ECM proteoglycans

Jupe, S., Ricard-Blum, S., Venkatesan, N.

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

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of Creative Commons Attribution 4.0 International (CC BY 4.0) License. For more information see our license.

This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

12/11/2022

https://reactome.org
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: 82

This document contains 1 pathway and 23 reactions (see Table of Contents)

https://reactome.org
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 up to 100 aggrecan molecules and these aggregates are stabilized by a link protein.

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-01-10</td>
<td>Authored</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2013-04-26</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2013-05-21</td>
<td>Reviewed</td>
<td>Venkatesan, N.</td>
</tr>
<tr>
<td>2013-05-22</td>
<td>Reviewed</td>
<td>Ricard-Blum, S.</td>
</tr>
</tbody>
</table>
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, Cabella-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).
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


### Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-01-10</td>
<td>Authored</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2013-04-26</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2013-05-21</td>
<td>Reviewed</td>
<td>Venkatesan, N.</td>
</tr>
<tr>
<td>2013-05-22</td>
<td>Reviewed</td>
<td>Ricard-Blum, S.</td>
</tr>
</tbody>
</table>
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).


**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-01-10</td>
<td>Authored</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2013-04-26</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2013-05-21</td>
<td>Reviewed</td>
<td>Venkatesan, N.</td>
</tr>
<tr>
<td>2013-05-22</td>
<td>Reviewed</td>
<td>Ricard-Blum, S.</td>
</tr>
</tbody>
</table>
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).


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-01-10</td>
<td>Authored</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2013-04-26</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2013-05-21</td>
<td>Reviewed</td>
<td>Venkatesan, N.</td>
</tr>
<tr>
<td>2013-05-22</td>
<td>Reviewed</td>
<td>Ricard-Blum, S.</td>
</tr>
</tbody>
</table>

https://reactome.org
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).

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-01-10</td>
<td>Authored</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2013-04-26</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2013-05-21</td>
<td>Reviewed</td>
<td>Venkatesan, N.</td>
</tr>
<tr>
<td>2013-05-22</td>
<td>Reviewed</td>
<td>Ricard-Blum, S.</td>
</tr>
</tbody>
</table>
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

VTN binds integrins alphaVbeta1, alphaVbeta3, alpha3beta5, alphaIIbbeta3

**Location:** ECM proteoglycans

**Stable identifier:** R-HSA-2426471

**Type:** binding

**Compartments:** plasma membrane, extracellular region


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**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-01-10</td>
<td>Authored</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2013-04-26</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2013-05-21</td>
<td>Reviewed</td>
<td>Venkatesan, N.</td>
</tr>
<tr>
<td>2013-05-22</td>
<td>Reviewed</td>
<td>Ricard-Blum, S.</td>
</tr>
</tbody>
</table>

https://reactome.org
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

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).

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).

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).
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).
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**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-01-10</td>
<td>Authored</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2013-04-26</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2013-05-21</td>
<td>Reviewed</td>
<td>Venkatesan, N.</td>
</tr>
<tr>
<td>2013-05-22</td>
<td>Reviewed</td>
<td>Ricard-Blum, S.</td>
</tr>
</tbody>
</table>
Secreted protein acidic and rich in cysteine (SPARC), also known as osteonectin or BM-40, binds Collagen type I, hydroxypatite and Ca\(^2+\), 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**

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, tenasin (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).


Literature references


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, tenasin (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 tenasin-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 tenasin 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.


**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-01-10</td>
<td>Authored</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2013-04-26</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2013-05-21</td>
<td>Reviewed</td>
<td>Venkatesan, N.</td>
</tr>
<tr>
<td>2013-05-22</td>
<td>Reviewed</td>
<td>Ricard-Blum, S.</td>
</tr>
</tbody>
</table>
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, tenasin (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). TNX, first identified in zebrafish (Weber et al. 1998), is the least well characterized member of the tenasin 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, Hauenberger 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**


