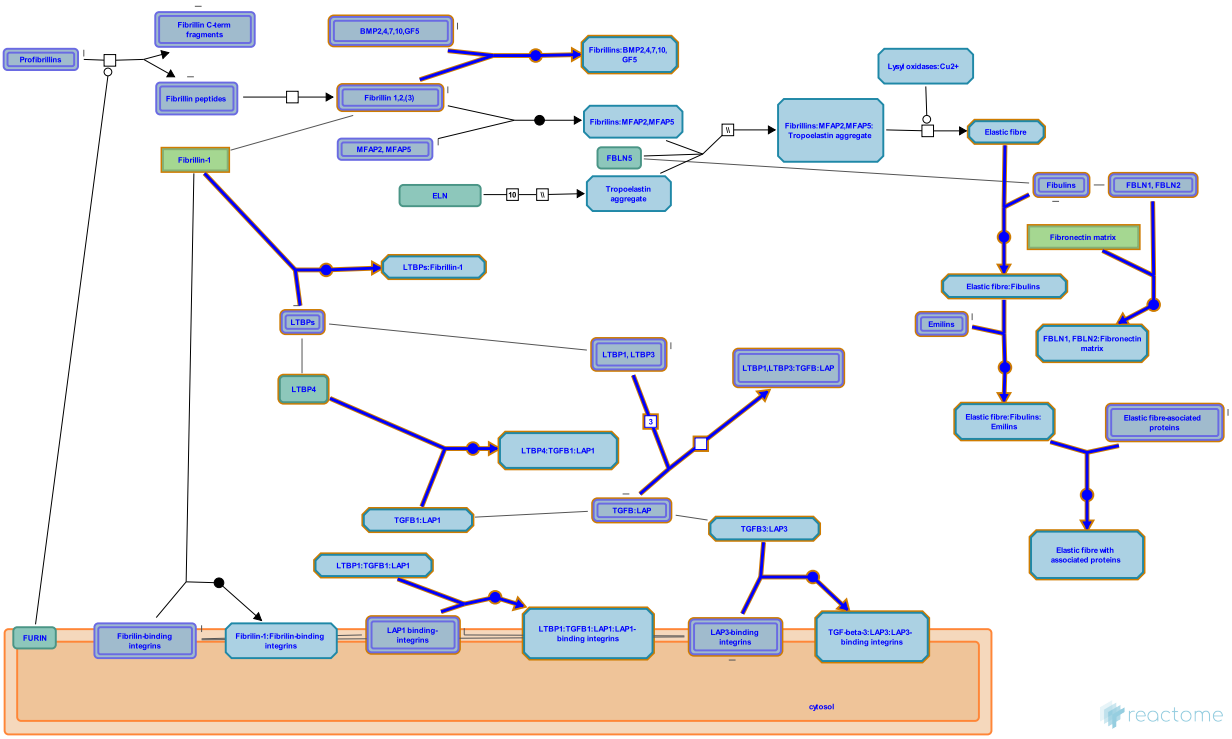
Molecules associated with elastic fibres



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09/11/2024

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

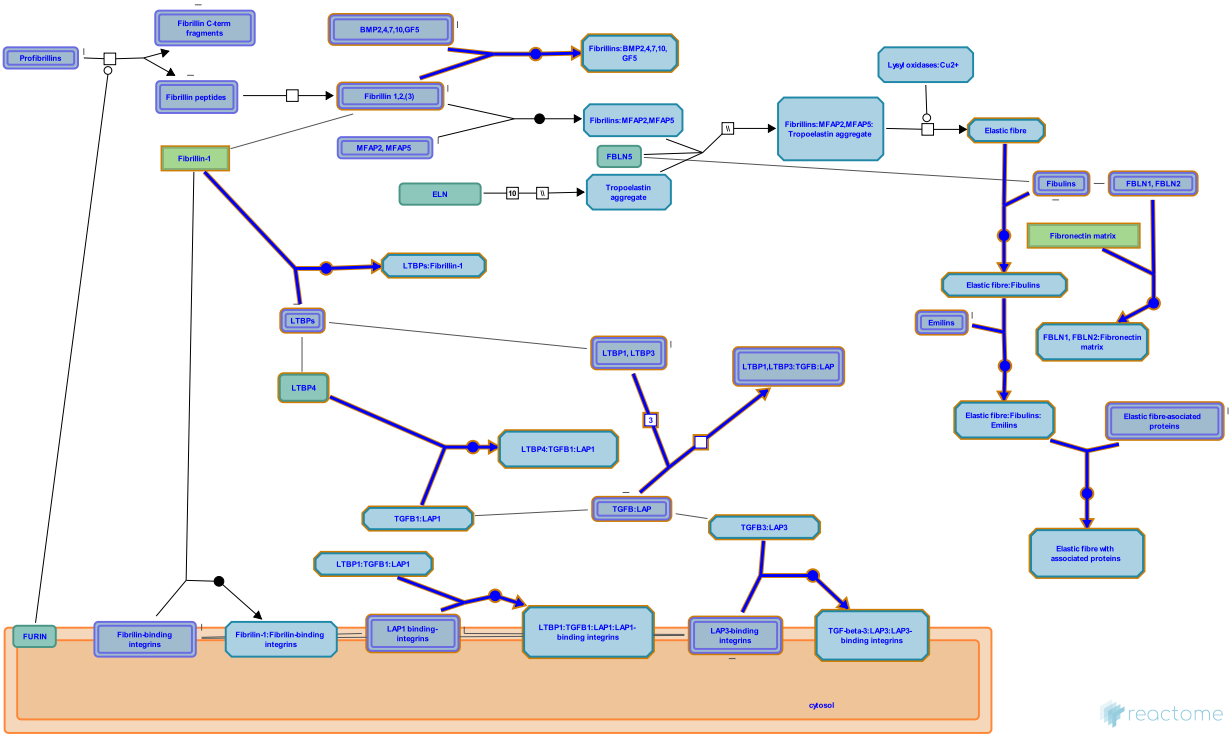
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Molecules associated with elastic fibres ↗

