNC was the first to be discovered and is the best characterised. Its subunits vary greatly in size due to glycosylation and splicing isoforms (Joester & Faissner 1999). During embryonic development TNC is expressed in neural, skeletal, and vascular tissues. In adults it is detectable only in tendon and tissues undergoing remodeling processes such as wound repair and neovascularization, or in pathological processes such as inflammation and tumorigenesis. TNR forms dimers and trimers (Norenberg et al. 1992) and is expressed only in the central nervous system. TNC and TNR-null mice (single and double knock-outs) have surprisingly normal gross phenotypes, but exhibit behavioural and wound healing abnormalities (Mackie & Tucker 1999, Montag-Sallaz & Montag 2003). TNX is the largest member of the family and is widely expressed during development, but in adults is limited to musculoskeletal, cardiac, and dermal tissue. It can form trimers, though it lacks the amino-terminal cysteine residues involved in hexamer formation. It is clearly associated with a variant of a heritable connective tissue disorder known as Ehler-Danlos Syndrome, which is associated with fibrillar collagen defects (Burch et al. 1997, Mao et al. 2002). TNY is thought to be an avian orthologue of TNX (Chiquet-Ehrismann 2004). TNN, first identified in zebrafish (Weber et al. 1998), is the least well characterized member of the tenascin family. It forms hexamers (Degen et al. 2007) and is expressed in developing skeletal tissue and neural crest cells, a pattern that partially overlaps with TNC.

TNC and TNR bind with high affinity to fibronectin (FN) (Chiquet-Ehrismann et al. 1991, Chung et al. 1995, Chung & Erickson 1997, Hauzenberger et al. 1999, Ingham et al. 2004, To & Midwood 2011, Pesheva et al. 1994), modulating the cell adhesion function of FN either by binding or restricting access of FN to integrin binding sites (Lightner & Erickson 1990) or by binding to cell receptors and altering their responsiveness to FN (Prieto et al. 1992, Fischer et al. 1997). The interaction of Tenascin and FN impacts tissue structure by controlling the assembly, maintenance, and turnover of the ECM at the cell surface (To & Midwood 2010).

Literature references

Chung, CY., Zardi, L., Erickson, HP. (1995). Binding of tenascin-C to soluble fibronectin and matrix fibrils. *J. Biol. Chem., 270*, 29012-7. ↗

Pesheva, P., Probstmeier, R., Skubitz, AP., McCarthy, JB., Furcht, LT., Schachner, M. (1994). Tenascin-R (J1 160/180 inhibits fibronectin-mediated cell adhesion--functional relatedness to tenascin-C. *J. Cell. Sci., 107*, 2323-33. ↗

Editions

2013-01-10	Authored	Jupe, S.
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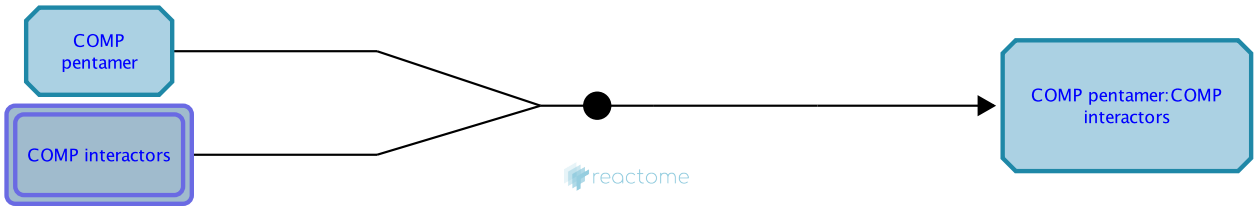
COMP binds collagen, fibronectin, aggrecan and matrilins ↗

