Elastic fibres in health and disease

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Elastic fibres are insoluble components of the extracellular matrix of dynamic connective tissues such as skin, arteries, lungs and ligaments. They are laid down during development, and comprise a cross-linked elastin core within a template of fibrillin-based microfibrils. Their function is to endow tissues with the property of elastic recoil, and they also regulate the bioavailability of transforming growth factor β. Severe heritable elastic fibre diseases are caused by mutations in elastic fibre components; for example, mutations in elastin cause supravalvular aortic stenosis and autosomal dominant cutis laxa, mutations in fibrillin-1 cause Marfan syndrome and Weill–Marchesani syndrome, and mutations in fibulins-4 and -5 cause autosomal recessive cutis laxa. Acquired elastic fibre defects include dermal elastosis, whereas inflammatory damage to fibres contributes to pathologies such as pulmonary emphysema and vascular disease. This review outlines the latest understanding of the composition and assembly of elastic fibres, and describes elastic fibre diseases and current therapeutic approaches.

Elastic fibres are insoluble components of the extracellular matrix (ECM) of extensible connective tissues such as large arteries, skin, lungs, ligaments and auricular cartilage (Ref. 1). They endow these tissues with the mechanical properties necessary to withstand repeated cycles of stretch and recoil through life. They also influence the bioavailability of transforming growth factor β (TGFβ) family growth factors (Ref. 2). Although fibrillin microfibrils arose in early metazoans (Refs 3, 4) (Fig. 1), elastin and elastic fibres emerged only during vertebrate evolution as an essential requirement to reinforce high-pressure circulatory systems (Ref. 5). Elastic fibres comprise an inner core of cross-linked elastin ensheathed within fibrillin microfibrils. These long-lasting structures begin to assemble during mid-gestation, with little adult elastic fibre assembly.

Mature elastic fibres have tissue-specific architectural arrangements that reflect different elastic requirements. Thus, arterial elastic fibres form concentric lamellar layers that support vascular elastic recoil. Dermal elasticity is based on integrated networks of thick reticular elastic fibres and thin fibres in the papillary dermis, and alveolar elastic fibres form fine networks that allow respiratory expansion and contraction (Ref. 1).

Although tropoelastin and fibrillin are the two principal structural components of elastic fibres, several 'accessory' molecules contribute to