Stable identifier: R-HSA-2129379



Proteins found associated with microfibrils include vitronectin (Dahlback et al. 1990), latent transforming growth factor beta-binding proteins (Kielty et al. 2002, Munger & Sheppard 2011), emilin (Bressan et al. 1993, Mongiat et al. 2000), members of the microfibrillar-associated proteins (MFAPs, Gibson et al.1996), and fibulins (Roark et al. 1995, Yanagisawa et al. 2002). The significance of these interactions is not well understood but may help mediate elastin-fibrillin interactions during elastic fibre assembly.

Proteoglycans such as versican (Isogai et al. 2002), biglycan, and decorin (Reinboth et al. 2002) can interact with the microfibrils. They confer specific properties including hydration, impact absorption, molecular sieving, regulation of cellular activities, mediation of growth factor association, and release and transport within the extracellular matrix (Buczek-Thomas et al. 2002). In addition, glycosaminoglycans have been shown to interact with tropoelastin through its lysine side chains (Wu et al. 1999) regulating tropoelastin assembly (Tu and Weiss, 2008).

Literature references

Kielty, CM., Shuttleworth, CA., Sherratt, MJ. (2002). Elastic fibres. *J Cell Sci, 115*, 2817-28. ↗

Wagenseil, JE., Mecham, RP. (2007). New insights into elastic fiber assembly. *Birth Defects Res. C Embryo Today, 81*, 229-40. ↗

Editions

2012-04-30	Authored	Jupe, S.
2012-11-02	Reviewed	Muiznieks, LD.
2012-11-12	Edited	Jupe, S.

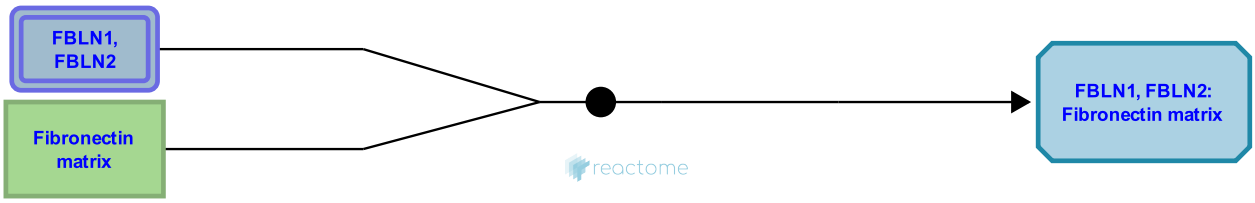
Fibulin-1 and -2 bind fibronectin ↗

Location: Molecules associated with elastic fibres

Stable identifier: R-HSA-2537665

Type: binding

Compartments: extracellular region



Fibulins are a family of 7 extracellular calcium binding proteins that have developmental roles (Twal et al. 2001). Fibulins 1-5 are found in association with elastic fibers. Fibulin-1 binds fibronectin (Balbona et al. 1992, Tran et al. 1997) suppressing fibronectin-mediated inhibitory effects on cell attachment and spreading (Twal et al. 2001). Fibulin-2 also binds fibronectin (Sasaki et al. 1995).