Location: ECM proteoglycans

Stable identifier: R-HSA-2424252

Type: binding

Compartments: extracellular region



Cartilage oligomeric matrix protein (COMP, thrombospondin-5) is a 524-kDa pentameric glycoprotein expressed primarily in cartilage, tendon, ligament and synovium. In adult cartilage, COMP is located primarily in the inter-territorial matrix between chondrocytes (Murphy et al. 1999). The mature protein is pentameric with each monomer linked to its neighbour by a disulphide bond, located at the amino terminus of the protein (Hedbom et al. 1992, Morgelin et al. 1992). COMP binds directly to collagen types I, II and IX (Rosenberg et al. 1998, Thur et al. 2001) at the fibril periphery. In addition it binds fibronectin (FN1) (Di Cesare et al. 2002), matrilins 1, 3 and 4 (Mann et al. 2004), and through the glycosaminoglycans heparan sulphate and chondroitin sulphate to aggrecan (Hauser et al. 1996, Chen et al. 2007).

Mutations in COMP lead to pseudoachondroplasia and multiple epiphyseal dysplasia (Jackson et al. 2012). COMP binding to FN1 and probably to other partners requires the presence of the divalent cations Ca2+, Mg2+ or Mn2+. Each COMP subunit binds approximately 10 calcium ions (Chen et al. 2000).

Literature references

Rosenberg, K., Olsson, H., Mörgelin, M., Heinegård, D. (1998). Cartilage oligomeric matrix protein shows high affinity zinc-dependent interaction with triple helical collagen. *J. Biol. Chem., 273*, 20397-403. ↗

Thur, J., Rosenberg, K., Nitsche, DP., Pihlajamaa, T., Ala-Kokko, L., Heinegård, D. et al. (2001). Mutations in cartilage oligomeric matrix protein causing pseudoachondroplasia and multiple epiphyseal dysplasia affect binding of calcium and collagen I, II, and IX. *J. Biol. Chem., 276*, 6083-92. ↗

Di Cesare, PE., Chen, FS., Moergelin, M., Carlson, CS., Leslie, MP., Perris, R. et al. (2002). Matrix-matrix interaction of cartilage oligomeric matrix protein and fibronectin. *Matrix Biol., 21*, 461-70. ↗

Mann, HH., Ozbek, S., Engel, J., Paulsson, M., Wagener, R. (2004). Interactions between the cartilage oligomeric matrix protein and matrilins. Implications for matrix assembly and the pathogenesis of chondrodysplasias. *J. Biol. Chem., 279*, 25294-8. ↗

Hauser, N., Paulsson, M., Heinegård, D., Mörgelin, M. (1996). Interaction of cartilage matrix protein with aggrecan. Increased covalent cross-linking with tissue maturation. *J. Biol. Chem., 271*, 32247-52. ↗

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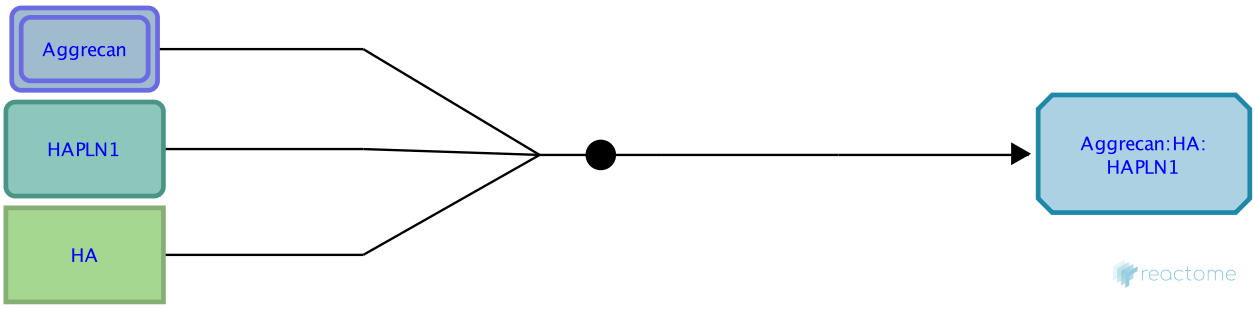
Aggrecan binds Hyaluronan and HAPLN1 ↗

