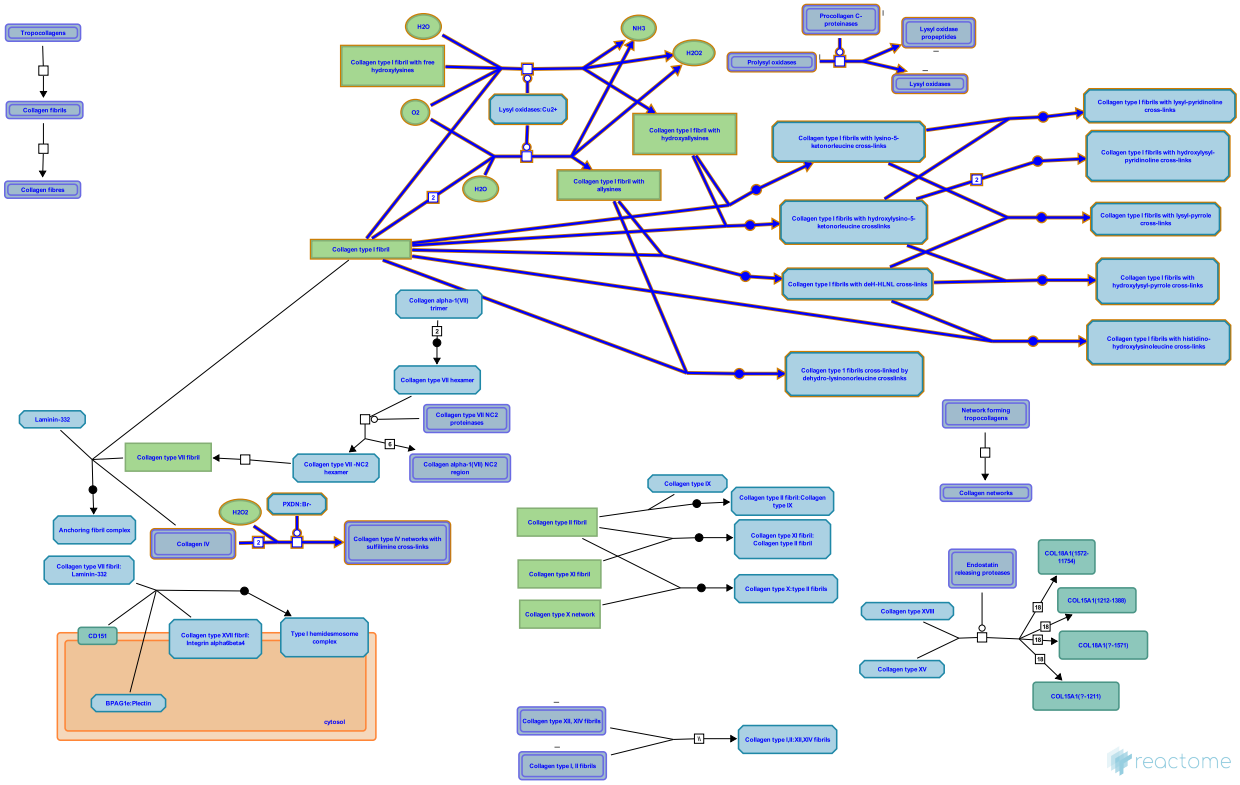
Crosslinking of collagen fibrils



Bhave, G., Jupe, S., Kalamajski, S., Obinger, C., Raleigh, S., Ricard-Blum, S., Vanacore, RM.

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17/11/2019

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. ↗

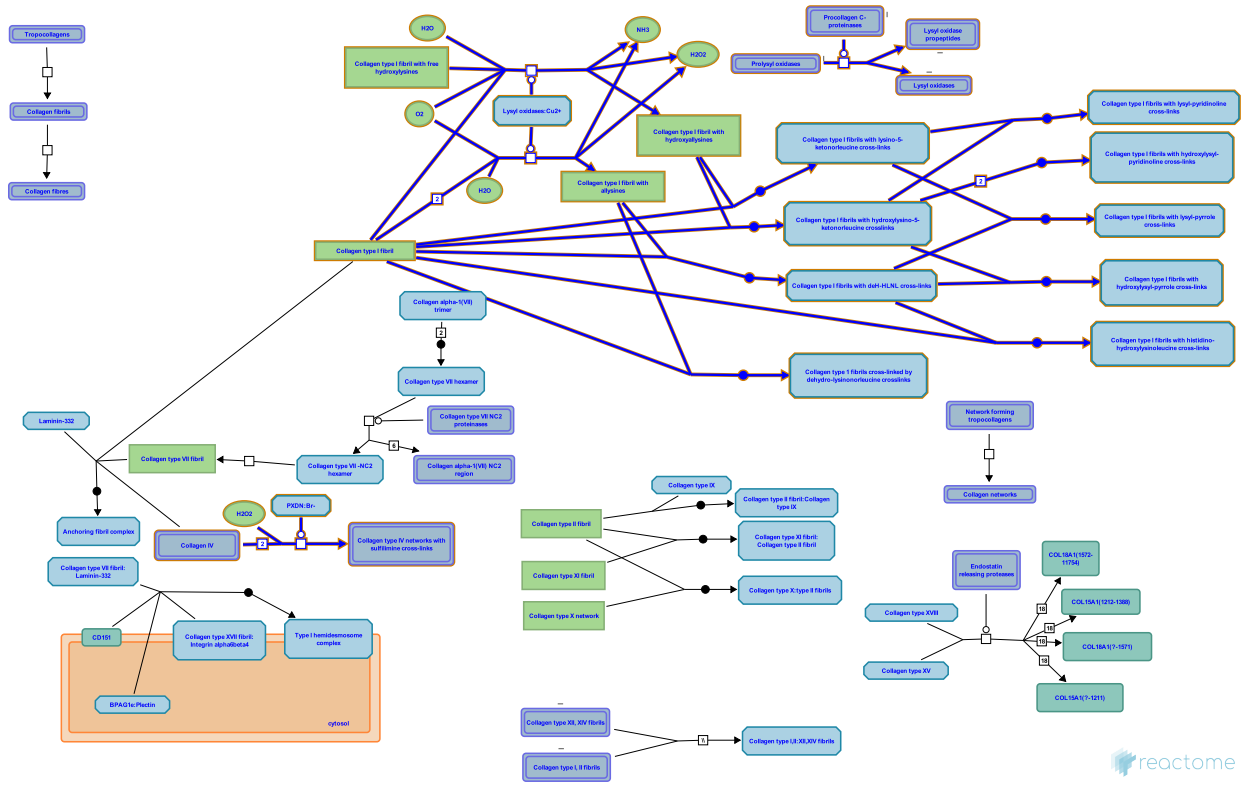
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Crosslinking of collagen fibrils ↗