Literature references

Timpl, R., Sasaki, T., Pan, TC., Chu, ML., Göhring, W. (1995). Binding of mouse and human fibulin-2 to extracellular matrix ligands. *J. Mol. Biol., 254*, 892-9. ↗

Argraves, WS., Strickland, DK., Godyna, S., Ingham, KC., Balbona, K., Tran, H. (1992). Fibulin binds to itself and to the carboxyl-terminal heparin-binding region of fibronectin. *J. Biol. Chem., 267*, 20120-5. ↗

Editions

2012-04-30	Authored	Jupe, S.
2012-11-02	Reviewed	Muiznieks, LD.
2012-11-12	Edited	Jupe, S.

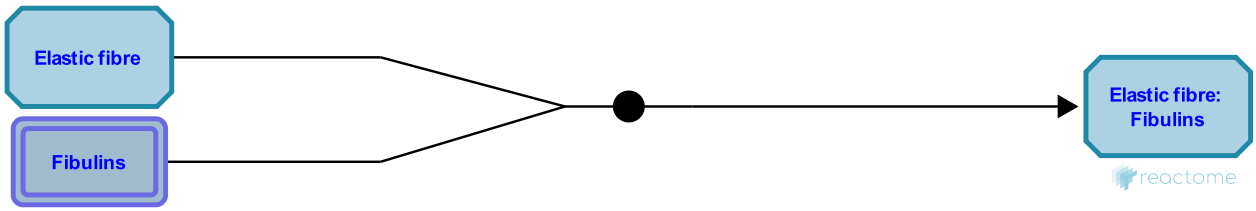
Fibulin binds elastic fibres ↗

Location: Molecules associated with elastic fibres

Stable identifier: R-HSA-1592387

Type: binding

Compartments: extracellular region



Fibulins are a family of 7 genes encoding calcium binding glycoproteins with distinct roles in elastogenesis. They are essential for elastic fibre formation, having a role in regulating and organising tropoelastin formation (Yanagisawa & Davis 2010). Fibulins 1-5 all bind elastin (Roark et al. 1995, Sasaki et al. 1999, Kobayashi et al. 2007). Fibulins 2, 4, 5 and 7 also bind fibrillin (Reinhardt et al. 1996, El Hallous et al. 2007, de Vega et al. 2007). Fibulin 6 has a role in the formation of the cleavage furrow during cytokinesis but its binding partners are unclear (Xu & Vogel 2011).

Literature references

Haudenschild, CC., Little, CD., Keene, DR., Roark, EF., Godyna, S., Argraves, WS. (1995). The association of human fibulin-1 with elastic fibers: an immunohistological, ultrastructural, and RNA study. *J Histochem Cytochem, 43*, 401-11. ↗

Hanisch, FG., Tsuda, T., Kobayashi, N., Kostka, G., Chu, ML., Bächinger, HP. et al. (2007). A comparative analysis of the fibulin protein family. Biochemical characterization, binding interactions, and tissue localization. *J. Biol. Chem., 282*, 11805-16. ↗

Timpl, R., Miosge, N., Sasaki, T., Abrams, WR., Göhring, W., Rosenbloom, J. (1999). Tropoelastin binding to fibulins, nidogen-2 and other extracellular matrix proteins. *FEBS Lett., 460*, 280-4. ↗

Editions

2012-04-30	Authored	Jupe, S.
2012-11-02	Reviewed	Muiznieks, LD.
2012-11-12	Edited	Jupe, S.

Emilin is found in elastic fibres ↗

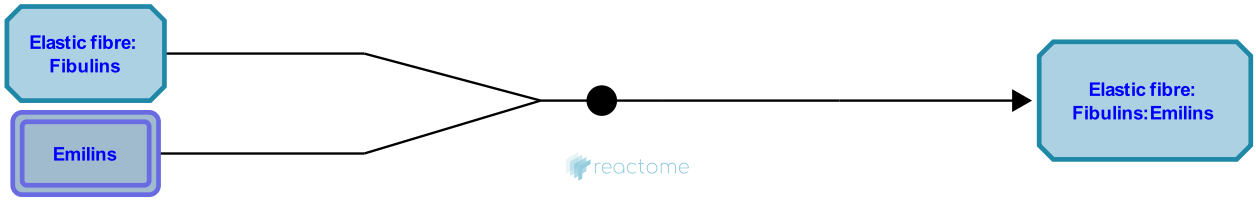
Location: Molecules associated with elastic fibres

Stable identifier: R-HSA-2328048

Type: binding

Compartments: extracellular region

Inferred from: Mouse emilin-1 binds human elastin and mouse fibulin-5 (Homo sapiens)



Elastin microfibril interface located protein (EMILIN)-1 is localized to the microfibril-elastin interface (Bressan et al. 1993). It can bind elastin and fibulin-5 (Zanetti et al. 2004). Emilin1 knockout mice have ultrastructural alterations of the elastic fibers in aorta and skin, abnormal cell morphology and anchorage of endothelial and smooth muscle cells to elastic lamellae, and abnormal elastic fibers in cultured embryonic fibroblasts.