Location: ECM proteoglycans

Stable identifier: R-HSA-2318623

Type: binding

Compartments: extracellular region



In articular cartilage the major non-fibrous macromolecules are aggrecan, hyaluronan (HA) and hyaluronan and proteoglycan link protein 1 (HAPLN1). The high negative charge density of these molecules leads to the binding of large amounts of water (Bruckner 2006). HA is bound by large aggregating proteoglycans (the hyalectans). Aggrecan (ACAN) is predominantly expressed in cartilage, versican is widely distributed, while brevican and neurocan are largely restricted to nervous tissues. ACAN is ~90% carbohydrate. The core protein is highly glycosylated, mostly by the glycosaminoglycan (GAG) chains chondroitin sulphate (CS) and keratan sulphate (KS). Each ACAN molecule has ~100 CS chains of around 20 kDa and ~60 KS chains of 5-15 kDa. CS is attached to an extended domain between globular domains 2 and 3, while KS is widely distributed. The core protein also contains sites for the attachment of N-linked and O-linked oligosaccharides (Nilsson et al. 1982).

The G1 N-terminal domain of ACAN has a lectin-like binding site with high affinity for HA (Watanabe et al. 1997, Hardingham 2006). HA is a long unbranched, unsulphated GAG synthesized free from protein attachment by three HA synthases (Spicer & McDonald 1998). It has an average molecular weight of several million Da. HA content steadily rises in aging cartilage and can reach 10% of the total GAG. ACAN, HA and the small glycoprotein HAPLN1, known as Link protein, are found in huge multi-molecular aggregates comprised of numerous ACAN monomers non-covalently bound to HA, stabilized by HAPLN1 which forms a ternary complex with the G1 domain of ACAN and HA (Ratcliffe & Hardingham 1983, Grover & Roughley 1994, Kiani et al. 2002).

Literature references

Ratcliffe, A., Hardingham, T. (1983). Cartilage proteoglycan binding region and link protein. Radioimmunoassays and the detection of masked determinants in aggregates. *Biochem. J., 213*, 371-8. ↗

Watanabe, H., Cheung, SC., Itano, N., Kimata, K., Yamada, Y. (1997). Identification of hyaluronan-binding domains of aggrecan. *J. Biol. Chem., 272*, 28057-65. ↗

Grover, J., Roughley, PJ. (1994). The expression of functional link protein in a baculovirus system: analysis of mutants lacking the A, B and B' domains. *Biochem. J., 300*, 317-24. ↗

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2013-05-22	Reviewed	Ricard-Blum, S.

IBSP binds collagen type I ↗

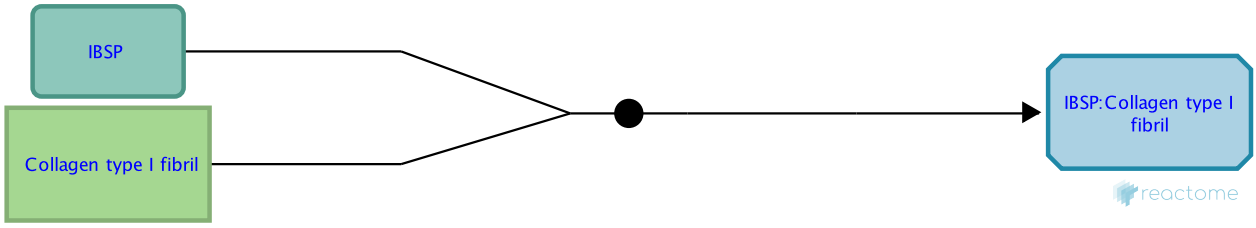
Location: ECM proteoglycans

Stable identifier: R-HSA-4086204

Type: binding

Compartments: extracellular region

Inferred from: Ibsp binds collagen type I (Rattus norvegicus)



Bone sialoprotein 2 (IBSP) is an anionic phosphorylated glycoprotein expressed almost exclusively in mineralized tissues. It is a potent nucleator of hydroxyapatite formation. The binding of IBSP to collagen is thought to be important for the initiation of bone mineralization and in the adhesion of bone cells to the mineralized matrix (Fujisawa et al. 1995, Tye et al. 2005).