Stable identifier: R-HSA-2243919



After removal of the N- and C-procollagen propeptides, fibrillar collagen molecules aggregate into microfibrillar arrays, stabilized by covalent intermolecular cross-links. These depend on the oxidative deamination of specific lysine or hydroxylysine residues in the telopeptide region by lysyl oxidase (LOX) with the subsequent spontaneous formation of covalent intermolecular cross-links (Pinnell & Martin 1968, Siegel et al. 1970, 1974, Maki 2009, Nishioka et al. 2012). Hydroxylysine is formed intracellularly by lysine hydroxylases (LH). There are different forms of LH responsible for hydroxylation of helical and telopeptide lysines (Royce & Barnes 1985, Knott et al.1997, Takaluoma et al. 2007, Myllyla 2007). The chemistry of the cross-links formed depends on whether lysines or hydroxylysines are present in the telopeptides (Barnes et al. 1974), which depends on the proportion of collagen lysines post-translationally converted to hydroxylysine by LH. The lysine pathway predominates in adult skin, cornea and sclera while the hydroxylysine pathway occurs primarily in bone, cartilage, ligament, tendons, embryonic skin and most connective tissues (Eyre 1987, Eyre & Wu 2005, Eyre et al. 2008). Oxidative deamination of lysine or hydroxylysine residues by LOX generates the allysine and hydroxyallysine aldehydes respectively. These can spontaneously react with either another aldehyde to form an aldol condensation product (intramolecular cross-link), or with an unmodified lysine or hydroxylysine residue to form intermolecular cross-links.

The pathway of cross-linking is regulated primarily by the hydroxylation pattern of telopeptide and triple-helix domain lysine residues. When lysine residues are the source of aldehydes formed by lysyl oxidase the allysine cross-linking pathway leads to the formation of aldimine cross-links (Eyre & Wu 2005). These are stable at physiological conditions but readily cleaved at acid pH or elevated temperature. When hydroxylysine residues are the source of aldehydes formed by lysyl oxidase the hydroxyallysine cross-linking pathway leads to the formation of more stable ketoimine cross-links.

Telopeptide lysine residues can be converted by LOX to allysine, which can react with a helical hydroxylysine residue forming the lysine aldehyde aldimine cross-link dehydro hydroxylysino norleucine

(deHHLNL) (Bailey & Peach 1968, Eyre et al. 2008). If the telopeptide residue is hydroxylysine, the hydroxyallysine formed by LOX can react with a helical hydroxylysine forming the Schiff base, which spontaneously undergoes an Amadori rearrangement resulting in the ketoimine cross link hydroxylysino 5 ketonorleucine (HLKNL). This stable cross-link is formed in tissues where telopeptide residues are predominanly hydroxylated, such as foetal bone and cartilage, accounting for the relative insolubility of collagen from these tissues (Bailey et al. 1998). In bone, telopeptide hydroxyallysines can react with the epsilon-amino group of a helical lysine (Robins & Bailey 1975). The resulting Schiff base undergoes Amadori rearrangement to form lysino-hydroxynorleucine (LHNL). An alternative mechanism of maturation of ketoimine cross-links has been reported in cartilage leading to the formation of arginoline (Eyre et al. 2010).

These divalent crosslinks greatly diminish as connective tissues mature, due to further spontaneous reactions (Bailey & Shimokomaki 1971, Robins & Bailey 1973) with neighbouring peptides that result in tri- and tetrafunctional cross-links. In mature tissues collagen cross-links are predominantly trivalent. The most common are pyridinoline or 3-hydroxypyridinium cross-links, namely hydroxylysyl-pyridinoline (HL-Pyr) and lysyl-pyridinoline (L-Pyr) cross-links (Eyre 1987, Ogawa et al. 1982, Fujimoto et al. 1978). HL-Pyr is formed from three hydroxylysine residues, HLKNL plus a further hydroxyallysine. It predominates in highly hydroxylated collagens such as type II collagen in cartilage. L-Pyr is formed from two hydroxylysines and a lysine, LKNL plus a further hydroxyallysine, found mostly in calcified tissues (Bailey et al. 1998). Trivalent collagen cross-links can also form as pyrroles, either Lysyl-Pyrrole (L-Pyrrole) or hydroxylysyl-pyrrole (HL-Pyrrole), respectively formed when LKNL or HLKNL react with allysine (Scott et al. 1981, Kuypers et al. 1992). A further three-way crosslink can form when DeH-HLNL reacts with histidine to form histidino-hydroxylysinonorleucine (HHL), found in skin and cornea (Yamauchi et al. 1987, 1996). This can react with an additional lysine to form the tetrafunctional cross-link histidinohydroxymerodesmosine (Reiser et al. 1992, Yamauchi et al. 1996).

