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Elastic fibres in health and disease

Cay M. Kielty

Elastic fibres are a major class of extracellular matrix fibres that are abundant in dynamic connective tissues such as arteries, lungs, skin and ligaments. Their structural role is to endow tissues with elastic recoil and resilience. They also act as an important adhesion template for cells, and they regulate growth factor availability. Mutations in major structural components of elastic fibres, especially elastin, fibrillins and fibulin-5, cause severe, often life-threatening, heritable connective tissue diseases such as Marfan syndrome, supravalvular aortic stenosis and cutis laxa. Elastic-fibre function is also frequently compromised in damaged or aged elastic tissues. The ability to regenerate or engineer elastic fibres and tissues remains a significant challenge, requiring improved understanding of the molecular and cellular basis of elastic-fibre biology and pathology, and ability to regulate the spatiotemporal expression and assembly of its molecular components.

Elastic fibres are major insoluble extracellular matrix (ECM) assemblies that are developmentally deposited during early post-natal life in elastic connective tissues such as the aorta and elastic arteries, skin, lung, ligaments and auricular cartilage (reviewed in Refs 1, 2, 3, 4). They comprise a central crosslinked core of elastin (~90% of the fibre), surrounded by a sheath of microfibrils that are based on the glycoprotein fibrillin (Fig. 1). Other microfibril- or elastic-fibre-associated molecules have been identified by immunochemical and other approaches (Table 1). Murine knock-out models have revealed the critical importance of several such molecules, including lysyl oxidase (LOX) and fibulin-4 and -5, for normal elastic-fibre formation (Refs 5, 6, 7, 8, 9).

An early stage in the formation of elastic fibres is the pericellular deposition of loose, roughly aligned arrays of fibrillin microfibrils that endow tissues with long-range elasticity (Ref. 2) (see 'Elastic-fibre functions'). Microfibrils have a complex ultrastructure and, using rotary shadowing and atomic force microscopy, isolated microfibrils appear as repeating globules on filamentous linear arrays (Refs 10, 11, 12, 13, 14). However, quick-freeze deep-etch microscopy has revealed that hydrated physiological microfibrils are likely to be cylindrical structures rather than beaded arrays, with inter-microfibril links (Ref. 15).

Fibrillin microfibril bundles form a template for the deposition of tropoelastin in the extracellular space (Refs 2, 4, 16, 17). Deposits of elastin first appear within microfibril bundles, then coalesce to form the central crosslinked elastin core of mature elastic fibres (Refs 1, 2). The elastin core appears to be formed from laterally packed, thin beaded filaments formed from crosslinked elastin (Ref. 18). Mature elastic fibres have an outer mantle of microfibrils, and some microfibrils also appear to be embedded within the elastin core.

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Accession information: DOI: 10.1017/S146239940600007X; Vol. 8; Issue 19; August 2006

Tissue organisation of elastic fibres

The functional properties of elastic fibres strongly reflect their tissue-specific architectures, in turn dictated by the organisation of the microfibril template, the orientation of the cells that deposit them, and the forces acting on the tissue (Refs 2, 4). In the aorta and elastic arteries, elastic fibres form concentric fenestrated lamellar layers within the medial layer that intercalate with vascular smooth muscle cells. The internal and external elastic laminae are thick concentric elastic-fibre layers that separate the intima and media, and the media and adventitia, respectively. In the developing aorta, subendothelial microfibril bundles are oriented parallel with the direction of blood flow and provide elastic anchorage for endothelial cells (Refs 19, 20). Lung elastic fibres form a fine highly branched network that is present throughout the respiratory tree, especially in the alveoli. Skin elasticity is imparted by an abundant elastic-fibre network that extends from the dermal–epidermal junction as cascades of microfibril bundles (oxytalan fibres), through perpendicular elaunin fibres in the papillary dermis that contain small amounts of elastin, to thick horizontally aligned elastic fibres in the reticular dermis. Longitudinally oriented elastic fibres that run parallel to collagen fibrils are relatively abundant in ligament, but sparse in tendons. In elastic cartilage, a thin fibre meshwork is interspersed with interterritorial collagen fibrils and also surrounds chondrocyte lacunae.

Molecular composition of elastic fibres

The molecular constituents and associated molecules of elastic fibres are listed in Table 1. While roles of elastin and fibrillin are relatively well defined, less is known about how elastic-fibre-associated molecules contribute to their assembly and function.

Elastin core

Elastin is a very long-lasting protein and the most abundant component of elastic fibres, with little turnover in healthy tissues (Refs 1, 21). It is encoded by a single-copy gene on chromosome 7q11.2, and secreted as a soluble tropoelastin precursor (65–70 kDa) that can exist as globules or extended polypeptides (Refs 4, 22, 23, 24). The primary tropoelastin transcript undergoes tissue-specific alternative splicing, which may allow fine-tuning of the functional properties of assembled elastin in different tissues. Tropoelastin has a multidomain structure, with repeating hydrophobic and lysine-rich crosslinking domains, each encoded by separate exons (Fig. 2a). LOX and probably other members of this enzyme family direct the formation of crosslinked elastin (Refs 25, 26; reviewed in Refs 27, 28, 29). Proteoglycans, including biglycan (a small leucine-rich proteoglycan), have been detected within the elastin core (Ref. 30), and the glycosaminoglycan heparan sulphate might also be present (Ref. 31).

Microfibrils

Fibrillins, which form the structural framework of microfibrils, are large multidomain glycoproteins (~350 kDa) comprising mainly multiple calcium-binding epidermal growth factor (cbEGF)-like domains and also several eight-cysteine-containing (TB) motifs (Fig. 2b)

Figure 1. Schematic diagrams of the assembly of fibrillin microfibrils and elastic fibres. (*Legend; see next page for figure.*) (a) Newly secreted fibrillin-1 molecules assemble pericellularly into beaded microfibrils. Fibrillin-1 molecules associate laterally and linearly, through specific N- and C-terminal interactions. While fibrillin-1 can form dimers in vitro, it is not yet known whether dimers are intermediates of microfibril assembly in vivo. There are probably eight fibrillin-1 molecules in a microfibril cross-section (only two are shown here, for clarity). Microfibril-associated glycoprotein-1 (MAGP-1) binds the N-terminus of fibrillin-1 molecules, but it is not known whether this occurs before, during or after microfibril assembly. Assembled microfibrils form loose, roughly parallel bundles in the extracellular matrix. (b) Elastic fibres form in association with fibrillin microfibrils. Elastin, in the form of soluble tropoelastin molecules or small elastin aggregates, becomes associated with pre-formed microfibrils. Fibulin-5 can interact with both fibrillin-1 and tropoelastin, and might play a role in the deposition of tropoelastin onto microfibrils. It is not known how other elastin–microfibril interface molecules, such as fibulin-2 and -4, and emilin-1, might influence this process. Deposited elastin is stabilised by lysyl-derived crosslinks formed by the activities of lysyl oxidase (LOX) and/ or lysyl oxidase-like (LOXL), which may also interact with microfibrils. In mature elastic fibres, microfibrils are present at the periphery, and may also be embedded within the crosslinked elastin core.