Editions

2012-08-08	Authored	Jupe, S.
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2013-08-13	Reviewed	Ricard-Blum, S.

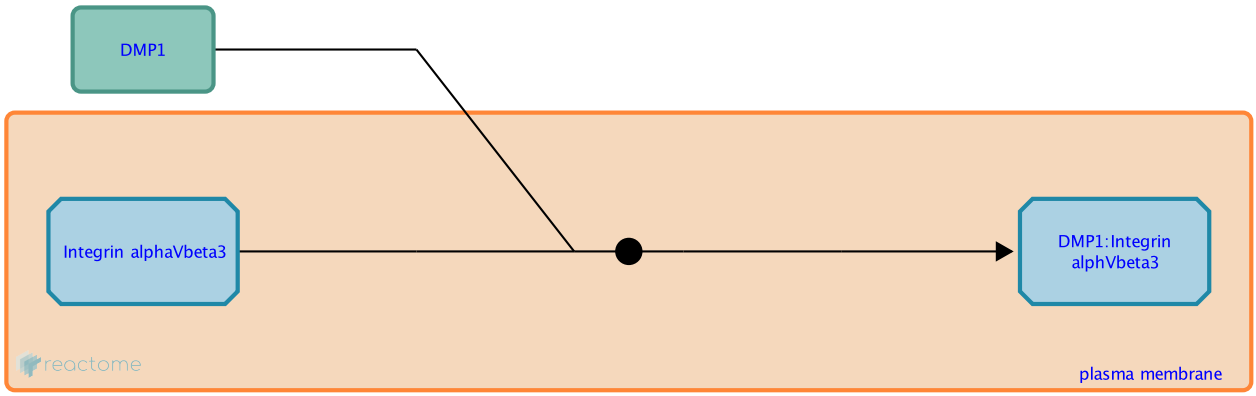
Dentin matrix protein 1 binds integrin alphaVbeta3 ↗

Location: ECM proteoglycans

Stable identifier: R-HSA-4086200

Type: binding

Compartments: plasma membrane, extracellular region



Dentin matrix phosphoprotein 1 (DMP1) is a non-collagenous, acidic extracellular matrix protein expressed chiefly in bone and dentin. DMP1 acts via interaction with alphaVbeta3 integrin (Wu et al. 2011).

Literature references

Wu, H., Teng, PN., Jayaraman, T., Onishi, S., Li, J., Bannon, L. et al. (2011). Dentin matrix protein 1 (DMP1) signals via cell surface integrin. *J. Biol. Chem., 286*, 29462-9. ↗

Editions

2012-08-08	Authored	Jupe, S.
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2013-08-13	Reviewed	Ricard-Blum, S.

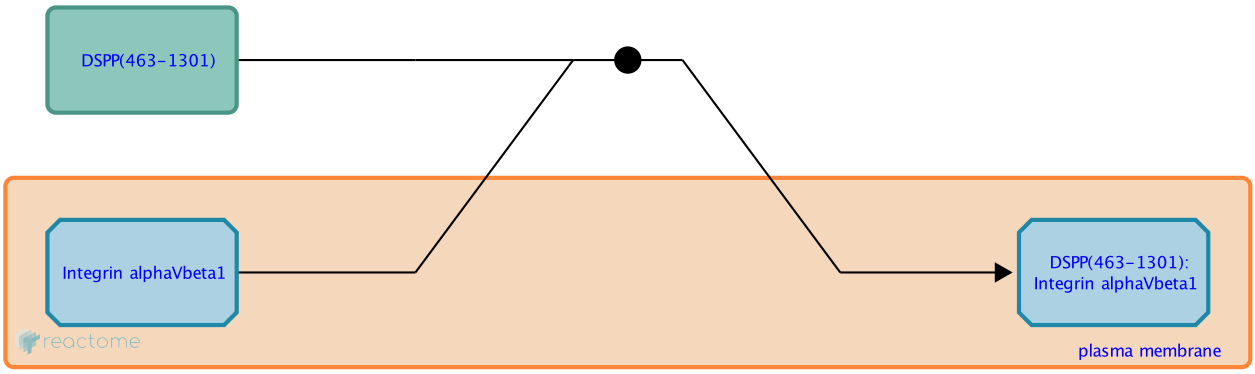
Dentin phosphoprotein binds integrin alphaVbeta1 ↗

