Assembly of collagen fibrils and other multimeric structures

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references


Reactome database release: 71

This document contains 3 pathways and 9 reactions (see Table of Contents)
Assembly of collagen fibrils and other multimeric structures

Collagen trimers in triple-helical form, referred to as procollagen or collagen molecules, are exported from the ER and trafficked through the Golgi network before secretion into the extracellular space. For fibrillar collagens namely types I, II, III, V, XI, XXIV and XXVII (Gordon & Hahn 2010, Ricard-Blum 2011) secretion is concomitant with processing of the N and C terminal collagen propeptides. These processed molecules are known as tropocollagens, considered to be the units of higher order collagen structures. They form within the extracellular space via a process that can proceed spontaneously, but in the cellular environment is regulated by many collagen binding proteins such as the FACIT (Fibril Associated Collagens with Interrupted Triple helices) family collagens and Small Leucine-Rich Proteoglycans (SLRPs). The architecture formed ultimately depends on the collagen subtype and the cellular conditions. Structures include the well-known fibrils and fibres formed by the major structural collagens type I and II plus several different types of supramolecular assembly (Bruckner 2010). The mechanical and physical properties of tissues depend on the spatial arrangement and composition of these collagen-containing structures (Kadler et al. 1996, Shoulders & Raines 2009, Birk & Bruckner 2011).

Fibrillar collagen structures are frequently heterotypic, composed of a major collagen type in association with smaller amounts of other types, e.g. type I collagen fibrils are associated with types III and V, while type II fibrils frequently contain types IX and XI (Wess 2005). Fibres composed exclusively of a single collagen type probably do not exist, as type I and II fibrils require collagens V and XI respectively as nucleators (Kadler et al. 2008, Wenstrup et al. 2011). Much of the structural understanding of collagen fibrils has been obtained with fibril-forming collagens, particularly type I, but some central features are believed to apply to at least the other fibrillar collagen subtypes (Wess 2005). Fibril diameter and length varies considerably, depending on the tissue and collagen types (Fang et al. 2012). The reasons for this are poorly understood (Wess 2005).

Some tissues such as skin have fibres that are approximately the same diameter while others such as tendon or cartilage have a bimodal distribution of thick and thin fibrils. Mature type I collagen fibrils in ten-

https://reactome.org
don are up to 1 cm in length, with a diameter of approx. 500 nm. An individual fibrillar collagen triple helix is less than 1.5 nm in diameter and around 300 nm long; collagen molecules must assemble to give rise to the higher-order fibril structure, a process known as fibrillogenesis, prevented by the presence of C-terminal propeptides (Kadler et al. 1987). In electron micrographs, fibrils have a banded appearance, due to regular gaps where fewer collagen molecules overlap, which occur because the fibrils are aligned in a quarter-staggered arrangement (Hodge & Petruska 1963). Collagen microfibrils are believed to have a quasi-hexagonal unit cell, with tropocollagen arranged to form supertwisted, right-handed microfibrils that interdigitate with neighbouring microfibrils, leading to a spiral-like structure for the mature collagen fibril (Orgel et al. 2006, Holmes & Kadler 2006).

Neighbouring tropocollagen monomers interact with each other and are cross-linked covalently by lysyl oxidase (Orgel et al. 2000, Maki 2006). Mature collagen fibrils are stabilized by lysyl oxidase-mediated cross-links. Hydroxylysyl pyridinoline and lysyl pyridinoline cross-links form between (hydroxy) lysine and hydroxylysine residues in bone and cartilage (Eyre et al. 1984). Arginoline cross-links can form in cartilage (Eyre et al. 2010); mature bovine articular cartilage contains roughly equimolar amounts of arginoline and hydroxylysyl pyridinoline based on peptide yields. Mature collagen fibrils in skin are stabilized by the lysyl oxidase-mediated cross-link histidinohydroxylysinonorleucine (Yamauch et al. 1987). Due to the quarter-staggered arrangement of collagen molecules in a fibril, telopeptides most often interact with the triple helix of a neighbouring collagen molecule in the fibril, except for collagen molecules in register staggered by 4D from another collagen molecule. Fibril aggregation in vitro can be unipolar or bipolar, influenced by temperature and levels of C-proteinase, suggesting a role for the N- and C-propeptides in regulation of the aggregation process (Kadler et al. 1996). In vivo, collagen molecules at the fibril surface may retain their N-propeptides, suggesting that this may limit further accretion, or alternatively represents a transient stage in a model whereby fibrils grow in diameter through a cycle of deposition, cleavage and further deposition (Chapman 1989).