Accession information: DOI: 10.1017/S146239940600007X; Vol. 8; Issue 19; August 2006

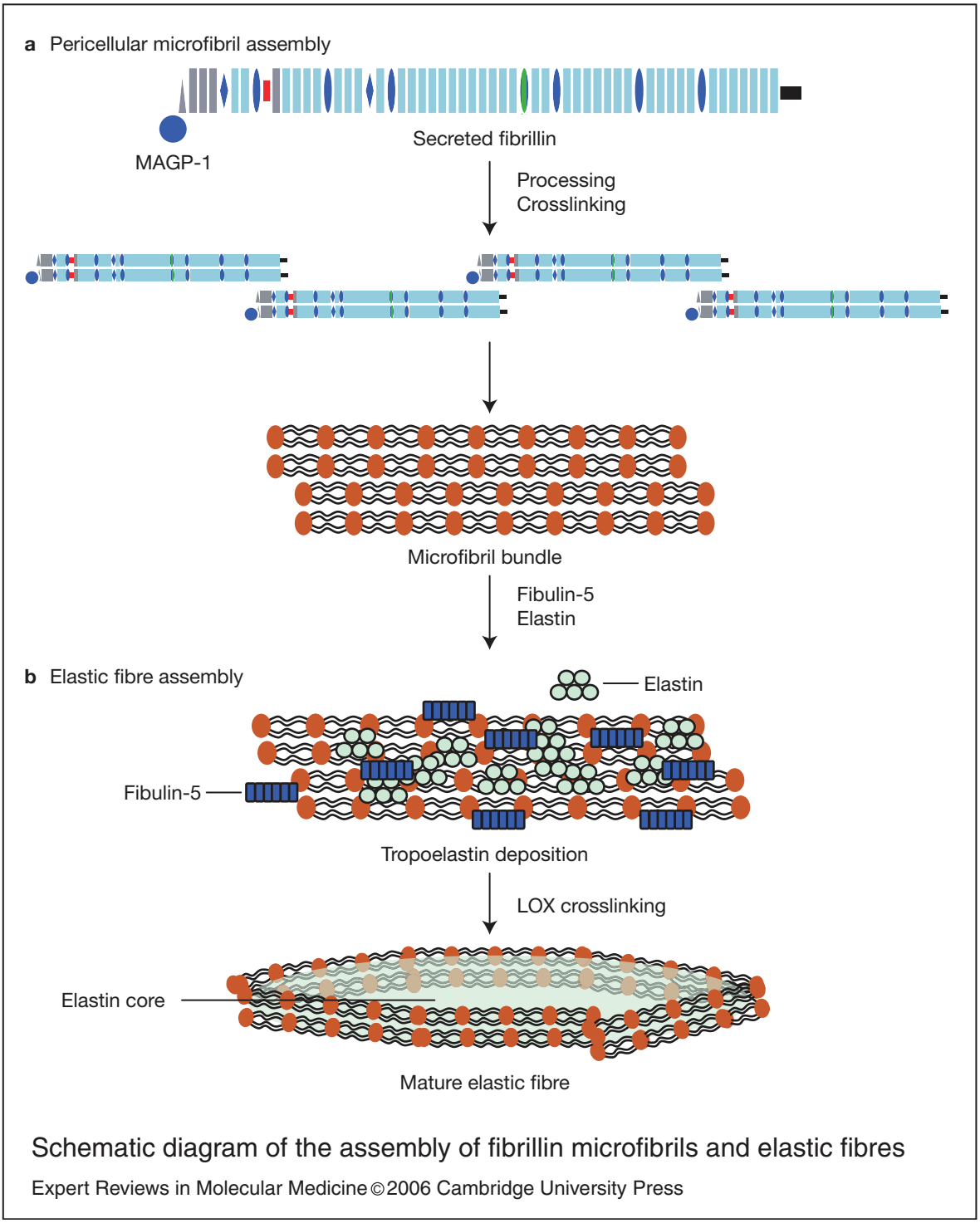


Figure 1. Schematic diagrams of the assembly of fibrillin microfibrils and elastic fibres. (*See previous page for legend.*)

(Refs 32, 33, 34; reviewed in Ref. 3). In humans, there are three fibrillin isoforms (fibrillins 1–3). However, in mouse, the fibrillin-3 gene is split onto two chromosomes (Ref. 34). Small-angle X-ray scattering and single-particle averaging has revealed that soluble fibrillin-1 molecules are relatively flexible rod-like molecules (Ref. 35).

Accession information: DOI: 10.1017/S146239940600007X; Vol. 8; Issue 19; August 2006

Table 1. Structural and associated molecules of microfibrils and elastic fibres

Molecule	Elastic-fibre location	Refs
Fibrillin-1	Microfibrils	36, 37, 38
Fibrillin-2	Microfibrils	36
Fibrillin-3	Unknown – likely in microfibrils	34
MAGP-1	Microfibrils	37, 58
MAGP-2	Some microfibrils	39, 40
LTBP-1	Some microfibrils; also fibronectin	41, 44, 63
LTBP-2	Microfibrils, elastic fibres	42, 44
LTBP-3	Fibrillar structures	44
LTBP-4	Fibrillar structures, fibrillin	44
Decorin	Microfibrils, microfibril–elastic-fibre interface	30, 67, 68
Biglycan	Elastic-fibre core	30, 68
Versican	Some microfibrils	47
Heparan sulphate	Microfibrils, elastic-fibre core	60, 61
Perlecan	Microfibrils	62
MFAP-1	Some microfibrils	159
MFAP-3	Some microfibrils	160
MFAP-4 (MAGP-36)	Some microfibrils	161
βIgH3	Elastic-fibre–collagen interface	162
Tropoelastin	Elastic-fibre core	1, 2
LOX	Newly secreted tropoelastin, microfibril–elastin interface	163
LOXL	Microfibril–fibulin-5–elastin interface	163
Fibulin-1	Elastic-fibre core	164, 165
Fibulin-2	Elastin–microfibril interface	64
Fibulin-4	Unknown – likely in elastic-fibre core	9
Fibulin-5	Elastic-fibre–cell interface	7, 8
Emilin-1	Elastin–microfibril interface	46
Emilin-2	Elastin–microfibril interface	46
Elastin-binding protein	Newly secreted tropoelastin	89, 91
Vitronectin	Some microfibrils in dermal tissues	166
Amyloid	Some microfibrils in dermal tissues	166
Collagen VIII	Vascular elastic fibres	48
Collagen XVI	Dermal microfibrils	167
Endostatin (C-terminus of collagen XVIII)	Vascular elastic fibres	168
Collagen VI	Some microfibrils	169

Abbreviations: βIGH3, also known as transforming growth factor-β-inducible gene-H3 and as keratoepithelin, on chromosome 5q31; LOX, lysyl oxidase; LOXL, lysyl oxidase-like; ITBP, latent-transforming-growth-factor-β-binding protein; MAGP, microfibril-associated glycoprotein; MFAP-1, microfibril-associated protein-1.

Accession information: DOI: 10.1017/S146239940600007X; Vol. 8; Issue 19; August 2006