Location: ECM proteoglycans

Stable identifier: R-HSA-4086132

Type: binding

Compartments: extracellular region, plasma membrane



DPP (also called “phosphophoryn”) is a highly acidic protein and is the major noncollagenous matrix component of dentin (13,–,15). The molecule is so-called because it is considered to be a “phosphate carrier” (16). DPP is exceedingly rich in aspartic acid and serine residues ((DSS)n), and about 90% of the serine residues are phosphorylated (17, 18). This enables DPP to have a strong affinity for calcium ion, and thus it significantly promotes the growth of hydroxyapatite crystals when bound to collagen fibrils in vitro.

Literature references

Eapen, A., Ramachandran, A., George, A. (2012). Dentin phosphoprotein (DPP) activates integrin-mediated anchorage-dependent signals in undifferentiated mesenchymal cells. *J. Biol. Chem., 287*, 5211-24. ↗

Editions

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2013-08-13	Edited	Jupe, S.
2013-08-13	Reviewed	Ricard-Blum, S.

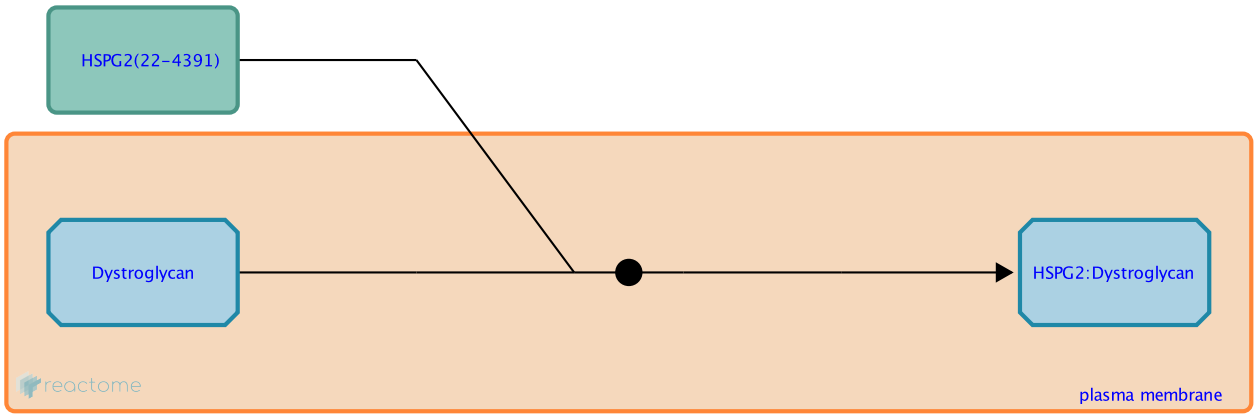
HSPG2 (perlecan) binds alpha-dystroglycan ↗

Location: ECM proteoglycans

Stable identifier: R-HSA-2396395

Type: binding

Compartments: plasma membrane, extracellular region



HSPG2 (perlecan) is a modular proteoglycan primarily located in the basement membranes of vascularized tissues. It is involved in several developmental processes, both during embryogenesis and in human disease such as cancer and diabetes (Iozzo et al. 1994). Domain V of the core protein binds alpha-dystroglycan (Talts et al. 1999), which in vivo forms a membrane-associated heterodimer with beta-dystroglycan (Peng et al. 1998).

Literature references

Talts, JF., Andac, Z., Göhring, W., Brancaccio, A., Timpl, R. (1999). Binding of the G domains of laminin alpha1 and alpha2 chains and perlecan to heparin, sulfatides, alpha-dystroglycan and several extracellular matrix proteins. *EMBO J., 18*, 863-70. ↗

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Table of Contents