Followed by: Elastic fibres bind associated proteins

Literature references

Colombatti, A., Braghetta, P., Bressan, GM., Bonaldo, P., Doliana, R., Mura, I. et al. (2004). EMILIN-1 deficiency induces elastogenesis and vascular cell defects. *Mol. Cell. Biol., 24*, 638-50. ↗

Editions

2012-04-30	Authored	Jupe, S.
2012-11-02	Reviewed	Muiznieks, LD.
2012-11-12	Edited	Jupe, S.

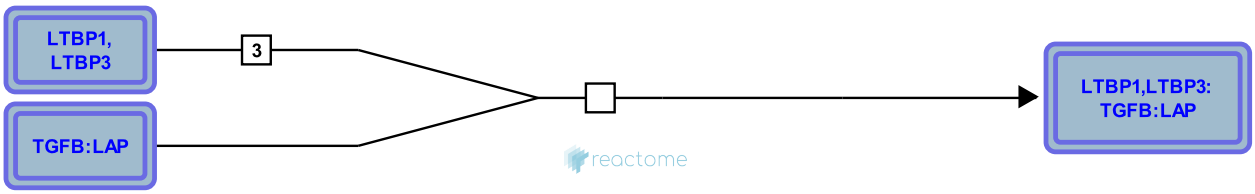
LTBP1, LTBP3 bind TGF-Beta ↗

Location: Molecules associated with elastic fibres

Stable identifier: R-HSA-2395328

Type: transition

Compartments: extracellular region



Transforming growth factor beta (TGF-beta) is a family of three cytokine 'isoforms' (encoded by three separate human genes) that control proliferation, cellular differentiation and other functions. TGF-beta originally referred to the founding member TGF-beta-1, now it is often used as a collective term for all three. TGF-beta is secreted from cells in latent form as part of a complex that includes two other proteins: the cleaved propeptide of TGF beta, known as latency associated peptide (LAP), and a member of the latent TGF beta binding protein (LTBP) family. LTBPs are members of the fibrillin/LTBP superfamily, characterised by the presence of unique TGF-binding protein (TB) domains, also known as 8 cys domains as they contain eight characteristic cysteines (Ramirez & Sakai 2010). LTBPs are microfibril-associated proteins that tether latent complexes of TGF-beta to microfibrils in the ECM (Taipale et al. 1996, Dallas et al. 2000, Isogai et al. 2003, Hyytiainen et al. 2004, Ono et al. 2009, Munger & Sheppard 2011). This allows TGF-beta to be targeted to the ECM where it is maintained in an inactive, latent state (Robertson et al. 2011).

LTBP1 and 3 bind all three isoforms of latent TGF-beta, while LTBP4 only weakly binds TGF-beta1 (Saharinen & Keski Oja 2000). LTBP2 does not bind TGF-beta and is a structural component of fibrillin microfibrils. The carboxyl termini of LTBP1 and LTBP4 binds to fibrillin. The incorporation of LTBP1 and LTBP4 into the ECM is abolished in fibrillin-1 null mice (Ono et al. 2009). The amino terminus of LTBPs binds ECM components such as collagen (Taipale et al. 1996) and fibronectin (Kantola et al. 2008). Fibulins compete for the LTBP sites in fibrillin (Ono et al. 2009).

Followed by: Latent TGF-beta-1 binds integrins

Literature references

Saharinen, J., Keski-Oja, J. (2000). Specific sequence motif of 8-Cys repeats of TGF-beta binding proteins, LTBPs, creates a hydrophobic interaction surface for binding of small latent TGF-beta. *Mol. Biol. Cell, 11*, 2691-704. ↗

Editions

2012-04-30	Authored	Jupe, S.
2012-11-02	Reviewed	Muiznieks, LD.
2012-11-12	Edited	Jupe, S.