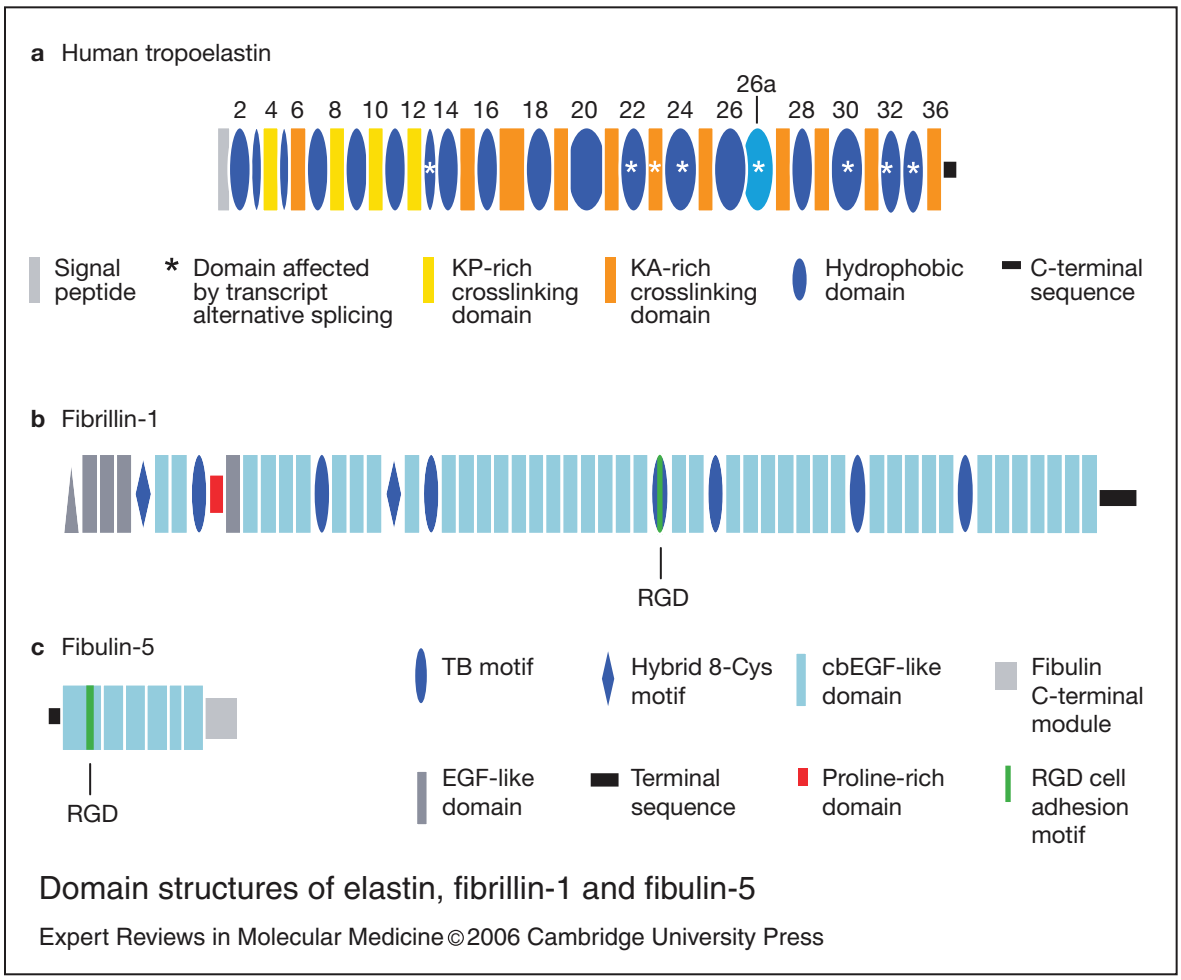


Figure 2. Domain structures of elastin, fibrillin-1 and fibulin-5. (a) Tropoelastin comprises alternating hydrophobic and crosslinking (KP- or KA-rich) domains. It undergoes complex alternative splicing in different elastic tissues. The unique C-terminal domain, which may play a key role in elastin assembly, contains two cysteine residues. (b) Fibrillin-1 is a large multidomain glycoprotein comprising 47 epidermal growth factor (EGF)-like domains, 43 of which are calcium binding (cbEGF-like domains). In the presence of calcium, these domains may adopt a relatively linear conformation. These domains are interspersed with seven TB (8-cysteine) motifs and two 'hybrid' domains that have similarities to both EGF-like domains and TB motifs. There are 14 *N*-glycosylation sites, and a potentially flexible proline-rich region is present towards the N-terminus. Removal of N- and C-terminal sequences by furin processing, upon secretion, facilitates assembly. At the N-terminus is a unique cysteine-containing motif (shown as a triangle). (c) Fibulin-5 is a small glycoprotein containing an atypical N-terminal cbEGF with an RGD cell attachment motif, five further contiguous cbEGF-like domains, and a C-terminal fibulin (FC) module.

Fibrillin-1 and -2, encoded by genes on chromosomes 15 and 5, respectively, have partially overlapping expression patterns. Fibrillin-2 is strongly expressed in developing tissues, whereas fibrillin-1 is the most abundant isoform throughout life (Refs 33, 36). Mass spectrometry analysis of microfibrils purified from three different adult tissues identified abundant fibrillin-1, but no fibrillin-2 (Ref. 37). However, immunofluorescence and immunochemical studies using antibodies specific for either fibrillin-1 or fibrillin-2 have indicated that both fibrillins colocalise in some microfibrils (Ref. 36). A recent study of how fibrillin-1 and -2 contribute to vasculogenesis, using knock-out mice, indicated that both fibrillins perform partially overlapping functions during aortic development (Ref. 38). Fibrillin-1 null mice died perinatally from ruptured aortic aneurysm and impaired lung

Accession information: DOI: 10.1017/S146239940600007X; Vol. 8; Issue 19; August 2006

function; fibrillin-2 null mice had an apparently normal aorta, but double null mice died in utero and had a much more severe vascular phenotype than the fibrillin-1 null mice.

Of the various microfibril-associated molecules (Table 1), microfibril-associated glycoprotein-1 (MAGP-1) is the strongest candidate for a microfibril structural component. It colocalises widely with microfibrils, and was detected in purified microfibril preparations by mass spectrometry (Ref. 37). MAGP-2 and LTBP-1 [a binding protein for latent transforming growth factor β (TGF-β)] also colocalise with microfibrils in certain tissues (Refs 39, 40, 41).

Elastic-fibre interface molecules

Molecules at the microfibril–elastin interface or in the pericellular–elastic-fibre interface include LTBP-2, fibulin-2, emilin-1, versican (a large chondroitin sulphate proteoglycan) and decorin (a small leucine-rich proteoglycan) (Refs 18, 42, 43, 44, 45, 46, 47). Collagen VIII, which has structural similarities with emilin-1 and forms hexagonal basement-membrane-associated networks, might also colocalise with vascular elastic fibres (Ref. 48).

Fibulin-5, a glycoprotein of ~55 kDa containing an Arg-Gly-Asp (RGD) motif and five cbEGF-like domains (Fig. 2c), is expressed by vascular smooth muscle cells and endothelial cells, mediates vascular cell adhesion through integrin receptors, influences smooth muscle cell proliferation and migration, and regulates elastin fibrillogenesis (Refs 7, 8, 49; reviewed in Ref. 50). It localises on the elastic lamina surfaces adjacent to endothelial cells, and throughout the aortic media. Its expression is markedly down-regulated in adult arteries, but is highly induced in vascular cells following injury, in atherosclerotic cells, and in neointimal cells following balloon angioplasty (Ref. 51). Fibulin-4 is also essential for elastic-fibre formation, since its absence abolishes normal elastogenesis and leads to irregular elastin aggregates (Ref. 9).

Assembly of elastic fibres

Recent approaches to understanding the molecular basis of the hierarchical assembly of microfibrils and elastic fibres (Fig. 1) have focused strongly on defining the interactions involved (summarised in Fig. 3).