Another mechanism which could be involved in the cross-linking of collagen IV networks is the sulfilimine bond (Vanacore et al. 2009), catalyzed by peroxidasin, an enzyme found in basement membrane (Bhave 2012).

To improve clarity inter-chain cross-linking is represented here for Collagen type I only. Although the formation of each type of cross-link is represented here as an independent event, the partial and random nature of lysine hydroxylation and subsequent lysyl oxidation means that any combination of these cross-linking events could occur within the same collagen fibril .

Literature references

Bailey, AJ., Paul, RG., Knott, L. (1998). Mechanisms of maturation and ageing of collagen. *Mech Ageing Dev, 106*, 1-56. ↗

Editions

2012-04-30	Authored	Jupe, S.
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2012-11-19	Reviewed	Ricard-Blum, S.

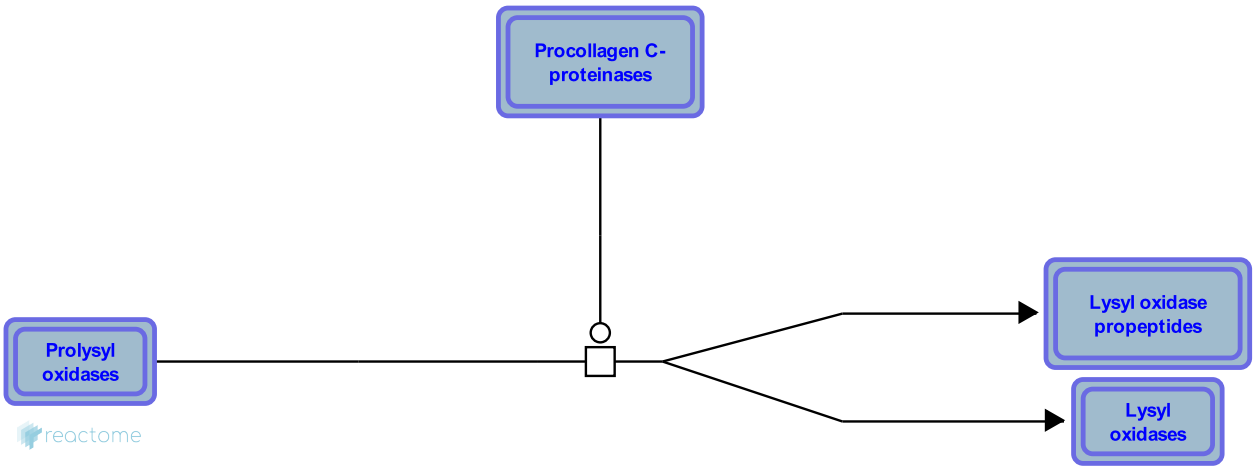
Prolysyl oxidase activation ↗

Location: Crosslinking of collagen fibrils

Stable identifier: R-HSA-2022141

Type: transition

Compartments: extracellular region



Lysyl oxidase (LOX) is secreted to the extracellular space in an inactive, proenzyme form (proLOX). This is proteolytically cleaved between Gly168 and Asp169 generating the mature 32-kDa enzyme. The activating proteinase is Bone morphogenetic protein 1 (BMP1), also called Procollagen C-proteinase (Cronshaw et al. 1995, Panchenko et al. 1996). Other extracellular proteases, including the BMP1 variant mammalian tolloid, tolloid-like (TLL) 1 and TLL2 proteases cleave proLOX at the correct physiological site but with lower efficiency (Uzel et al. 2001).

Followed by: Formation of allysine by LOX, Formation of hydroxyallysine by LOX

Literature references

Panchenko, MV., Stetler-Stevenson, WG., Trubetskoy, OV., Gacheru, SN., Kagan, HM. (1996). Metalloproteinase activity secreted by fibrogenic cells in the processing of prolysyl oxidase. Potential role of procollagen C-proteinase. *J Biol Chem, 271*, 7113-9. ↗

Uzel, MI., Scott, IC., Babakhanlou-Chase, H., Palamakumbura, AH., Pappano, WN., Hong, HH. et al. (2001). Multiple bone morphogenetic protein 1-related mammalian metalloproteinases process pro-lysyl oxidase at the correct physiological site and control lysyl oxidase activation in mouse embryo fibroblast cultures. *J Biol Chem, 276*, 22537-43. ↗

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2012-04-30	Authored	Jupe, S.
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2012-11-12	Edited	Jupe, S.
2012-11-19	Reviewed	Ricard-Blum, S.