In vivo, fibrils are often composed from more than one type of collagen. Type III collagen is found associated with type I collagen in dermal fibrils, with the collagen III on the periphery, suggesting a regulatory role (Fleischmajer et al. 1990). Type V collagen associates with type I collagen fibrils, where it may limit fibril diameter (Birk et al. 1990, White et al. 1997). Type IX associates with the surface of narrow diameter collagen II fibrils in cartilage and the cornea (Wu et al. 1992, Eyre et al. 2004). Highly specific patterns of crosslinking sites suggest that collagen IX functions in interfibrillar networking (Wess 2005). Type XII and XIV collagens are localized near the surface of banded collagen I fibrils (Nishiyama et al. 1994). Certain fibril-associated collagens with interrupted triple helices (FACITs) associate with the surface of collagen fibrils, where they may serve to limit fibril fusion and thereby regulate fibril diameter (Gordon & Hahn 2010). Collagen XV, a member of the multiplexin family, is almost exclusively associated with the fibrillar collagen network, in very close proximity to the basement membrane. In human tissues collagen XV is seen linking banded collagen fibers subjacent to the basement membrane (Amenta et al. 2005). Type XIV collagen, SLRPs and discoidin domain receptors also regulate fibrillogenesis (Ansorge et al. 2009, Kalamajski et al. 2010, Flynn et al. 2010).

Collagen IX is cross-linked to the surface of collagen type II fibrils (Eyre et al. 1987). Type XII and XIV collagens are found in association with type I (Walchli et al. 1994) and type II (Watt et al. 1992, Eyre 2002) fibrils in cartilage. They are thought to associate non-covalently via their COL1/NC1 domains (Watt et al. 1992, Eyre 2002).

Some non-fibrillar collagens form supramolecular assemblies that are distinct from typical fibrils. Collagen VII forms anchoring fibrils, composed of antiparallel dimers that connect the dermis to the epidermis (Bruckner-Tuderman 2009). During fibrillogenesis, the nascent type VII procollagen molecules dimerize in an antiparallel manner. The C-propeptides are then removed by Bone morphogenetic protein 1
(Rattenholl et al. 2002) and the processed antiparallel dimers aggregate laterally. Collagens VIII and X form hexagonal networks and collagen VI forms beaded filament (Gordon & Hahn 2010, Ricard-Blum et al. 2011).

**Literature references**


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Formation of collagen fibrils

Location: Assembly of collagen fibrils and other multimeric structures

Stable identifier: R-HSA-1474266

Type: transition

Compartments: extracellular region

Collagen fibrils are the principal tensile element of the extracellular matrix in a wide range of animal connective tissues. They have a 67 nm axial periodicity in most tissues, 65 nm in vertebrate skin, and are near-circular in transverse section. Fibril diameter depends both on tissue type and stage of development, covering a range of 20-500 nm in vertebrates. Fibril length is less well characterised but fibrils with lengths in the range 1-100 micrometres have been isolated.

Fibril formation is spontaneous (Fallas et al. 2010, Birk & Brückner 2011), but influenced by developmental state and the cellular environment. Several models have been proposed including the simple surface nucleation and propagation (SNAP) model (Trotter et al. 2000) but the mechanism of fibril assembly and regulation of fibril diameter and length are not completely understood (Holmes et al. 2001, Banos et al. 2008). Fibrils frequently contain more than one type of collagen, and the outer surface of fibrils frequently interacts with proteoglycans, fine-tuning its structural and signaling properties (Wess 2005, Kalamajski & Oldberg 2010, Ricard-Blum et al. 2011).

Individual fibril-forming collagen molecules are around 300nm in length. Complete fibrils exhibit a 67 nm periodicity, seen with many different imaging methods. This is due to a staggered overlap of molecules which leads to regions where fewer molecules overlap with a periodicity of 67 nm (Hodge & Petrusska 1963, Wess 2005). Laterally, molecules are believed to be packed into a quasi-hexagonal structure (Trus & Piez 1980) resulting in locally ordered crystalline regions interspersed with disordered regions across the lateral plane of the fibril (Hulmes 2002). Interactions between molecules stabilize the fibril, including the formation of divalent and subsequently trivalent crosslinks, unique to collagen, that involve lysine or hydroxylysine residues.