Microfibril assembly

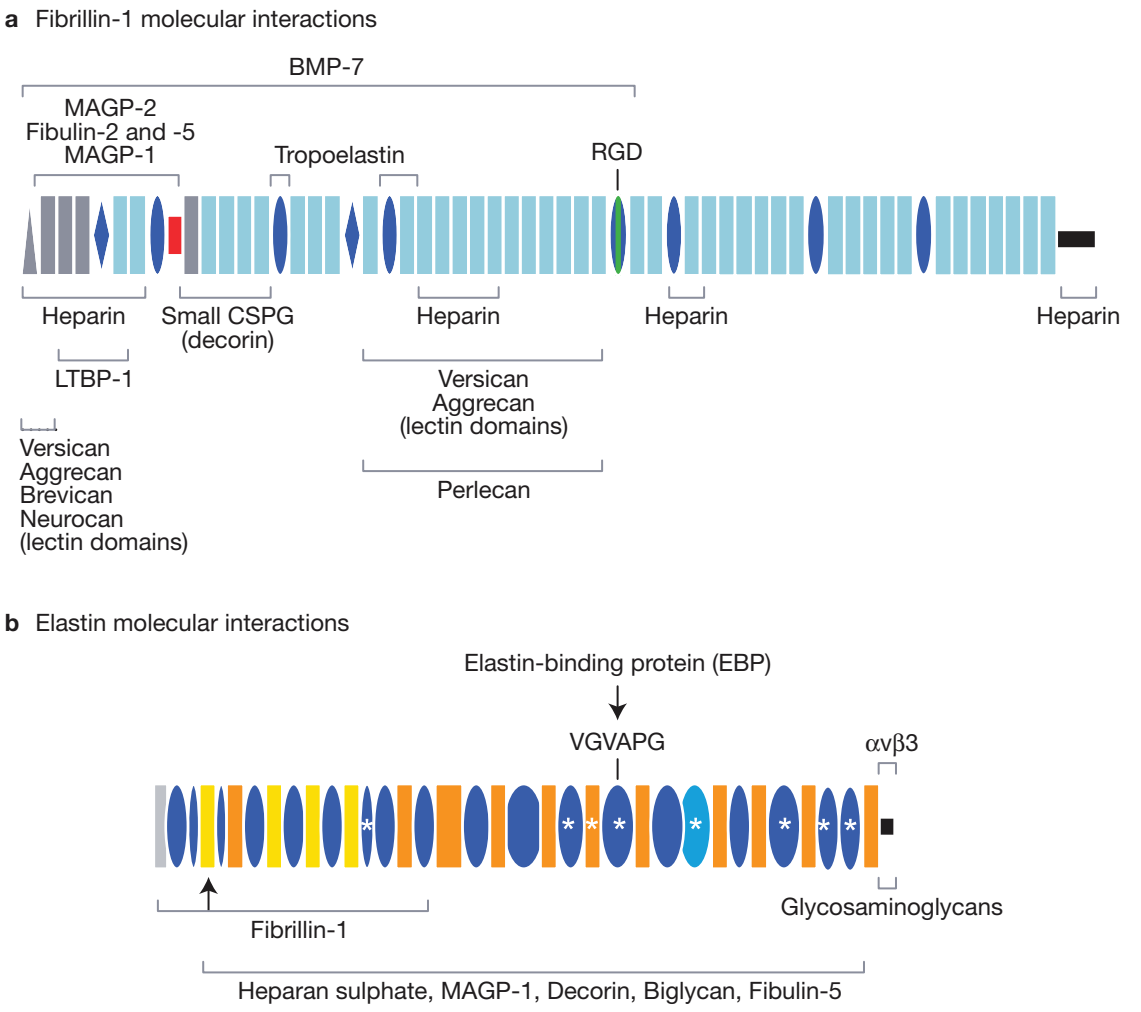
Fibrillin microfibril assembly is a multistep process. Secreted fibrillin molecules undergo N- and C-terminal processing by enzymes of the furin/PACE family, as a prerequisite for directional linear molecular accretion and lateral interactions (Refs 52, 53, 54). Assembled microfibrils are stabilised by transglutaminase crosslinks (Ref. 55). The molecular interactions involved in microfibril assembly have been elucidated using recombinant fibrillin-1 fragments and in vitro binding assays (Refs 54, 56, 57). High-affinity binding occurs between N-terminal fragments, between furin-processed C-terminal fragments, and between N- and C-terminal fragments (Ref. 54). The sequence that occurs after the C-terminal furin cleavage site also interacts with N-terminal fragments. These interactions may drive linear and lateral assembly.

MAGP-1 strongly binds an N-terminal sequence in a calcium-dependent manner (Refs 58, 59) (Fig. 3), which, in microfibrils, localises at or close to the beads. This interaction inhibits N- and C-terminal interactions but not the homotypic N-terminal interactions (Ref. 54). In tissues, it is not known whether MAGP-1 associates with microfibrils before or after their assembly.

Heparan sulphate plays an important role in microfibril assembly. Microfibril assembly is effectively ablated by supplementing cell cultures with heparin (Ref. 60). Heparin was shown to interact with fibrillin-1 at three sites. Using BIAcore technology, and heparin saccharides analogous to S-domains of heparan sulphate, four high-affinity heparin-binding sites on fibrillin-1 were identified, and their kinetics defined (Ref. 61) (Fig. 3). Heparin does not inhibit fibrillin-1 N- and C-terminal interactions, but heparin competes both with MAGP-1 to bind the fibrillin-1 N-terminus and with tropoelastin to bind a central fibrillin-1 sequence. In vivo, heparan sulphate may regulate microfibril and elastic-fibre assembly.

Fibrillin microfibrils form bundles that support the deposition of tropoelastin, or can integrate into basement membranes such as the dermal–epidermal junction through interactions with perlecan (Ref. 62). Fibrillin-1 has also been shown to interact directly with LTBP-1 (Ref. 63), fibulin-2 (Ref. 45), versican (Ref. 47), and with small chondroitin sulphate proteoglycans (Ref. 64).

Accession information: DOI: 10.1017/S146239940600007X; Vol. 8; Issue 19; August 2006



Molecular interactions of fibrillin-1 and elastin

Figure 3. Molecular interactions of fibrillin-1 and elastin. Molecules that bind fibrillin-1 and tropoelastin are shown above and below the schematics, with the grey lines representing the regions within which the binding sites for the various molecules occur. (a) Fibrillin-1. In vitro assays have revealed that fibrillin-1 can interact with many different matrix molecules. The N-terminus is particularly 'sticky', interacting with high affinity both homotypically and with MAGP-1 and -2, fibulin-2 and -5, lecticans, heparin, LTBP-1, small chondroitin sulphate proteoglycans, and BMP-7. The central region of fibrillin-1 contains binding sites for tropoelastin, heparin, versican and perlecan; bound tropoelastin can be transglutaminase-crosslinked to fibrillin-1. There are two further heparin-binding sites towards the C-terminus. It is not known which molecules interact with fibrillin-1 in tissues. Proteomic analysis of purified tissue microfibrils identified only fibrillin-1 and MAGP-1. (b) Elastin. There is a fibrillin-1 crosslink site towards the N-terminus of tropoelastin. Heparan sulphate, MAGP-1, decorin, biglycan and fibulin-5 all bind tropoelastin, but their binding sites have not been identified. The VGVAPG motif within tropoelastin binds cells through the elastin-binding protein (EBP). The C-terminus of tropoelastin may bind cells through integrin-dependent and -independent mechanisms, and it also binds glycosaminoglycans.. Abbreviations: BMP-7, bone morphogenetic protein 7; LTBP-1, latent-transforming-growth-factor-β-binding protein; MAGP-1, microfibril-associated glycoprotein-1.

Accession information: DOI: 10.1017/S146239940600007X; Vol. 8; Issue 19; August 2006

Elastic-fibre assembly

A widely accepted model of elastic-fibre assembly involves the initial deposition of soluble, newly secreted tropoelastin molecules onto microfibrils, then the subsequent accretion of additional tropoelastin molecules that become covalently crosslinked by LOX (taken here to refer to one or more members of this enzyme family), to form the insoluble elastin core (Fig. 1). Real-time microscopy, using an in vitro cell culture system, has indicated that elastin globules, possibly associated with microfibrils, may aggregate hierarchically to form larger fibrillar structures, and that this aggregation process is coupled to cell motion (Refs 16, 17). The pro-regions of LOX (the originally identified enzyme) and of a second isoform designated lysyl oxidase-like (LOXL; an enzyme that is important in elastic-fibre renewal in adult tissues) play a significant role in directing the deposition of both enzymes onto elastic fibres by mediating interactions with tropoelastin (Ref. 65).

The molecular basis of fibrillin-1 interactions with tropoelastin have been defined (Refs 58, 59). There are two high-affinity binding sites for tropoelastin on fibrillin-1 (Ref. 59). Tropoelastin can become transglutaminase crosslinked to a specific fibrillin-1 sequence in one of these sites, within the TB2 motif towards the centre of the molecule (Refs 59, 60). This crosslink site maps to an exposed microfibril feature adjacent to the beads (Refs 59, 66).

Elastin also interacts in vitro with other microfibril-associated molecules, including MAGP-1 or biglycan (Refs 58, 59, 67, 68) (Fig. 3). Its interactions with MAGP-1 might contribute to deposition of tropoelastin onto microfibril templates.