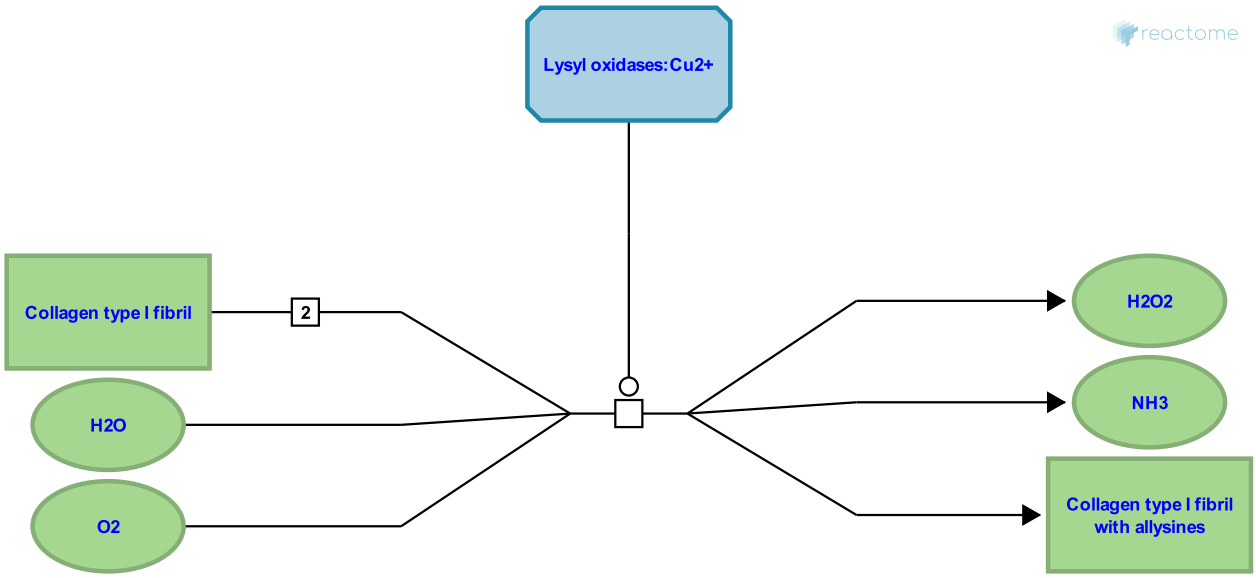
Formation of allysine by LOX ↗

Location: Crosslinking of collagen fibrils

Stable identifier: R-HSA-2002466

Type: transition

Compartments: extracellular region



Lysine residues can be converted to allysine by lysyl oxidase. In this representative reaction a single lysine residue in each collagen chain is shown as converted to allysine (Pinnell et al. 1968).

Preceded by: Prolysyl oxidase activation

Followed by: Formation of dehydro-lysinonorleucine cross-links, Formation of dehydro-hydroxylysinonorleucine cross-links

Literature references

Pinnell, SR., Martin, GR. (1968). The cross-linking of collagen and elastin: enzymatic conversion of lysine in peptide linkage to alpha-aminoadipic-delta-semialdehyde (allysine) by an extract from bone. *Proc Natl Acad Sci U S A, 61*, 708-16. ↗

Editions

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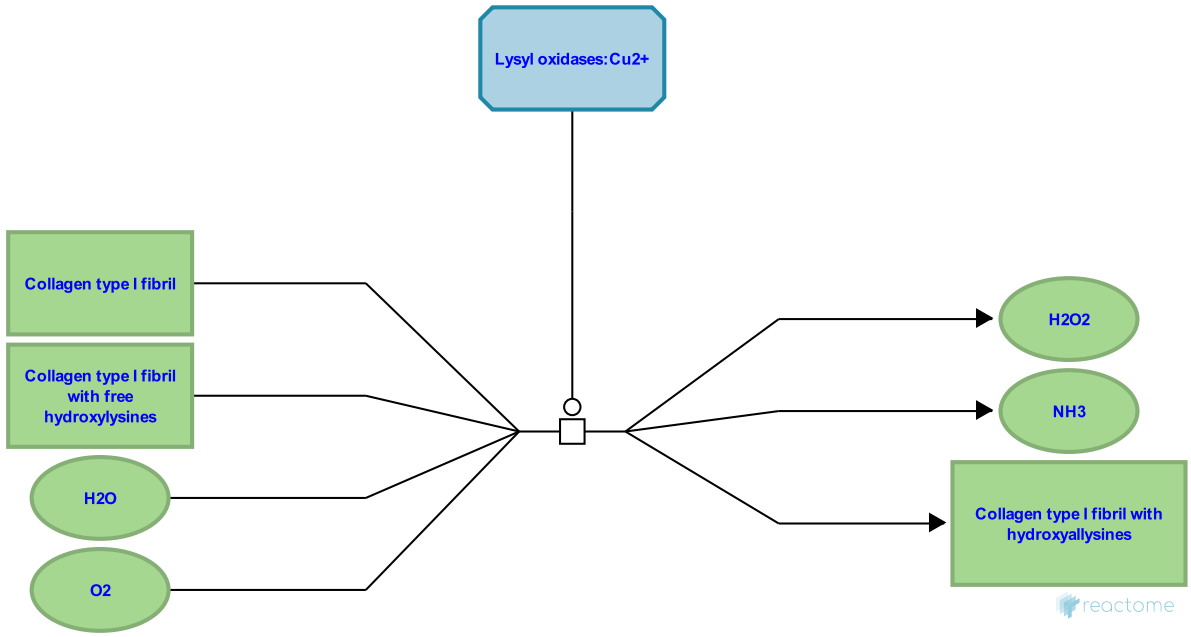
Formation of hydroxyallysine by LOX ↗

Location: Crosslinking of collagen fibrils

Stable identifier: R-HSA-2395340

Type: transition

Compartments: extracellular region



Hydroxylysines residues can be converted to hydroxyallysines by lysyl oxidase. In this representative reaction a single hydroxylysine residue in each collagen chain is shown as converted to hydroxyallysine (Pinnell et al. 1968, Siegel 1979).