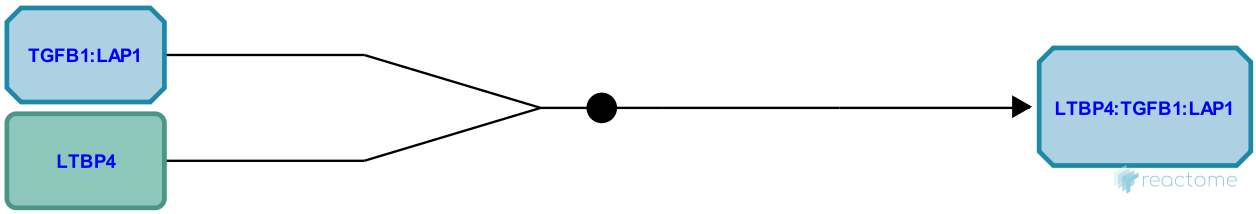
LTBP4 binds TGF-Beta-1 ↗

Location: Molecules associated with elastic fibres

Stable identifier: R-HSA-2395364

Type: binding

Compartments: extracellular region



Transforming growth factor (TGF) beta (TGF-beta) is a family of three cytokine 'isoforms' (encoded by three separate human genes) that control proliferation, cellular differentiation and other functions. TGF-beta originally referred to the founding member TGF-beta-1, now it is often used as a collective term for all three. TGF-beta is secreted from cells in latent form as part of a complex that includes two other proteins: the cleaved propeptide of TGF beta, known as latency associated peptide (LAP), and a member of the latent TGF beta binding protein (LTBP) family. LTBPs are members of the fibrillin/LTBP superfamily, characterised by the presence of unique TGF-binding protein (TB) domains, also known as 8 cys domains as they contain eight characteristic cysteines (Ramirez & Sakai 2010). LTBPs are microfibril-associated, proteins that tether latent complexes of TGF-beta to microfibrils in the ECM (Taipale et al. 1996, Dallas et al. 2000, Isogai et al. 2003, Hyytiainen et al. 2004, Ono et al. 2009, Munger & Sheppard 2011). LTBP1 and 3 bind all three isoforms of latent TGF-beta, while LTBP4 only weakly binds TGF-beta1 (Saharinen & Keski Oja 2000). LTBP2 does not bind TGF-beta and is a structural component of fibrillin microfibrils. The carboxyl terminus of LTBP1 binds to fibrillin-1. LTBP1 and LTBP4 incorporation into the ECM is abolished in fibrillin-1 null mice (Ono et al. 2009). The amino terminus of LTBPs binds ECM components such as collagen (Taipale et al. 1996) and fibronectin (Kantola et al. 2008). Fibulins compete for the LTBP sites in fibrillin (Ono et al. 2009).

Literature references

Sakai, LY., Rifkin, DB., Isogai, Z., Mazzieri, R., Chen, Y., Ono, RN. et al. (2003). Latent transforming growth factor beta-binding protein 1 interacts with fibrillin and is a microfibril-associated protein. *J. Biol. Chem., 278*, 2750-7. ↗

Editions

2012-04-30	Authored	Jupe, S.
2012-11-02	Reviewed	Muiznieks, LD.
2012-11-12	Edited	Jupe, S.