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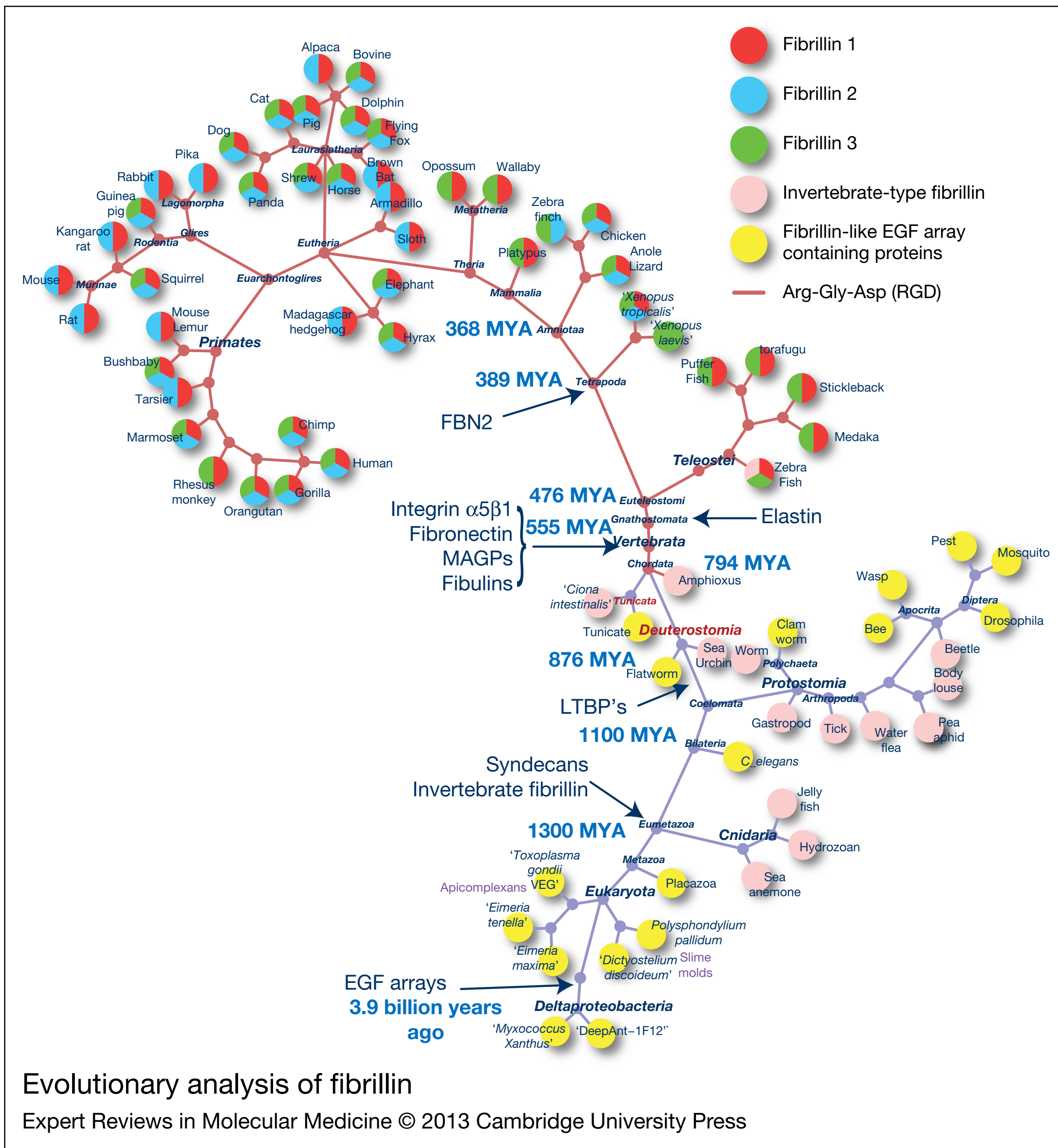

Figure 1. Evolutionary analysis of fibrillin. A list of species from the fibrillin (FBN) sequence alignment was generated, and used to create a common tree using the National Center for Biotechnology Information (NCBI) Taxonomy Browser. The resulting tree was imported into Cytoscape version 2.7, and generated using the organic layout. FBN types were identified using phylogenetic analysis and domain analysis of the FBN multiple sequence alignments and FBN types were mapped onto the common tree. Identified sequences were grouped into 5 categories: vertebrate FBNs 1-3, invertebrate FBN and fibrillin-like epidermal growth factor (EGF) array-containing proteins. The latter sequences had a high identity to FBN sequences but only contained EGF domains organised in arrays. Also indicated are the sequences, from the appearance of chordates that contain the arg-gly-asp (RGD) cell binding motif (branches shown in light brown). By comparison, branches shown in light purple precede chordates and RGD. The first emergence of other key extracellular proteins that interact with FBN is shown (dark blue arrows), along with the evolutionary timescale in million years ago (MYA).

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elastic fibre assembly and function. From initial microfibril formation to the deposition and cross-linking of tropoelastin monomers upon microfibrils, these accessory proteins support the progression of elastic fibre formation in a spatially and temporally appropriate manner. For example, small fibulins influence the association of elastin with its cross-linking enzymes, thereby facilitating its stable deposition on microfibrils (*see* the Assembly of elastic fibres section).

Aberrant elastic fibre formation and/or altered homoeostasis cause many inherited and acquired diseases, with phenotypes ranging from mild (e.g. loose skin) to severe and potentially life-threatening (e.g. vascular defects) (*see* the Elastic fibre disorders section). Heritable elastic fibre disorders include Marfan syndrome (MFS) caused by fibrillin-1 mutations (Ref. 6) and autosomal dominant cutis laxa (ADCL) caused by elastin mutations (Ref. 7). Mutations in accessory glycoproteins such as fibulins-4 or -5 cause autosomal recessive cutis laxa (ARCL) (Ref. 8), and in a disintegrin-like and metalloprotease (reprolysin-type) with thrombospondin-10 (ADAMTS-10) cause Weill–Marchesani syndrome (WMS) (Ref. 9). Acquired elastic fibre disorders arise wherever elastic fibre structure and/or function are compromised; for example, actinic elastosis and vascular degeneration, as well as acquired forms of cutis laxa (CL) and pseudoxanthoma elasticum (PXE).