Mice knock-out studies have shown that fibulin-4 and -5 play critical but as yet poorly understood roles in vascular elastic-fibre formation (Refs 7, 8, 9) (see 'Elastic-fibre interface molecules'). LOXL colocalises with fibulin-5 and binds a C-terminal fibulin-5 sequence (Ref. 25). The juxtaposition of fibulin-5 to tropoelastin and LOXL may facilitate elastin crosslinking. Recombinant rat fibulin-5 bound tropoelastin in a calcium-dependent manner, but no significant binding was observed for fibrillin-1, laminin or collagen I (Ref. 7). In a separate study, recombinant fibulin-5 associated with pre-formed elastic fibres deposited by cultured cells (Ref. 8). Fibulin-5 also interacts with emilin-1 (Ref. 46). Full-length recombinant human fibulin-5 was also found to bind to tropoelastin in a calcium-independent manner, to an N-terminal fibrillin-1 fragment and to isolated microfibrils (Ref. 69). These data support a role for fibulin-5 interactions with microfibrils during early elastic-fibre formation.

Elastic-fibre functions

Elastic fibres serve at least three critical functions. They are major structural elements that are responsible for endowing the properties of elastic recoil and resilience on dynamic connective tissues. Molecular components or molecules associated with fibrillin microfibrils and elastic fibres regulate the activity of the TGF-β family of growth factors in elastic tissues. Elastic-fibre molecules also directly mediate cell attachment, and thereby regulate migration, survival and differentiation.

Elasticity

Studies on invertebrate and mammalian microfibrils have shown that individual microfibrils and microfibril bundles have elastic properties (Refs 70, 71, 72). Isolated microfibrils were shown to be relatively extensible, using a molecular combing and atomic force microscopy approach (Ref. 72). Individual microfibrils had a Young's modulus that is approximately two orders of magnitude stiffer than elastin, so elasticity in microfibril-containing tissues may arise primarily from reversible alterations in microfibril bundle reorganisations while individual microfibrils might act as reinforcing fibres. Untensioned isolated microfibrils have a regular periodicity of ~56 nm, but isolated extended microfibrils up to ~150 nm have also been observed (Refs 11, 13). One study suggests that microfibrils may be reversibly extensible in the range of 56 to 100 nm but that irreversible deformation occurs at higher periodicities (Ref. 13). The importance of calcium in the elasticity of tissue microfibrils has also been shown (Refs 73, 74). At the whole-tissue level, X-ray fibre diffraction has proved effective at defining microfibril bundle architecture and reversible changes induced by extension. Small-angle X-ray scattering showed strong third-order patterns in untensioned hydrated ciliary zonules (Refs 75, 76), and thus that adjacent

Accession information: DOI: 10.1017/S146239940600007X; Vol. 8; Issue 19; August 2006

microfibrils are usually staggered at a periodicity of one-third of the axial unit cell length. However, following tissue extension of more than 50%, there was decreased lateral spacing between individual microfibrils and increased alignment along the axis of the applied force. Following release of strain, the characteristic staggered arrangement was recovered, indicating that microfibril bundle elasticity is reversible. Raman spectroscopy revealed that mechanical extension of microfibril bundles induces reversible conformational changes associated with an apparent decrease in randomly coiled regions of protein and an increase in α-helical regions (Ref. 75).

Elastic fibres comprising both microfibrils and crosslinked elastin were an essential evolutionary advance required to support the appearance of vertebrate high-pressure circulatory systems and many other elastic-tissue functions (Ref. 77). Elastin is extremely insoluble due to extensive lysyl-derived crosslinks, and the crosslinked elastin core of the fibre provides the major contribution to tissue elasticity. It imparts the properties of extensibility and elastic recoil in repeated cycles of stretch and recoil (Ref. 4). The driving force of elastin elasticity is likely to be entropic, where stretching decreases the entropy of the elastic aggregate and elastic recoil is then driven by a spontaneous return to maximum entropy. Elastin is a two-phase material with a compact amorphous and highly dynamic hydrophobic 'domain' comprising distorted β-strands, fluctuating turns and buried hydrophobic residues, and main-chain polar atoms that form hydrogen bonds with water (Ref. 78). Water makes relaxed elastin dynamic and supports its elasticity. Several models of elastin organisation (isotropic or anisotropic) have been proposed to account for its elasticity (Refs 4, 22, 78).

TGF-β-family activation

Accumulating genetic and biochemical evidence shows that fibrillin microfibrils play a key role in the extracellular regulation of TGF-β activation and signalling (reviewed in Ref. 79). The TGF-β family of growth factors are powerful regulators of cell survival, proliferation and differentiation, of tissue morphogenesis, and of cellular responses to injury (reviewed in Ref. 80). Excess TGF-β activation is strongly implicated in the pathogenesis of the fibrillinopathies (see 'Marfan syndrome and related fibrillinopathies').

It remains unclear precisely how microfibrils regulate TGF-β. Fibrillin-1 might control TGF-β1 availability through tissue-specific associations with LTBP-1 (Ref. 79). LTBP-1 intracellularly forms a large latent complex with TGF-β1, which is then covalently linked through a disulphide bond with the latency-associated propeptide (LAP) of TGF-β and the penultimate TB module of LTBP-1, and is efficiently secreted (reviewed in Refs 81, 82). LTBP-1 binds an N-terminal region of fibrillin-1 (Ref. 63). However, this model remains to be confirmed since LTBP-1 is not an integral component of microfibrils, it only colocalises with fibrillin microfibrils in some tissues (Refs 41, 43), there is no direct evidence that the excess TGF-β signalling in Marfan syndrome involves LTBP-1, and LTBP genes are not linked to Marfan-like diseases. LTBP-3 also binds TGF-β1 strongly but does not interact with fibrillin-1 (Ref. 63), whereas LTBP-4 binds LAP-TGF-β only weakly, and LTBP-2 does not bind it at all. Bone morphogenetic protein (BMP)-7 – a member of the TGF-β superfamily – can directly bind fibrillin-1 (Ref. 83). Fibrillin-2 null mice models have revealed that fibrillin-2 and BMPs 4 and 7 are functionally and genetically linked (Refs 84, 85). Emilin-1, an elastic-fibre-associated molecule, inhibits TGF-β signalling independently of fibrillins, by binding to proTGF-β and inhibiting its pericellular furin processing (Ref. 86). Thus, current models of how microfibrils regulate TGF-β include structural relationships with LTBP-1 and emilin-1, and possibly direct growth factor binding.

Cell adhesion

Elastic fibres play an important role in cell–matrix interactions in elastic connective tissues. Electron microscopy and biochemical studies have shown that endothelial cells interact directly with their subendothelial elastic-fibre-rich matrix, while smooth muscle cells are closely juxtaposed to the medial elastic-fibre lamellae at cellular dense plaques (Refs 19, 20). Studies (see below) have revealed that these interactions are mediated mainly through integrins, which are heterodimeric transmembrane receptors (reviewed in Ref. 87) that recognise RGD motifs within matrix molecules and link the vascular ECM directly to

Accession information: DOI: 10.1017/S146239940600007X; Vol. 8; Issue 19; August 2006

the cellular cytoskeletal framework. Such integrin-mediated cell–elastic-fibre interactions influence cell survival, phenotype, proliferation, migration and ECM expression and deposition. Integrins expressed by vascular endothelial cells and smooth muscle cells include α1β1, α2β1, α5β1, α6β1 and αvβ3 (reviewed in Ref. 88). Major elastic-fibre molecules that mediate cell adhesion are outlined below.

Elastin

Cells interact with elastin through the elastin-binding protein (EBP, alternatively spliced form of β-galactosidase; 67 kDa), which binds the tropoelastin hexapeptide VGVAPG (Refs 89, 90, 91). Interactions of VGVAPG peptides with this G-protein-coupled receptor stimulate actin polymerisation, thereby influencing cell proliferation and migration (Refs 92, 93). Signalling through this receptor also profoundly influences smooth muscle cell proliferation and phenotype (Refs 90, 93). The C-terminus of elastin interacts with integrin αvβ3 in a saturable, divalent-cation-dependent manner; this is not an RGD-mediated mechanism since elastin lacks this motif (Ref. 94). In addition, a cell interaction site within the last 17 C-terminal residues of tropoelastin has been identified that mediates cell adhesion through cell-surface proteoglycans containing heparan sulphate and/or chondroitin sulphate (Ref. 95). Certain elastin proteolytic fragments are highly chemotactic (Refs 96, 97).