Preceded by: Prolysyl oxidase activation

Followed by: Formation of lysino-5-ketonorleucine cross-links, Formation of hydroxylysino-5-ketonorleucine cross-links

Literature references

Pinnell, SR., Martin, GR. (1968). The cross-linking of collagen and elastin: enzymatic conversion of lysine in peptide linkage to alpha-aminoadipic-delta-semialdehyde (allysine) by an extract from bone. *Proc Natl Acad Sci U S A, 61*, 708-16. ↗

Siegel, RC. (1979). Lysyl oxidase. *Int Rev Connect Tissue Res, 8*, 73-118. ↗

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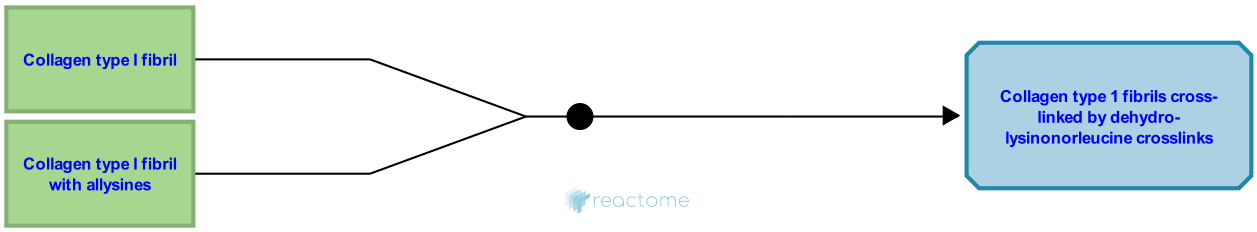
Formation of dehydro-lysinonorleucine cross-links ↗

Location: Crosslinking of collagen fibrils

Stable identifier: R-HSA-2243931

Type: binding

Compartments: extracellular region



Allysine residues can condense with lysine residues forming dehydro-lysinonorleucine (deH-LNL) cross-links. In this representative reaction, all allysine residues are shown as converted to deH-LNL though partial conversion, or conversion to other cross-linked forms is possible (Reiser et al. 1992, Bailey & Peach 1968).

Preceded by: Formation of allysine by LOX

Literature references

Bailey, AJ., Peach, CM. (1968). Isolation and structural identification of a labile intermolecular crosslink in collagen. *Biochem Biophys Res Commun, 33*, 812-9. ↗

Reiser, K., McCormick, RJ., Rucker, RB. (1992). Enzymatic and nonenzymatic cross-linking of collagen and elastin. *FASEB J., 6*, 2439-49. ↗

Editions

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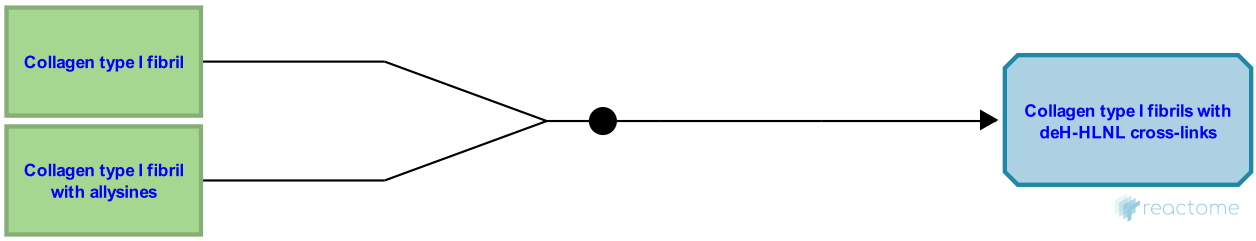
Formation of dehydro-hydroxylysino-norleucine cross-links ↗

Location: Crosslinking of collagen fibrils

Stable identifier: R-HSA-2395257

Type: binding

Compartments: extracellular region



Allysine residues condense with hydroxylysine residues to form the aldimine dehydro-hydroxylysino-norleucine (deH-HLNL), first identified by Bailey & Peach (1968).

Preceded by: Formation of allysine by LOX

Followed by: Formation of histidino-hydroxylysinonorleucine cross-links

Literature references

Bailey, AJ., Peach, CM. (1968). Isolation and structural identification of a labile intermolecular crosslink in collagen. *Biochem Biophys Res Commun, 33*, 812-9. ↗

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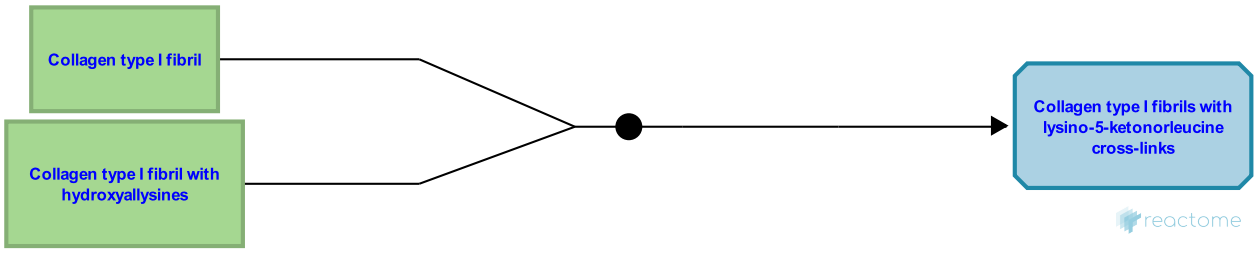
Formation of lysino-5-ketonorleucine cross-links ↗

Location: Crosslinking of collagen fibrils

Stable identifier: R-HSA-2395314

Type: binding

Compartments: extracellular region



In bone, cross-links are formed between telopeptide hydroxallysine residues and helical lysines (Robins & Bailey 1975). The resulting Schiff base undergoes Amadori rearrangement to form lysino-5-ketonorleucine (LKNL).