In this review, we describe the current understanding of microfibril and elastic fibre composition and formation, delineate the diseases associated with elastic fibre defects and summarise the latest therapeutic advances.

Composition of elastic fibres

The structural and associated components of elastic fibres are outlined below; their roles in elastic fibre formation and function are further delineated below (*see* the Assembly of elastic fibres section).

Structural molecules

Elastin

Elastin is the most abundant protein of elastic fibres, comprising approximately 90% of the mature structure. It is encoded by a gene on chromosome 7q11.2, and secreted as the soluble precursor tropoelastin (60–70 kDa) from elastogenic cells such as fibroblasts, smooth muscle cells and auricular chondrocytes. Tropoelastin has a multi-domain structure comprising alternating hydrophobic and lysine-containing (lysine–alanine and lysine–proline) cross-linking domains. The lysine–alanine-rich domains preferentially participate in desmosine cross-link formation (Ref. 10). The primary transcript can undergo tissue-specific alternative splicing that modifies elastin incorporation into fibres (Ref. 7).

Tropoelastin is an asymmetric molecule, which has two functionally distinct regions (Ref. 11): an N-terminal elastic coil that endows spring-like properties on tropoelastin, and a C-terminal cell interactive module that facilitates cell adhesion via an association between the $\alpha v\beta 3$ integrin and a GRKRK motif (Ref. 12). They are separated by a bridge region, within which are domains shown to contain sites of contact for coacervation (Ref. 13). Destabilisation of this region by mutagenesis has been shown to impair elastogenesis (Ref. 14).

Fibrillins

Fibrillin molecules assemble to form microfibrils (Refs 15, 16). In man, there are three fibrillin genes, each encoding 350 kDa multi-domain glycoproteins (fibrillins 1–3) (Ref. 4). Each fibrillin comprises 43 calcium-binding epidermal growth factor-like (cbEGF) domains, five EGF-like domains, seven eight-cysteine-containing (TB) motifs and two hybrid domains with similarities to TB and cbEGF-like domains (Fig. 2). There is a unique proline-rich region in the N-terminal region of fibrillin-1, with corresponding regions of fibrillin-2 and fibrillin-3 being richer in glycine.

Fibrillin-1 (gene on chromosome 15q21.1) is the most abundant fibrillin isoform; it is expressed throughout life and is required for microfibril homoeostasis, whereas fibrillin-2 (gene on chromosome 5q23-q31) and fibrillin-3 (gene on chromosome 19p3) are expressed predominantly during development (Refs 17, 18, 19, 20). Overlapping expression of fibrillins occurs in developing blood vessels, cartilage, bone and lungs, but tissue-specific differences are also apparent, e.g. fibrillin-1 in dermis, fibrillin-2 in peripheral nerves and fibrillin-3 in cartilage, perichondrium and developing bronchi (Ref. 20). Fibrillin-2 may form the inner core of many fibrillin-1 containing microfibrils (Ref. 21). Although rarely detected in adult skin, fibrillin-2

