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: 79

This document contains 3 pathways and 9 reactions (see Table of Contents)
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-
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-stagger 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 (An-sorge 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**


**Editions**

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Formation of collagen fibrils

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