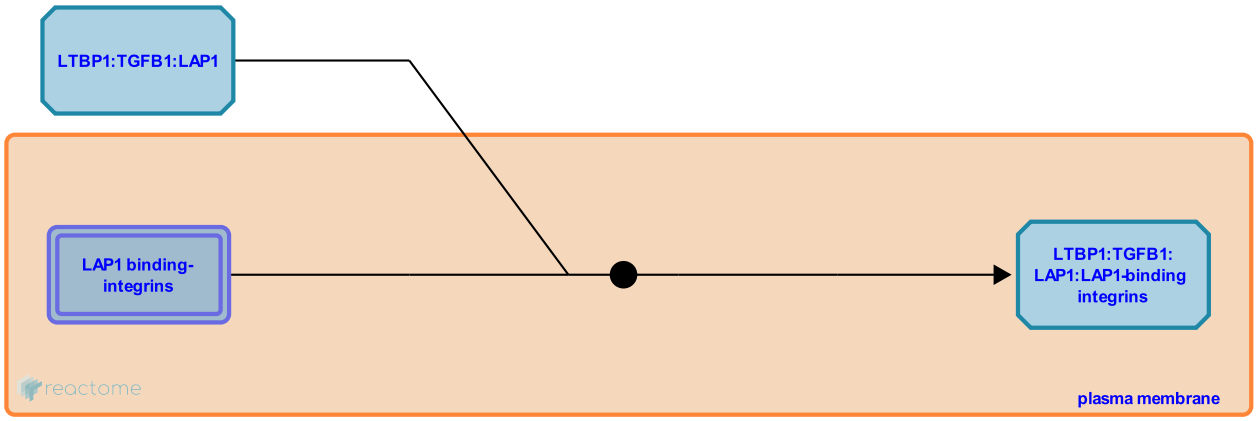
Latent TGF-beta-1 binds integrins ↗

Location: Molecules associated with elastic fibres

Stable identifier: R-HSA-2395320

Type: binding

Compartments: plasma membrane



The LAPs of TGF beta-1 and TGF beta-3 contain RGD sequences near the carboxyl termini that are bound by RGD binding integrins. The TGF beta-1 form of LAP (LAP1) binds the integrins alphaVBeta1 (Munger et al. 1998), alphaVBeta3 (Ludbrook et al. 2003), alphaVBeta5 (Munger et al. 1998), alphaVBeta6 (Munger et al. 1999, Araya et al. 2006), alphaVBeta8 (Mu et al. 2002, Araya et al. 2006) and alpha8Beta1 (Lu et al. 2002). Binding to integrins alphaVBeta6 and alphaVBeta8 leads to TGF beta activation.

Preceded by: LTBP1, LTBP3 bind TGF-Beta

Literature references

Garat, C., Sheppard, D., Rifkin, DB., Matthay, MA., Griffiths, MJ., Kawakatsu, H. et al. (1999). The integrin alpha v beta 6 binds and activates latent TGF beta 1: a mechanism for regulating pulmonary inflammation and fibrosis. *Cell, 96*, 319-28. ↗

Harpel, JG., Rifkin, DB., Giancotti, FG., Munger, JS. (1998). Interactions between growth factors and integrins: latent forms of transforming growth factor-beta are ligands for the integrin alphavbeta1. *Mol. Biol. Cell, 9*, 2627-38. ↗

Nishimura, SL., Broaddus, VC., Kawakatsu, H., Baron, JL., Fjellbirkeland, L., Sheppard, D. et al. (2002). The integrin alpha(v)beta8 mediates epithelial homeostasis through MT1-MMP-dependent activation of TGF-beta1. *J. Cell Biol. , 157*, 493-507. ↗

Lu, M., Steadele, M., Busald, C., Schnapp, LM., Munger, JS., Tellier, M. (2002). Integrin alpha8beta1 mediates adhesion to LAP-TGFbeta1. *J. Cell. Sci., 115*, 4641-8. ↗

Horgan, CM., Delves, CJ., Ludbrook, SB., Barry, ST. (2003). The integrin alphavbeta3 is a receptor for the latency-associated peptides of transforming growth factors beta1 and beta3. *Biochem. J., 369*, 311-8. ↗

Editions

2012-04-30	Authored	Jupe, S.
2012-11-02	Reviewed	Muiznieks, LD.
2012-11-12	Edited	Jupe, S.

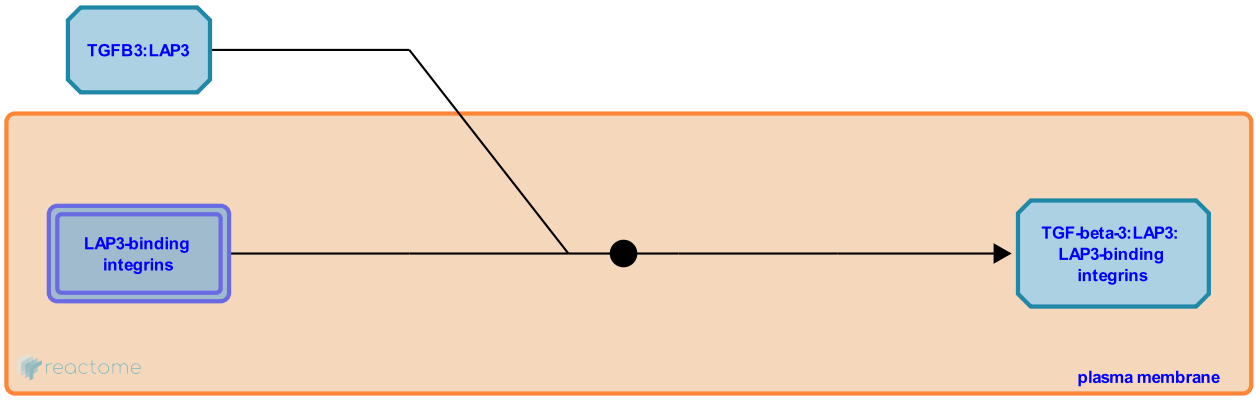
Latent TGF-beta-3 binds integrins ↗

Location: Molecules associated with elastic fibres

Stable identifier: R-HSA-2396029

Type: binding

Compartments: plasma membrane



The LAPs of TGF-beta1 and TGF-beta3 contain RGD sequences near the carboxyl termini that are bound by RGD-binding integrins. LAP3 binds alphaVBeta1, 3, 5 and 6 (Ludbrook et al. 2003) and 8 (Kitamura et al. 2011). Binding to integrins alphaVBeta6 and alphaVBeta8 leads to TGF-beta activation.