Followed by: Formation of collagen fibres

Literature references


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Collagens IV, VI, VIII and X form open networks. Type IV networks are irregular. Type VIII and X form hexagonal networks. Type VI collagen forms tetramers which aggregate linearly to form beaded filaments, but also associates laterally through the globular domains so forming a network (Baldock et al. 2003, Knupp et al. 2006, ). Type IV collagen is the predominant collagen type in basement membranes (Parkin et al. 2011). It assembles into three distinct networks with differing combinations of alpha chains, namely alpha1.alpha1.alpha2, alpha3.alpha4.alpha5 and alpha1.alpha2.alpha5.alpha6, (Siebold et al. 1988, Gunwar et al. 1998, Borza et al. 2001), the last of these forms through the association of alpha5.alpha5.alpha6 triple-helical protomers and alpha1.alpha1.alpha2 protomers, interacting tail-to-tail at the retained NC1 domains. Further associations are formed by tetramerization of the 7S domain at the N terminus (Timpl et al. 1981, Siebold et al. 1987). These interactions are the most significant for network formation, but a third interaction occurs whereby type IV collagen dimers interact through lateral association (Yurchenco & Furthmayr 1984, Yurchenco & Ruben 1987, Yurchenko & Patton 2009). Collagen type VI forms tetramers and subsequently several types of higher-order structure (Ball et al. 2001, Beecher et al. 2011) that are probably influenced by the association of other matrix constituents such as hyaluronan (Kiely et al. 1992), fibrillin (Ueda & Yue 2003), biglycan and decorin (Wiberg et al. 2001).

Type VIII collagen forms a hexagonal lattice in Descemet's membrane (Shuttleworth 1997). These are thought to be derived from tetrahedral structures that form when 4 type VIII molecules associate via hydrophobic patches on their C-termini, which then associate via their N-terminals (Stephan et al. 2004). Type X collagen is very similar to type VIII and in vitro forms hexagonal arrays, believed to arise from interactions of the globular domains (Kwan et al. 1991, Jacenko et al. 2001). In vivo type X collagen is found associated with cartilage fibrils in the form of fine filaments (Schmidt & Linsenmayer 1990), which may represent hexagonal lattices that have collapsed during sample preparation (Gordon & Hahn 2010).

Literature references

Anchoring fibril formation

**Location:** Assembly of collagen fibrils and other multimeric structures

**Stable identifier:** R-HSA-2214320

**Compartments:** extracellular region

Collagen VII forms anchoring fibrils, composed of antiparallel dimers that connect the dermis to the epidermis (Bruckner-Tuderman 2009, Has & Kern 2010). During fibrillogenesis, the nascent type VII procollagen molecules dimerize in an antiparallel manner. The C-propeptide is then removed by Bone morphogenetic protein 1 (Rattenholl et al. 2002) and the processed antiparallel dimers laterally aggregate (Villone et al. 2008, Gordon & Hahn 2010).

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Crosslinking of collagen fibrils

Location: Assembly of collagen fibrils and other multimeric structures

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 allylsine and hydroxyallylsine 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 allylsine 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 hydroxyallylsine cross-linking pathway leads to the formation of more stable ketoimine cross-links.

Telopeptide lysine residues can be converted by LOX to allylsine, which can react with a helical hy-
droxylysine residue forming the lysine aldehyde aldimine cross-link dehydro hydroxylysino norleucine (deHHLNL) (Bailey & Peach 1968, Eyre et al. 2008). If the telopeptide residue is hydroxylsine, 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 predominantly 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 hydroxlysines 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**

Formation of collagen fibres

**Location:** Assembly of collagen fibrils and other multimeric structures

**Stable identifier:** R-HSA-2213201

**Type:** transition

**Compartments:** extracellular region

Fibrils are components of larger suprafibrillar structures, fibres. The organisation of fibrils varies between tissues; in the cornea fibrils are arranged in parallel within layers but layers have different orientations. In articular cartilage, fibrils are arranged in mostly parallel layers (Wess 2005). Interactions between fibrils are thought to be largely mediated by surface-associated macromolecules, such as anionic glycosaminoglycans (GAGs) and small leucine-rich proteoglycans such as decorin.

**Preceded by:** Formation of collagen fibrils

**Literature references**


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Collagen XI cross-links with collagen II

**Location:** Assembly of collagen fibrils and other multimeric structures

**Stable identifier:** R-HSA-2299620

**Type:** binding

**Compartments:** extracellular region

Type XI collagen molecules are cross-linked by lysyl oxidase-mediated bonds (Wu & Eyre 1995) primarily in a head-to-tail manner (Eyre et al. 2006). Homopolymers of type XI collagen can form in vitro (Bruckner & van der Rest 1994, Blaschke et al. 2000). Type XI collagen molecules can cross-link with type II collagen forming heterofibrils (Eyre & Wu 2004, 2005).