[https://reactome.org](https://reactome.org)
## Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-01-10</td>
<td>Authored</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2013-04-26</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2013-05-21</td>
<td>Reviewed</td>
<td>Venkatesan, N.</td>
</tr>
<tr>
<td>2013-05-22</td>
<td>Reviewed</td>
<td>Ricard-Blum, S.</td>
</tr>
</tbody>
</table>
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**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-01-10</td>
<td>Authored</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2013-04-26</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2013-05-21</td>
<td>Reviewed</td>
<td>Venkatesan, N.</td>
</tr>
<tr>
<td>2013-05-22</td>
<td>Reviewed</td>
<td>Ricard-Blum, S.</td>
</tr>
</tbody>
</table>
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


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
<th>Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-01-10</td>
<td>Authored</td>
<td>Jupe, S.</td>
<td></td>
</tr>
<tr>
<td>2013-04-26</td>
<td>Edited</td>
<td>Jupe, S.</td>
<td></td>
</tr>
<tr>
<td>2013-05-21</td>
<td>Reviewed</td>
<td>Venkatesan, N.</td>
<td></td>
</tr>
<tr>
<td>2013-05-22</td>
<td>Reviewed</td>
<td>Ricard-Blum, S.</td>
<td></td>
</tr>
</tbody>
</table>
**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**

<table>
<thead>
<tr>
<th>Date</th>
<th>Type</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012-08-08</td>
<td>Authored</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2013-08-13</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2013-08-13</td>
<td>Reviewed</td>
<td>Ricard-Blum, S.</td>
</tr>
</tbody>
</table>
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


Editions

<table>
<thead>
<tr>
<th>Edition</th>
<th>Authored</th>
<th>Edited</th>
<th>Reviewed</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012-08-08</td>
<td>Jupe, S.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2013-08-13</td>
<td></td>
<td>Jupe, S.</td>
<td></td>
</tr>
<tr>
<td>2013-08-13</td>
<td></td>
<td></td>
<td>Ricard-Blum, S.</td>
</tr>
</tbody>
</table>

https://reactome.org
Dentin phosphoprotein binds integrin alphaVbeta1

Location: ECM proteoglycans

Stable identifier: R-HSA-4086132

Type: binding

Compartments: plasma membrane, extracellular region

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


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012-08-08</td>
<td>Authored</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2013-08-13</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2013-08-13</td>
<td>Reviewed</td>
<td>Ricard-Blum, S.</td>
</tr>
</tbody>
</table>
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**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012-08-08</td>
<td>Authored</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2013-08-13</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2013-08-13</td>
<td>Reviewed</td>
<td>Ricard-Blum, S.</td>
</tr>
</tbody>
</table>
# Table of Contents

1. Introduction

2. ECM proteoglycans
   - SLRPs bind TGF Beta
   - DCN binds collagen I, II, III, VI fibrils
   - BGN binds Collagen types I, VI, (IX)
   - BGN binds Collagen types II, III
   - VTN binds collagens I, IV and VI
   - VTN binds collagens II, III and V
   - VTN binds integrins alphaVbeta1, alphaVbeta3, alpha3beta5, alphaIIIBbeta3
   - VTN binds Plasminogen activator inhibitor-1
   - AGRN binds Alpha-dystroglycan
   - AGRN binds LRP4:MUSK
   - AGRN binds Laminins with gamma-1 subunit
   - AGRN binds NCAM1, PTPRS
   - AGRN binds Beta amyloid fibril via GAG chains
   - SPARC binds Collagen type I fibril, hydroxylapatite and Ca2+
   - TNC binds Integrin alphaVbeta3, alphaVbeta6, alpha2beta1, alpha7beta1, alpha8beta1, alpha9beta1, alphaXbeta1
   - Tenascins C, R, (X, N) bind lecticans
   - Tenascins C, R, (X, N) bind fibronectin matrix
   - COMP binds collagen, fibronectin, aggrecan and matrilins
   - Aggrecan binds Hyaluronan and HAPLN1
   - IBSP binds collagen type I
   - Dentin matrix protein 1 binds integrin alphaVbeta3
   - Dentin phosphoprotein binds integrin alphaVbeta1
   - HSPG2 (perlecan) binds alpha-dystroglycan

---

Table of Contents