Fibrillin-1

Human smooth muscle cells exhibit RGD- and cation-dependent adhesion to microfibrils (Ref. 98). Fibrillin-1 mediates adhesion mainly through a single RGD motif in its TB6 module (Refs 99, 100, 101). A corresponding RGD motif in fibrillin-2 is similarly active. Fibrillin-1 interacts with cells through αvβ3 (Refs 99, 100, 102), and ligates the α5β1 receptor (Ref. 101). There is a requirement for domains upstream to the RGD motif for optimal cell adhesion (Ref. 102). These interactions can profoundly influence cell behaviour and gene expression (Refs 101, 103).

Fibulin-5

Fibulin-5 also interacts directly with vascular cells in an RGD- and cation-dependent manner, a function that may contribute to its roles in elastic-fibre deposition and modulation of smooth muscle cell phenotype (Refs 7, 8, 50). Recombinant fibulin-5, expressed in a bacterial system, interacted with integrins αvβ3 and αvβ5 (RGD-dependent) and α9β1 (not RGD-dependent) on integrin-overexpressing CHO cells (Ref. 7).

Clinical implications

Heritable elastic-fibre disorders

Genetic disorders of elastic fibres, which are often life-threatening, highlight the importance of elastic fibres in all elastic connective tissues, but particularly the cardiovasculature (Table 2).

Marfan syndrome and related fibrillinopathies

Marfan syndrome (MFS; OMIM 154700) is a relatively common autosomal dominant hereditary disorder of connective tissue, with major cardiovascular, skeletal and ocular defects (reviewed in Refs 104, 105). It is caused by mutations in the gene for fibrillin-1. Premature death is often caused by acute aortic dissection, following elastic-fibre degeneration and progressive dilatation of the ascending aorta.

Mutations in fibrillin-1 may cause Marfan syndrome as a direct consequence of altered or reduced secretion or assembly of mutant molecules, and increased susceptibility of microfibrils that contain mutant molecules to proteolytic damage. The Marfan syndrome pathology has also recently been strongly associated with excess TGF-β signalling (Refs 106, 107), which results in developmental defects such as defective mitral valvulogenesis (Ref. 106) and widening of the distal airspace due to failure of alveolar septation (Ref. 107), as well as TGF-β-mediated increased cell proliferation, and altered ECM deposition and turnover. TGF-β receptor (TGFBR)II mutations cause Marfan syndrome II and familial thoracic aortic aneurysms and dissections (Refs 108, 109). Novel heterozygous TGFBRI mutations have also been described in two patients with Furlong syndrome, which has some clinical similarities to Marfan syndrome (Ref. 110). Loeys–Dietz aortic aneurysm syndrome, a disorder that phenotypically overlaps Marfan syndrome with aggressive cardiovascular defects, is also caused by enhanced TGF-β

Accession information: DOI: 10.1017/S146239940600007X; Vol. 8; Issue 19; August 2006

Table 2. Heritable disorders of elastic fibres

Disease	Affected gene and location	Clinical effects	Genotype to phenotype
Marfan syndrome and related fibrillinopathies (Refs 104, 105)	Fibrillin-1 gene on chromosome 15q21.1	Vascular disease, including aortic aneurysms and dissections, and skeletal and ocular defects	Altered fibrillin-1 expression, secretion and/or microfibril and elastic-fibre assembly; increased microfibril/elastic-fibre degradation; enhanced TGF-β signalling, possibly due to fibrillin interactions with large TGF-β latent complex
Marfan syndrome II, Loeys–Dietz syndrome, familial thoracic aortic aneurysms and dissections (Refs 108, 109, 110)	TGF-β receptor II (TGFBRII) gene on chromosome 3p24-p25	Severe vascular disease, including familial thoracic aortic aneurysms and dissections, and skeletal, ocular craniofacial and neurocognitive defects	Enhanced TGF-β signalling; loss of association between elastic fibres and smooth muscle cells in the absence of inflammation, suggesting defective elastogenesis; increased expression of collagen
Beal's syndrome; congenital contractural arachnactyly (Ref. 104)	Fibrillin-2 gene on chromosome 5q23	Multiple flexion contractures, arachnodactyly, kyphoscoliosis, abnormal pinnae and muscular hypoplasia, crumpled ears	Altered fibrillin-2 expression, secretion and/or microfibril and elastic-fibre assembly
Arterial tortuosity syndrome (Refs 139, 140, 141, 142)	*SLC2A10* gene (encoding GLUT-10) on chromosome 20q13.1	Autosomal recessive disorder; tortuosity, elongation, stenosis and aneurysm in the major arteries	Fragmentation of elastic fibres in the medial layer of the arterial wall
Supravalvular aortic stenosis and Williams–Beuren syndrome (Refs 112, 114, 115, 116, 117, 118, 119)	Elastin gene on chromosome 7q11	Whole arterial tree affected by narrowing; increased elastinolytic activity	Abnormal deposition of elastin in arterial walls, leading to increased proliferation of arterial smooth muscle cells and formation of hyperplastic intimal lesions; elastinolytic enzymes secreted by arterial smooth muscle cells contribute to arterial lesions
Autosomal recessive cutis laxa (Refs 120, 122)	Elastin gene on chromosome 7q11	Redundant, pendulous and inelastic skin, associated with severe aortic disease and pulmonary emphysema	Abnormal structure of dermal and vascular elastic fibres

(continued on next page)

Accession information: DOI: 10.1017/S146239940600007X; Vol. 8; Issue 19; August 2006

Table 2. Heritable disorders of elastic fibres (*continued*)

Disease	Affected gene and location	Clinical effects	Genotype to phenotype
Autosomal dominant cutis laxa (Refs 120, 121, 123, 125, 126, 127, 128, 129)	Elastin gene on chromosome 7q11; fibulin-5 gene on chromosome 14q32.1; fibulin-4 gene on chromosome 11q13	Milder disease than autosomal recessive cutis laxa. In addition to loose skin, symptoms can include gastrointestinal diverticula, hernias and genital prolapse, pulmonary artery stenosis, aortic and arterial dilatation and tortuosity, and emphysema. Fibulin-4 mutation causes cutis laxa, with vascular tortuosity and bone fragility	Abnormal structure of dermal and vascular elastic fibres. Elastin mutations are towards 3′ end of elastin gene, which may interfere with elastin assembly; mutated fibulin-5 may be overexpressed, due to altered transcription, processing and/or mRNA stability. Fibulin-4 mutation reported to cause underdeveloped elastic fibres during early life; fibulin-4 and -5 contributions to elastic-fibre formation may be disrupted
Acquired cutis laxa (Ref. 124)	Unknown underlying genetic defect	Pendulous, redundant, or coarsely wrinkled areas of skin; usually affects adults, and often leads to systemic elastolysis, causing aortic rupture, emphysema and hernias	Increased inflammatory destruction of elastic fibres due to altered interaction between elastin and fibulin-5
Age-related macular degeneration (Refs 130, 131)	Fibulin-5 gene on chromosome 14q32.1. (Second disease locus: complement factor H)[a]	Irreversible visual loss	Degenerative and neovascular changes within the retina at the macula, including deposits of protein and lipid in Bruch's membrane, which contains elastic fibres
Pseudoxanthoma elasticum (Refs 112, 132, 133, 134, 135, 136, 137, 138)	*ABCC6* on chromosome 16p13.1	Dermal, ocular and cardiovascular lesions	Accumulation of morphologically abnormal and mineralised elastic fibres

[a]Inflammation is another important pathway in age-related macular degeneration, and there is an association with the complement factor H gene, a regulator of complement.