Preceded by: Formation of hydroxyallysine by LOX

Followed by: Formation of lysyl-pyrrole cross-links, Formation of lysyl-pyridinoline cross-links

Literature references

Robins, SP., Bailey, AJ. (1975). The chemistry of the collagen cross-links. The mechanism of stabilization of the reducible intermediate cross-links. *Biochem. J., 149*, 381-5. ↗

Seibel, MJ., Robins, SP., Bilezikian, JP. (2006). Fibrillogenesis and Maturation of Collagens, Dynamics of Bone and Cartilage Metabolism. *Academic Press*, 407-418.

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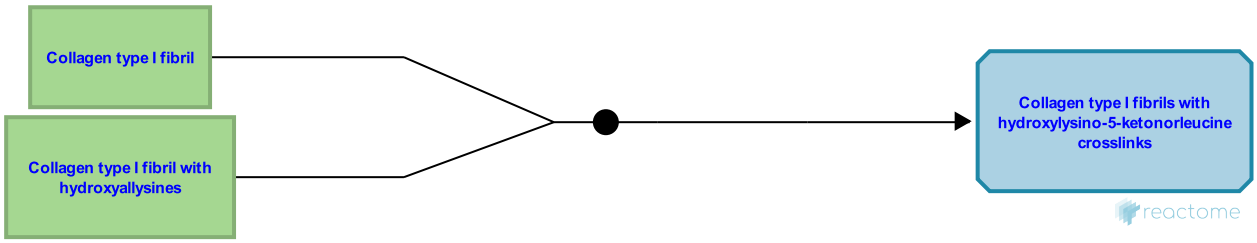
Formation of hydroxylysino-5-ketonorleucine cross-links ↗

Location: Crosslinking of collagen fibrils

Stable identifier: R-HSA-2395302

Type: binding

Compartments: extracellular region



Hydroxyallysine and hydroxylysine can react forming the Schiff base, which spontaneously undergoes an Amadori rearrangement resulting in the ketoimine cross-link hydroxylysino-5-ketonorleucine (HLKNL). This is much more stable than the aldimine crosslinks (Bailey et al. 1998).

Preceded by: Formation of hydroxyallysine by LOX

Followed by: Formation of hydroxylysyl-pyrrole cross-links, Formation of hydroxylysyl-pyridinoline cross-links

Literature references

Lehto, M., Sims, TJ., Bailey, AJ. (1985). Skeletal muscle injury--molecular changes in the collagen during healing. *Res Exp Med (Berl), 185*, 95-106. ↗

Reiser, K., McCormick, RJ., Rucker, RB. (1992). Enzymatic and nonenzymatic cross-linking of collagen and elastin. *FASEB J., 6*, 2439-49. ↗

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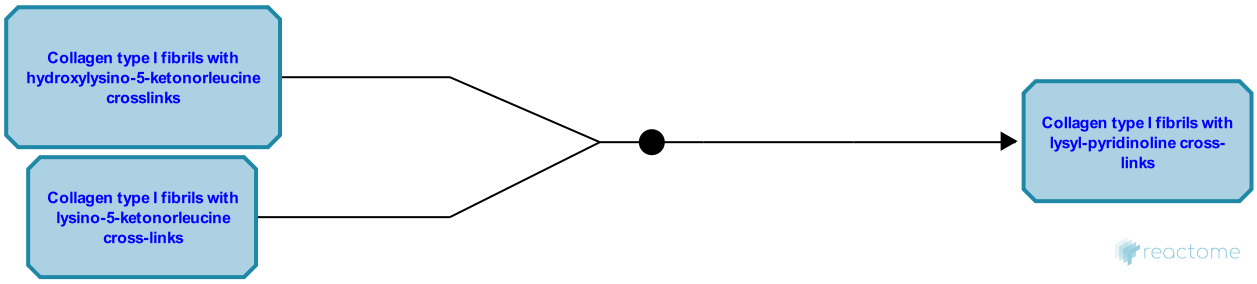
Formation of lysyl-pyridinoline cross-links ↗

Location: Crosslinking of collagen fibrils

Stable identifier: R-HSA-2395322

Type: binding

Compartments: extracellular region



Lysyl-pyridinoline (L-Pyr) cross-links are formed from two hydroxylysine residues and a lysine residue (LKNL plus a further hydroxyallysine contributed by HLKNL), found mostly in calcified tissues (Bailey et al. 1998).

Preceded by: Formation of lysino-5-ketonorleucine cross-links

Literature references

Siegel, RC., Fu, JC., Uto, N., Horiuchi, K., Fujimoto, D. (1982). Collagen cross-linking: lysyl oxidase dependent synthesis of pyridinoline in vitro: confirmation that pyridinoline is derived from collagen. *Biochem. Biophys. Res. Commun., 108*, 1546-50. ↗

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Formation of hydroxylysyl-pyridinoline cross-links ↗

Location: Crosslinking of collagen fibrils

Stable identifier: R-HSA-2395223

Type: binding

Compartments: extracellular region

Hydroxylysyl-pyridinoline (HL-Pyr) is formed from three hydroxylysine residues, (HLKNL plus a further hydroxyallysine donated by a second HLKNL). It predominates in highly hydroxylated collagens such as type II collagen in cartilage.