Literature references

Nishimura, SL., Pittet, JF., Somanath, S., Publicover, J., Lou, J., Gauldie, J. et al. (2011). Mouse and human lung fibroblasts regulate dendritic cell trafficking, airway inflammation, and fibrosis through integrin ?v?8-mediated activation of TGF-?. *J. Clin. Invest., 121*, 2863-75. ↗

Horgan, CM., Delves, CJ., Ludbrook, SB., Barry, ST. (2003). The integrin alphavbeta3 is a receptor for the latency-associated peptides of transforming growth factors beta1 and beta3. *Biochem. J., 369*, 311-8. ↗

Editions

2012-04-30	Authored	Jupe, S.
2012-11-02	Reviewed	Muiznieks, LD.
2012-11-12	Edited	Jupe, S.

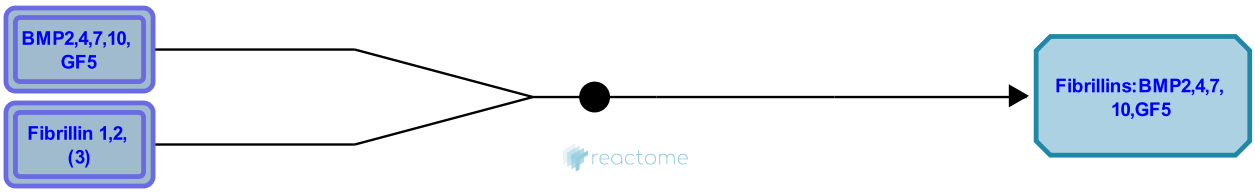
Fibrillins bind BMPs ↗

Location: Molecules associated with elastic fibres

Stable identifier: R-HSA-2396399

Type: binding

Compartments: extracellular region



Fibrillins can bind the prodomains of TGF-beta superfamily members bone morphogenic factor (BMP) 2, 4, 7, 10, and growth and differentiation factor (GDF) 5 (Sengle et al. 2008). Prodomain binding by ECM constituents may be a targeting mechanism for TGF family members (Sengle et al. 2011).

Literature references

Sakai, LY., Alvarez, J., Ono, RN., Bächinger, HP., Keene, DR., Charbonneau, NL. et al. (2008). Targeting of bone morphogenetic protein growth factor complexes to fibrillin. *J. Biol. Chem., 283*, 13874-88. ↗

Editions

2012-04-30	Authored	Jupe, S.
2012-11-02	Reviewed	Muiznieks, LD.
2012-11-12	Edited	Jupe, S.

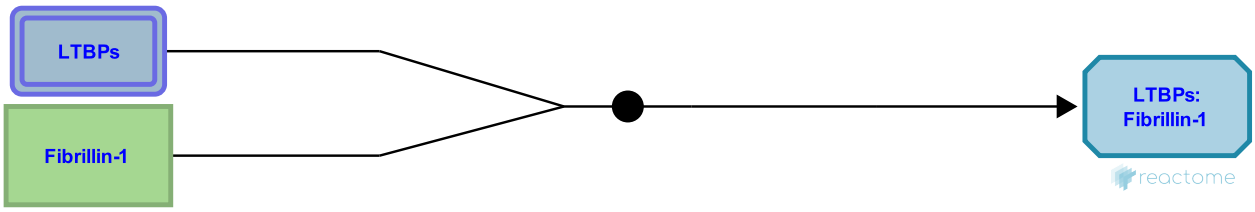
Fibrillin-1 binds latent TGF-beta ↗

Location: Molecules associated with elastic fibres

Stable identifier: R-HSA-2328033

Type: binding

Compartments: extracellular region



TGF-beta is released from cells as a latent complex of three proteins: TGF-beta (which is encoded by three human genes), the processed TGF-beta propeptide (latency-associated peptide LAP), and a member of the latent TGF-beta binding protein (LTBP) family. LTBPs are microfibril (fibrillin)-associated proteins that bind LAP, tethering latent TGF-beta to microfibrils in the ECM (Taipale et al. 1996, Hyytiainen et al. 2004).