Abbreviations: ABCC6, adenosine triphosphate (ATP)-binding cassette (ABC) gene subfamily C 6; LOX, lysyl oxidase; LOXL, lysyl oxidase-like; LTBP, latent-transforming-growth-factor-β-binding protein; MAGP, microfibril-associated glycoprotein; MFAP-1, microfibril-associated protein-1; TGF-β, transforming growth factor β.

signalling, in this case due to cytoplasmic kinase mutations in TGFBRI and II (Ref. 111).

Fibrillin-1 mutations have been identified in a range of overlapping Marfan-syndrome-like phenotypes – the so-called type-1 fibrillinopathies. They include Marfan syndrome, neonatal Marfan syndrome, atypically severe Marfan syndrome, ectopia lentis, kyphoscoliosis, familial arachnodactyly, familial ascending aortic aneurysms and dissections, MASS phenotype (mitral valve prolapse, aortic valve delation without dissection, skeletal and skin abnormalities), Shprintzen-Goldberg syndrome, isolated skeletal features, 'new variant of Marfan

Accession information: DOI: 10.1017/S146239940600007X; Vol. 8; Issue 19; August 2006

syndrome', and Weill–Marchesani syndrome (Ref. 112). Recently, it has been shown that losartan, an angiotensin II type 1 receptor blocker, can prevent increased TGF-β signalling associated with Marfan syndrome (Ref. 113).

Mutations in fibrillin-2 cause congenital contractural arachnodactyly, also known as Beal's syndrome, which is characterised by multiple flexion contractures, arachnodactyly, severe kyphoscoliosis, abnormal pinnae and muscular hypoplasia (Ref. 104). Some of the clinical pathology is similar to Marfan syndrome, but aortic root dilatation is rare.

Supravalvular aortic stenosis and Williams–Beuren syndrome

Supravalvular aortic stenosis (SVAS) (OMIM 185500) is inherited in an autosomal dominant manner or as part of a complex developmental disorder, Williams–Beuren syndrome (WBS) (reviewed in Refs 112, 114, 115). In both cases, the symptoms of SVAS are similar. The mechanism of obstructive vascular disease in SVAS and WBS involves decreased deposition of elastin associated with increased vascular cell proliferation (Refs 116, 117, 118).

SVAS is caused by mutations in the elastin gene, including deletions and point mutations in the 5′ and middle region of the gene, many of which lead to premature termination codons and unstable mRNA (Ref. 119). Haploinsufficiency of elastin underlies the pathology of SVAS, but genotype–phenotype correlations have proved difficult. Patients with severe SVAS may present with angina and dyspnea, systolic murmur, and left ventricular hypertrophy leading to congestive heart failure. Some SVAS patients exhibit a diffuse narrowing of the ascending aorta, with disorganised elastic-fibre lamellae and smooth muscle cell hypertrophy in the medial layer. Others develop a localised fibrous ring above the aortic valves or, more commonly, exhibit increased medial thickness with fibrous thickening. Other major arteries that may also exhibit stenosis and wall thickening include the pulmonary, coronary, carotid and renal arteries.

WBS is a more complex developmental disorder associated with neurobehavioural, facial and metabolic defects (Refs 114, 115). It is caused by microdeletions on chromosome 7q that delete the elastin gene and up to 27 additional genes.

Cutis laxa

Cutis laxa (CL) is a heterogeneous group of disorders characterised by excess, sagging and inelastic skin (Refs 120, 121, 122, 123; reviewed in Ref. 112). Although acquired cutis laxa is caused by dermal inflammation and associated elastic-fibre degeneration, its pathogenesis involves an underlying genetic susceptibility in which the interaction of specific elastin and fibulin-5 gene alleles render elastic fibres susceptible to inflammatory destruction (Ref. 124). In addition, there are at least three recessive (ARCL) heritable forms of cutis laxa – CL type I (OMIM 219100), CL type II (OMIM 219200) and De Barsy syndrome (OMIM 219150) – as well as an X-linked form (OMIM 304150) and an autosomal dominant form (ADCL) (OMIM 123700). Mutations in the elastin gene, mostly occurring in the 3′ end of the coding region, have been shown to cause ADCL (Refs 120, 125, 126, 127, 128). In at least one case, mutant protein was secreted, and interfered with deposition in a dominant negative manner (Ref. 123). ARCL can be caused by mutations in the gene encoding fibulin-5 (Ref. 122). A new recessive cutis laxa syndrome, associated with vascular tortuosity and bone fragility, has recently been described and shown to be caused by mutation in the fibulin-4 gene (Ref. 129). These disease linkages highlight the critical importance of the relationship between elastin and fibulins in the elastic-fibre system.

Age-related macular degeneration

Selected missense mutations in the fibulin-5 gene have been identified as one cause of age-related macular degeneration (AMD), and associated defects in the elastic fibres of Bruch's membrane of the eye (Ref. 130). These mutant fibulin-5 molecules may not be efficiently secreted, which may contribute to this pathology (Ref. 131).

Pseudoxanthoma elasticum

Pseudoxanthoma elasticum (PXE; OMIM 177850, 264800) is a rare heritable multisystem disorder that is associated with progressive calcification and fragmentation of elastic fibres in cutaneous, ocular and vascular sites (reviewed in Refs 112, 132, 133). The underlying defect is mutations in the gene encoding ABCC6 [adenosine triphosphate (ATP)-binding cassette (ABC) gene subfamily C] on chromosome

Accession information: DOI: 10.1017/S146239940600007X; Vol. 8; Issue 19; August 2006

16p13.1 (Refs 134, 135, 136, 137, 138). The exact physiological function of ABCC6 is unknown but it can actively transport glutathione *S*-conjugates. Lesions in the skin, blood vessels and Bruch's membrane of the eye contain fragmented elastic fibres and calcium deposits. Mineralisation of elastic fibre is initially apparent within the core, but subsequently fragmentation occurs. Other ECM components such as fibronectin, vitronectin and proteoglycans are associated with altered elastic fibres in PXE skin lesions.

Arterial tortuosity syndrome

Arterial tortuosity syndrome (ATS) is an autosomal recessive disorder characterised by tortuosity, elongation, stenosis and aneurysm formation in the major arteries, because of elastic-fibre disruption in the medial layer of the arterial wall (Refs 139, 140). Within chromosome 20q13.1, the candidate region was narrowed to 1.2 Mb, which contains seven genes. Mutations in one of these genes, *SLC2A10*, encoding the facilitative glucose transporter GLUT-10, have now been identified in six ATS families (Ref. 140). GLUT-10 deficiency is associated with upregulation of the TGF-β pathway in the arterial wall, a finding also seen in Marfan syndrome II and Loeys–Dietz syndrome (see 'Marfan syndrome and related fibrillinopathies'), in which aortic aneurysms are also associated with arterial tortuosity. A link has previously been suggested between GLUT-10 and type 2 diabetes (Refs 141, 142). Thus, the finding that GLUT-10 deficiency upregulates TGF-β and can alter arterial morphogenesis might provide new insights into microangiopathic changes in diabetes and suggest therapies targeting TGF-β signalling.

Degenerative elastic-fibre disorders

All the major elastic-fibre molecules are readily degraded by matrix proteins of the serine proteinase and matrix metalloproteinase classes, especially neutrophil elastase and MMP12 (metalloelastase) (Ref. 143). Consequently, loss of elastic-fibre architecture and function is a pathological feature of a number of degenerative and inflammatory diseases of man, including pulmonary emphysema and chronic obstructive pulmonary disease, vascular aneurysm, and photo- and chrono-aged skin. In damaged tissues, the proportion of microfibrils to elastin declines and then the elastin core is degraded. Other acquired disorders of elastic tissues include nevus anelasticus, papula elastorrhexis, anetoderma, acquired cutis laxa and postinflammatory elastolysis (reviewed in Ref. 144). In blood vessels, injury to the vascular endothelium, mediated by proinflammatory cytokines, vasoactive molecules and proteases, leads to degradation and remodelling of the subendothelial matrix including the internal elastic lamina, and subsequently vascular smooth muscle cell proliferation and neointima formation (reviewed in Ref. 145).