Preceded by: Formation of hydroxylysino-5-ketonorleucine cross-links

Literature references

Fujimoto, D., Moriguchi, T. (1978). Pyridinoline, a non-reducible crosslink of collagen. Quantitative determination, distribution, and isolation of a crosslinked peptide. *J. Biochem., 83*, 863-7. ↗

Henkel, W., Glanville, RW., Greifendorf, D. (1987). Characterisation of a type-I collagen trimeric cross-linked peptide from calf aorta and its cross-linked structure. Detection of pyridinoline by time-of-flight secondary ion-mass spectroscopy and evidence for a new cross-link. *Eur. J. Biochem., 165*, 427-36. ↗

Stone, PJ., Bryan-Rhadfi, J., Shaw, HA., Franzblau, C. (1992). Isolation of hydroxylysyl pyridinoline, a mature collagen crosslink from neonatal rat aorta smooth muscle cell cultures. *Matrix, 12*, 381-7. ↗

Editions

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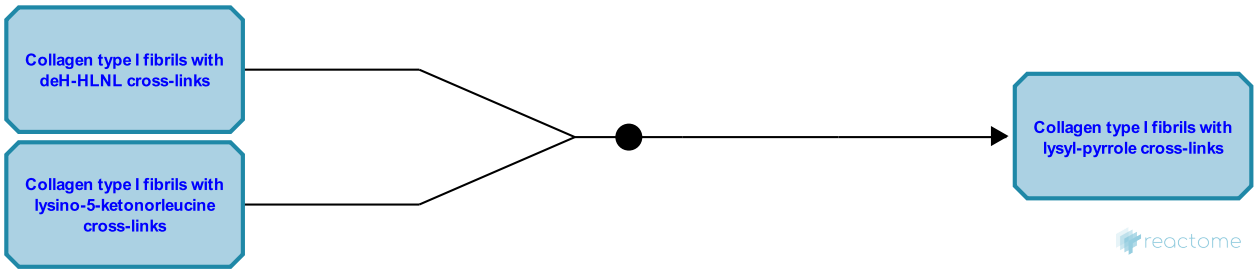
Formation of lysyl-pyrrole cross-links ↗

Location: Crosslinking of collagen fibrils

Stable identifier: R-HSA-2250301

Type: binding

Compartments: extracellular region



Trivalent collagen cross-links can also form as pyrroles. Lysyl-Pyrrole (L-Pyrrole) is formed when Lysino-ketonorleucine (LKNL) reacts with Hydroxylysino-norleucine (deH-HLNL) (Eyre et al. 2008), with structures based on a 3-hydroxypyrrole, believed to be the core structure of the pyrrole cross-links in bone collagen, rather than a pyrrole lacking a hydroxyl on the ring as depicted earlier.

Preceded by: Formation of lysino-5-ketonorleucine cross-links

Literature references

Scott, JE., Hughes, EW., Shuttleworth, A. (1981). A collagen-associated Ehrlich chromogen: a pyrrolic cross-link?. *Bioscience Reports, 1*, 611-618.

Kuypers, R., Tyler, M., Kurth, LB., Jenkins, ID., Horgan, DJ. (1992). Identification of the loci of the collagen-associated Ehrlich chromogen in type I collagen confirms its role as a trivalent cross-link. *Biochem J, 283*, 129-36. ↗

Banse, X., Sims, TJ., Bailey, AJ. (2002). Mechanical properties of adult vertebral cancellous bone: correlation with collagen intermolecular cross-links. *J. Bone Miner. Res., 17*, 1621-8. ↗

Editions

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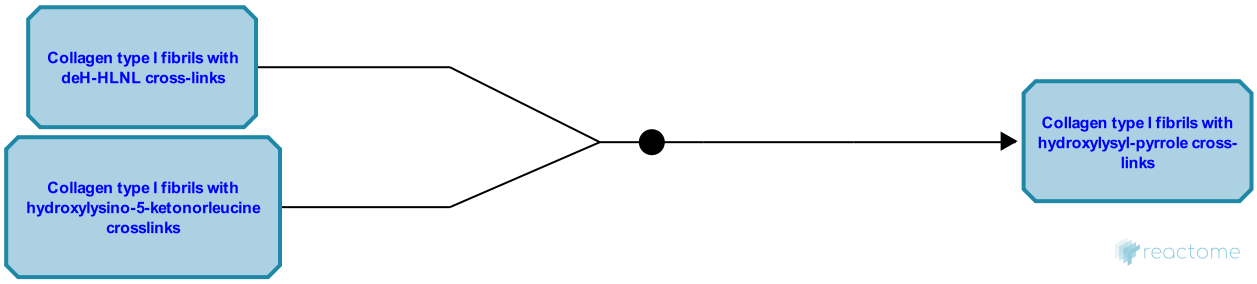
Formation of hydroxylysyl-pyrrole cross-links ↗

Location: Crosslinking of collagen fibrils

Stable identifier: R-HSA-2395324

Type: binding

Compartments: extracellular region



Trivalent collagen cross-links can form as pyrroles. Hydroxylysyl-Pyrrole (HL-Pyrrole) is formed when Hydroxylysino-ketonorleucine (HLKNL) reacts with hydroxylysino-norleucine (deH-HLNL) (Eyre et al. 2008). The mechanism of pyrrole cross-links has been revised to a structure based on 3-hydroxypyrrole, rather than a pyrrole lacking a hydroxyl on the ring as depicted earlier (Bailey et al. 1998).