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Collagen IX is cross-linked to the surface of collagen type II fibrils

**Location:** Assembly of collagen fibrils and other multimeric structures

**Stable identifier:** R-HSA-2213210

**Type:** binding

**Compartments:** extracellular region

Certain fibril-associated collagens with interrupted triple helices (FACITs) associate with the surface of collagen fibrils, where they may serve to limit fibril fusion and thereby regulate fibril diameter (Gordon & Hahn 2010, Ricard-Blum et al. 2011). Collagen IX cross-linked to the surface of collagen type II fibrils is thought to both regulate fibril diameter and stabilize interfibrillar connections (Eyre et al. 2004). An alternative model suggests that collagen II and XI form a biological alloy (Blaschke et al. 2000).

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Type XII and XIV collagens associate with type I and type II fibrils.

**Location:** Assembly of collagen fibrils and other multimeric structures

**Stable identifier:** R-HSA-2213205

**Type:** omitted

**Compartments:** extracellular region

Certain fibril-associated collagens with interrupted triple helices (FACITs) associate with the surface of collagen fibrils, where they may serve to limit fibril fusion and thereby regulate fibril diameter (Ansorge et al. 2009, Gordon & Hahn 2010). Type XII and XIV colalgens are found in association with type I (Wälchli et al. 1994) and type II (Watt et al. 1992, Eyre 2002).

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Type X collagen associates with collagen type II fibrils

Location: Assembly of collagen fibrils and other multimeric structures

Stable identifier: R-HSA-2213208

Type: binding

Compartments: extracellular region

In vivo type X collagen is found associated with cartilage fibrils in the form of fine filaments (Schmidt & Linsenmayer 1990), which may represent hexagonal lattices that have collapsed during sample preparation (Gordon & Hahn 2010).

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Hemidesmosome formation

Location: Assembly of collagen fibrils and other multimeric structures

Stable identifier: R-HSA-2213192

Type: binding

Compartments: plasma membrane, extracellular region, cytosol

Type XVII collagen is a component of hemidesmosomes (HDs) (Has & Kern 2010). It associates with integrin alpha6beta4 (a6b4) (Hopkinson et al. 1999). The extracellular region of a6b4 extends from the cell membrane into the basement membrane to bind laminins, with a preference for laminin-332 (Hopkinson & Jones 2000, Sugawara et al. 2008), which is a component of anchoring fibrils. Laminins are complex glycoproteins, consisting of alpha, beta and gamma chains bound into a cross-shaped molecule. Laminin-332 is a complex of alpha-3, beta-2 and gamma-2 subunits. The cytoplasmic domain of integrin beta-4 interacts with other hemidesmosomal components, plectrin and BPAG1. The interaction of a6b4 and plectrin is likely to be the initial step in HD formation (de Pereda et al. 2009). The cytoplasmic domain of collagen type XVII (BP180) binds to integrin beta-4, plectin and BPAG1 (Hopkinson & Jones 2000, Koster et al. 2003). The transmembrane protein CD151 (tetraspanin-24) associates with a6b4 (Sterk et al. 2002) and is essential for the correct assembly of basement membranes in human kidney and skin, possibly having a role in integrin alpha-3 maturation and cell surface expression (Karamatic Crew et al. 2003).

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Release of endostatin-like peptides

Location: Assembly of collagen fibrils and other multimeric structures

Stable identifier: R-HSA-2213200

Type: transition

Compartments: extracellular region

Collagens XV and XVIII are basement membrane associated collagens that can be cleaved to generate the antiangiogenic peptides restin (endostatin-XV) and endostatin (endostatin-XVIII), respectively (O'Reilly et al. 1997, Ramachandran et al. 1997, Sasaki et al. 2000). Endostatin fragments of differing molecular size (14-30 kDa) have been identified in vivo. Furthermore the C-terminal domains of several other collagens (IV, VIII, XIX) have anti-angiogenic and anti-tumoral activities (Ricard-Blum & Ballut 2011). Several proteases are able to generate endostatin from collagen XVIII including MMP-3, -7, -9, -13 and -20 and cathepsins B, V, S and L (Heljasvaara et al. 2005, Ma et al. 2007, Veillard et al. 2011). Endostatin inhibits proliferation of endothelial cells, angiogenesis and tumor growth in vivo (O'Reilly et al. 1997).

Literature references


Editions

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<td>Jupe, S.</td>
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<td>Kalamajski, S., Raleigh, S.</td>
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