Elastic fibres in tissue engineering and regeneration

The importance of elastic fibres to dynamic tissue function renders them a major target for tissue engineering, in the form of biomaterials and biological coatings. Strategies to regenerate elastic fibres in vascular tissues are complex, but show therapeutic promise.

Elastin coacervates

As a highly nonpolar molecule that comprises multiple alternating hydrophobic and lysine-rich domains, tropoelastin molecules form insoluble aggregates following LOX-driven covalent crosslinking. Interactions between the hydrophobic domains contribute to correctly juxtaposing lysine residues prior to crosslink formation. In vitro, tropoelastin has the intrinsic capacity to undergo similar ordered assembly through a process of self-aggregation or 'coacervation', in which the protein comes out of solution as a second phase on increasing solution temperature (Refs 146, 147, 148). The transition appears to be a nucleation process, and the temperature at which the transition takes place depends on elastin concentration, ionic strength and pH.

The coacervation behaviour of various short recombinant fragments of tropoelastin has been described (Refs 146, 147, 148, 149, 150). Three hydrophobic domains flanking two crosslinking domains of human tropoelastin are enough to support self-assembly leading to aligned lysines and the formation of crosslinks similar to native elastin, and with solubility and mechanical properties similar to native elastin.

The coacervation process, using short elastin fragments or full-length tropoelastin, essentially

Accession information: DOI: 10.1017/S146239940600007X; Vol. 8; Issue 19; August 2006

provides the basis for fabrication of vascular elastin-like matrices. In an in situ atomic force microscopy study, conducted at variable temperatures, elastin peptides self-assembled in a substrate-dependent manner. On hydrophilic mica surfaces the peptides adsorbed as discrete, rounded aggregates, whereas adsorption to hydrophobic highly ordered pyrolitic graphite induced a fibrillar arrangement (Ref. 151). The order observed on graphite may be due to hydrophobic peptide–substrate interactions that facilitate organisation of the peptides at the graphite–solution interface and act as a template for fibril growth.

Very large synthetic elastin assemblies have been formed by chemically crosslinking recombinant human tropoelastin with bis(sulphosuccinimidyl) suberate, and used to construct elastic sponges, sheets and tubes (Ref. 152). These synthetic elastin constructs also had similar extensibility properties to those of native elastin, with Young's moduli ranging from 220 to 280 kPa and linearity of extension to at least 150%. The constructs behaved as hydrogels and displayed stimuli-responsive characteristics towards temperature and salt concentrations. Growth and proliferation of cells were supported in vitro and in vivo implants were well tolerated. The domain encoded by human tropoelastin exon 30 alone assembles with an ultrastructural organisation similar to amyloid networks, with antiparallel β-sheet conformation predominant in the exon 30 fibres (Ref. 153). We have produced recombinant human tropoelastin, and characterised coascervation in the absence or presence of other elastic-fibre molecules, thereby generating composite elastic-fibre biomaterials. Elastin coascervation occurs at a lower temperature in the presence of a fibrillin-1 fragment that contains the transglutaminase crosslink site to elastin (Ref. 66). Elastin–fibrillin composite materials may provide more-physiological cell-adhesion characteristics and a biological approach to regulating TGF-β1 in tissue engineering.

Recombinant human elastin can act as an anti-thrombogenic coating on synthetic scaffolds (Ref. 154). Three commercially available synthetic materials coated with adsorbed elastin all demonstrated reduced platelet activation and adhesion in platelet-rich plasma in vitro.

Elastic-fibre deposition

In cell cultures, tropoelastin expression is generally low, and ordered elastic fibres are not often deposited. However, smooth muscle cells seeded within fibrin gels have been shown to remodel their ECM over four weeks and to deposit abundant elastic fibres (Ref. 155). This system opens possibilities for generating engineered tissue constructs with functional elastic fibres, and indicates that elastogenesis can be achieved within three-dimensional cultured structures. More recently, small-diameter vessels, with ovine smooth muscle cells and endothelial cells embedded in fibrin gels, have been described (Ref. 156). The implanted vessels integrated well with the native vessel and demonstrated patency and similar blood flow rates. By 15 weeks post-implantation, they exhibited remarkable matrix remodelling with production of abundant elastic and collagen fibres and orientation of smooth muscle cells perpendicular to the direction of blood flow. Thus, fibrin-based graft models hold significant promise for vascular constructs.

Retroviral-mediated overexpression of the versican proteoglycan variant V3, which lacks chondroitin sulphate chains, profoundly alters arterial smooth muscle cells, inducing significantly increased expression of tropoelastin and formation of ordered elastic fibres in long-term cell cultures (Ref. 157). When V3-overexpressing smooth muscle cells were seeded into ballooned rat carotid arteries, by four weeks they had produced a highly structured neointima significantly enriched in ordered elastic-fibre lamellae containing elongated smooth muscle cells arranged in parallel arrays and separated by densely packed elastic fibres and collagen bundles. Expression of the V3 variant of versican thus offers a powerful new therapeutic approach for the deposition of elastic fibres in vascular conduits (Ref. 158)

Research in progress, and outstanding research questions

Perhaps the major outstanding challenge in elastic-fibre biology is to explain, at molecular and cellular levels, precisely how microfibrils and elastic fibres are assembled, and how and when the extensive repertoire of associated molecules contributes to generate functional elastic fibres. Understanding this complex

Accession information: DOI: 10.1017/S146239940600007X; Vol. 8; Issue 19; August 2006

multistep, multimolecular process will provide the basis for new insights into the pathogenesis of the heritable and acquired diseases that disrupt elastic-fibre formation and function. An important new theme to emerge recently has been the importance of elastic-fibre molecules in regulating cell behaviour, both through direct adhesion events and through TGF-β signalling.

Despite exceptional recent research progress in understanding elastic-fibre assembly and function, many questions remain to be addressed. What defines the specificity of elastic-fibre-mediated growth factor signalling events, and how are they controlled in vivo? What regulates the coordinated expression of elastic-fibre genes during development, and is it possible to recapitulate this level of control to achieve functional elastic-tissue regeneration? What will be the most effective approaches to treating heritable elastic-fibre disorders: knocking out the diseased gene allele using genetic approaches such as RNA interference; therapies based on protecting elastic fibres from proteolytic attack; or strategies such as angiotensin I inhibitors? Can we exploit understanding of the molecular organisation of elastic fibres to engineer robust replacement elastic tissues such as small-diameter arteries and ligaments? By generating answers to these questions, we will enhance elastic-fibre function in health and disease.

Acknowledgements and funding

I thank the anonymous peer reviewers for their comments. Research from my laboratory reported in this article was funded by the Medical Research Council (UK), the Körber Foundation, and the NorthWest Development Agency (UK). C.M.K. is a Royal Society-Wolfson Merit Award holder.

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Further reading, resources and contacts

Marfan syndrome websites:

http://www.umd.be:2030/
http://www.marfan.org
http://www.marfan.org.uk
http://www.marfanworld.org/

Williams syndrome websites:

http://www.williams-syndrome.org/
http://www.williams-syndrome.org.uk/
http://www.wsf.org/

Pseudoxanthoma elasticum websites:

http://www.pxenape.org/
http://www.bbc.co.uk/health/conditions/pxe1.shtml

Information and programme details of the fourth European Symposium on Elastin (Lyons, France; 9–12 July 2006) can be found at:

http://web.ujf-grenoble.fr/BIO/elastin2006/

Author's institute URL: http://www.manchester.ac.uk

Accession information: DOI: 10.1017/S146239940600007X; Vol. 8; Issue 19; August 2006

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Citation details for this article

Cay M. Kielty (2006) Elastic fibres in health and disease. Expert Rev. Mol. Med. Vol. 8, Issue 19, August 2006, DOI: 10.1017/S146239940600007X

Accession information: DOI: 10.1017/S146239940600007X; Vol. 8; Issue 19; August 2006