Preceded by: Formation of hydroxylysino-5-ketonorleucine cross-links

Literature references

Scott, JE., Hughes, EW., Shuttleworth, A. (1981). A collagen-associated Ehrlich chromogen: a pyrrolic cross-link?. *Bioscience Reports, 1*, 611-618.

Kuypers, R., Tyler, M., Kurth, LB., Jenkins, ID., Horgan, DJ. (1992). Identification of the loci of the collagen-associated Ehrlich chromogen in type I collagen confirms its role as a trivalent cross-link. *Biochem J, 283*, 129-36. ↗

Banse, X., Sims, TJ., Bailey, AJ. (2002). Mechanical properties of adult vertebral cancellous bone: correlation with collagen intermolecular cross-links. *J. Bone Miner. Res., 17*, 1621-8. ↗

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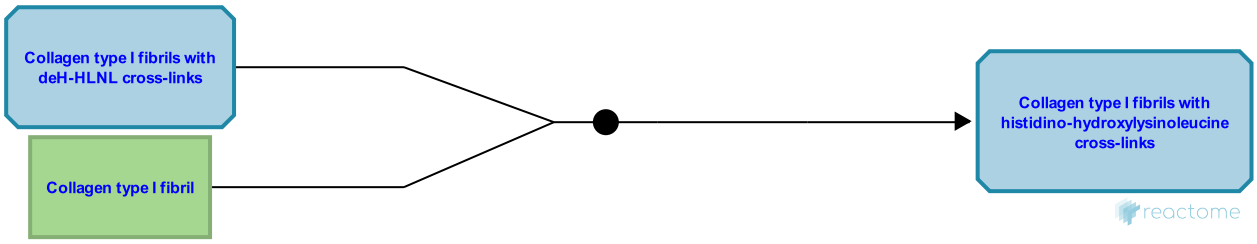
Formation of histidino-hydroxylysinonorleucine cross-links ↗

Location: Crosslinking of collagen fibrils

Stable identifier: R-HSA-2243926

Type: binding

Compartments: extracellular region



Histidino-hydroxylysinonorleucine (HHL) cross-links, formed when deH-HLNL reacts with a histidine residue, have been identified in skin and cornea (Yamauchi et al. 1987, 1996, Okada et al. 1997).

Preceded by: Formation of dehydro-hydroxylysino-norleucine cross-links

Literature references

Okada, K., Kondo, A., Ishikawa, O., Miyachi, Y. (1997). Histidinohydroxylysinonorleucine, a trifunctional cross-link of type I collagen, in sun-exposed and sun-protected human skin. *Br. J. Dermatol., 137*, 1014-5. ↗

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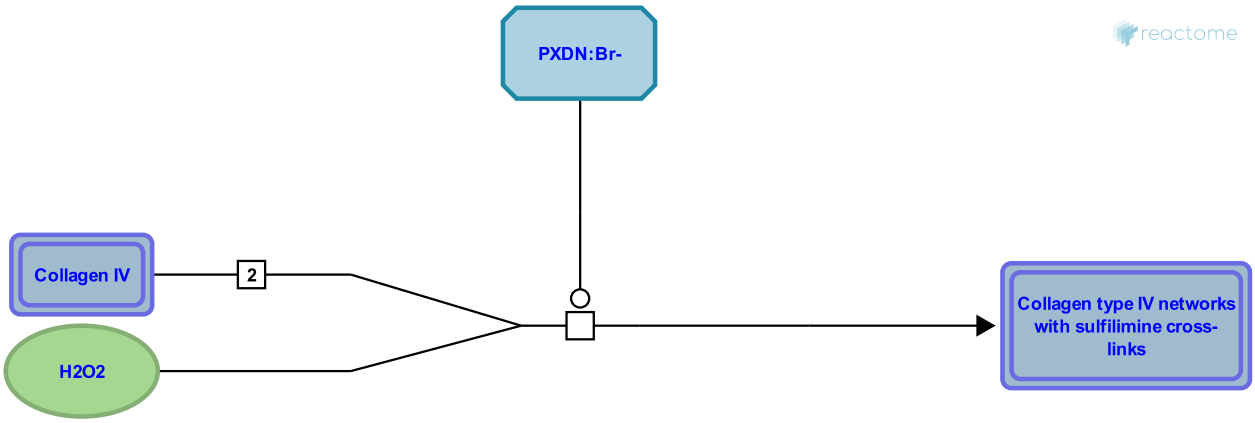
Collagen type IV sulfilimine cross-linking by peroxidasin ↗

Location: Crosslinking of collagen fibrils

Stable identifier: R-HSA-2559639

Type: transition

Compartments: extracellular region



A recently discovered sulfilimine (S=N) bond between a methionine sulfur and hydroxylysine nitrogen reinforces the collagen IV network (Vanacore et al. 2005, 2009). Peroxidasin, an enzyme found in basement membranes, indirectly catalyzes formation of the sulfilimine bond by producing the reactive intermediates hypobromous acid from peroxide and free Br- (Bhave 2012, MacCall et al. 2014).

Literature references

Bhave, G., Cummings, CF., Vanacore, RM., Kumagai-Cresse, C., Ero-Tolliver, IA., Rafi, M. et al. (2012). Peroxidasin forms sulfilimine chemical bonds using hypohalous acids in tissue genesis. *Nat. Chem. Biol., 8*, 784-90. ↗

Vanacore, RM., Ham, AJ., Voehler, M., Sanders, CR., Conrads, TP., Veenstra, TD. et al. (2009). A sulfilimine bond identified in collagen IV. *Science, 325*, 1230-4. ↗

Editions

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Table of Contents