LTBP1 and LTBP4 incorporation into ECM requires fibrillin-1 (Ono et al. 2009). The protein–protein interaction sites between LTBPs and fibrillins have been determined using recombinant protein fragments and surface plasmon resonance (Ono et al. 2009). LTBP4 binds to the first hybrid domain of fibrillin-1 (Hyb1), whereas LTBP1 binds to a site involving both Hyb1 and adjacent EGF-like domains 2 and 3. Previous studies showed that the carboxyl terminus of LTBP1 binds to fibrillin-1, whereas the amino terminus of LTBPs is mainly responsible for binding ECM components made in cell culture generally, and fibronectin specifically (Kantola et al. 2008).

Literature references

Saharinen, J., Sakai, LY., Mundy, GR., Dallas, SL., Bruder, SP., Bonewald, LF. et al. (2000). Role of the latent transforming growth factor beta binding protein 1 in fibrillin-containing microfibrils in bone cells in vitro and in vivo. *J. Bone Miner. Res., 15*, 68-81. ↗

Editions

2012-04-30	Authored	Jupe, S.
2012-11-02	Reviewed	Muiznieks, LD.
2012-11-12	Edited	Jupe, S.

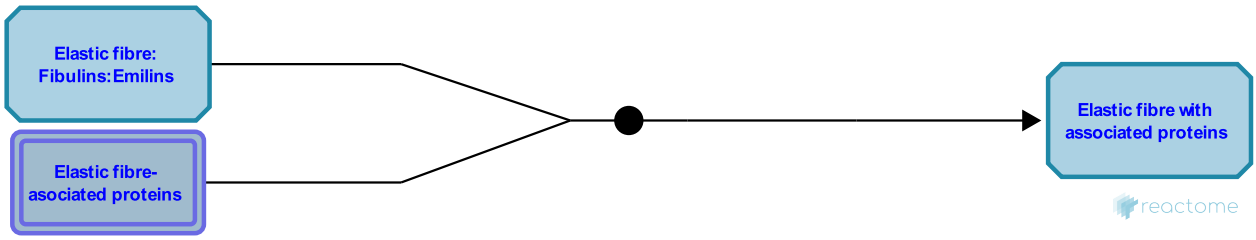
Elastic fibres bind associated proteins ↗

Location: Molecules associated with elastic fibres

Stable identifier: R-HSA-2161282

Type: binding

Compartments: extracellular region



Other proteins found associated with elastic fibres include vitronectin (Dahlback et al. 1989,1990, Hintner et al. 1991) and and a structurally unrelated group of proteins collectively termed microfibrillar-associated proteins (MFAPs) (Gibson et al. 1996, 2000, Abrams et al. 1995, Toyashima et al. 1999). The significance of these interactions is not well understood. Vitronectin is present in plasma, extracellular matrix, and the alpha granules of blood platelets. It has been implicated as a regulator of many processes including coagulation, fibrinolysis, pericellular proteolysis, complement dependent immune response, cell attachment and spreading (Zhuang et al. 1996). It interacts with integrins alphaVbeta1 (Marshall et al. 1995), alphaVbeta3 (Pytela et al. 1985), alphaVbeta5 (Panetti & McKeown Longo 1993) and alphaIIbBeta3 (Pytela et al. 1986) through Arg Gly Asp (RGD) cell binding sequences. The MFAPs are not a structurally related family but grouped due to their localization with microfibrils. MFAP1 was originally called 'associated microfibril protein' (AMP). It is a 54 kDa protein, processed to 32 kDa, localizing to fibrillin-containing microfibrils in several tissues including zonule fibers (Horrigan et al. 1992). MFAP3 is a 41 kDa serine-rich protein localized to zonular microfibrils, found in extracts of developing nuchal ligament, also expressed in fetal aorta and lung (Abrams et al. 1995). MFAP4 is a 29 kDa protein localized to fibrillin-containing microfibrils surrounding elastic fibers in aorta, skin and spleen (Toyoshima et al. 1999).

Preceded by: Emilin is found in elastic fibres

Literature references

Furuichi, H., Itano, T., Kobayashi, R., Shishibori, T., Yamashita, K., Toyoshima, T. (1999). Ultrastructural distribution of 36-kD microfibril-associated glycoprotein (MAGP-36) in human and bovine tissues. *J Histochem Cytochem, 47*, 1049-56. ↗

Hintner, H., Breathnach, SM., Dahlbäck, B., Dahlbäck, K., Pepys, MB. (1991). Tissue vitronectin in normal adult human dermis is non-covalently bound to elastic tissue. *J. Invest. Dermatol., 96*, 747-53. ↗

Editions

2012-04-30	Authored	Jupe, S.
2012-11-02	Reviewed	Muiznieks, LD.
2012-11-12	Edited	Jupe, S.

Table of Contents