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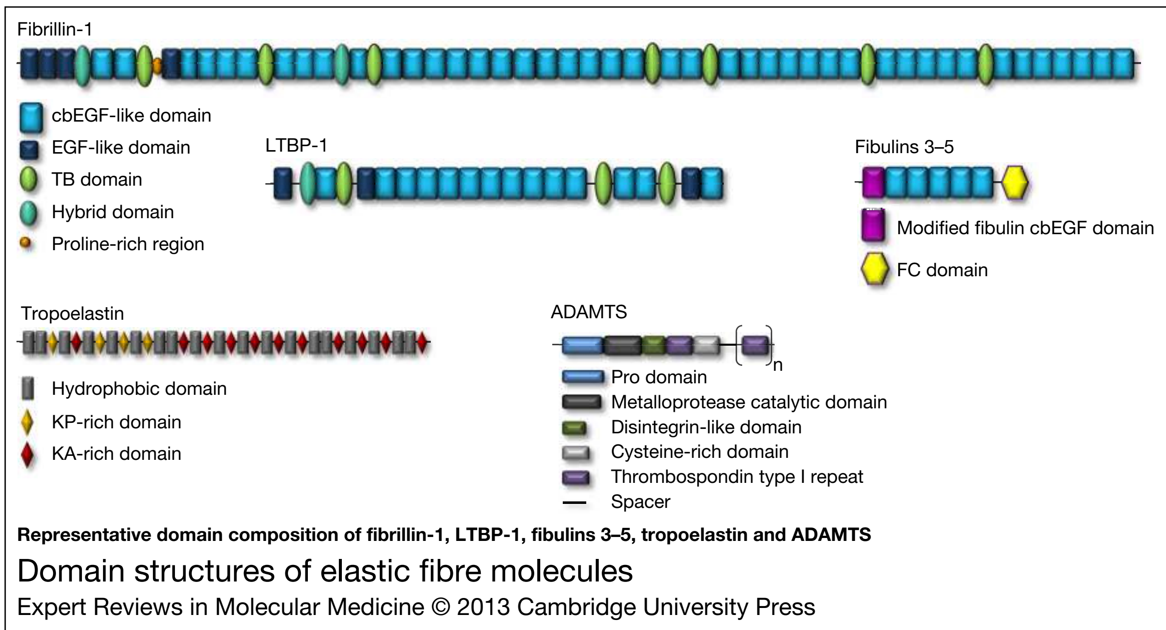

Figure 2. Domain structures of elastic fibre molecules. The domain organisations of fibrillins, latent TGFβ-binding protein (LTBPs), fibulins, a disintegrin-like and metalloprotease (reprolysin-type) with thrombospondin (ADAMTS) and ADAMTS-like (ADAMTSL) molecules and tropoelastin are shown, with keys for domain types.

expression can increase during wound healing and in sclerosis (Ref. 22). Mouse models confirm the critical importance of fibrillin-1 to vascular development and function. Fibrillin-1 null mice die perinatally from ruptured aortic aneurysm, whereas fibrillin-2 null mice have seemingly normal formation of the aorta, although double-null mice have a much more severe aortic phenotype than fibrillin-1 null mice (Ref. 23). Both fibrillins thus perform partially overlapping functions during the development of the aorta and great arteries, with fibrillin-1 able to compensate for loss of fibrillin-2 but not vice versa. The fibrillin-3 gene is disrupted in rodents; so fibrillin-3 is not critical to all mammalian life (Ref. 19).

Accessory molecules associated with microfibrils and elastic fibres

Many microfibril and elastic fibre-associated molecules have been identified by microscopy and immunochemical approaches (reviewed in Ref. 1; updated in Table 1). We summarise here selected molecules shown by functional analysis, mouse models and/or heritable diseases to contribute to elastic fibre formation and function; microfibril-associated molecules include the latent TGFβ binding proteins (LTBPs), ADAMTS isoforms and microfibril-associated glycoprotein (MAGPs) and elastic fibre-associated molecules include the small fibulins 3–5 and lysyl oxidase (LOX).

LTBPs: LTBPs 1–4 are large extracellular glycoproteins with a multi-domain structure that has similarities to the fibrillins, comprising cbEGF and TB domains, with an N-terminal cysteine-rich domain. They are expressed in many tissues including heart, placenta, lung, kidney, skeletal muscle and ovary and have cbEGF and TB domain homology with fibrillins (Refs 4, 54) (Fig. 2). The third TB domain of LTBPs 1–4 can covalently bind the propeptide (latency-associated peptide, LAP) of the cytokine TGFβ (Refs 55, 56), which is rendered inactive when associated with its propeptide (forming the small latent complex). Association of this complex with LTBP forms the large latent complex, which can be sequestered within the ECM, thereby regulating TGFβ bioavailability (Refs 54, 55, 56). C-terminal regions of LTBPs 1, 2 and 4 can interact directly with fibrillin-1 through TB4 (Ref. 56), thus implicating fibrillin microfibrils in regulating TGFβ activity. LTBP-1 (and thus latent TGFβ) can be deposited in the

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Table 1. Microfibril and elastic fibre-associated molecules (updated from Ref. 1)

Molecule	Elastic-fibre location	Refs
Fibrillin-1	Microfibrils	(17, 21, 24)
Fibrillin-2	Microfibrils	(17)
Fibrillin-3	Unknown – likely in microfibrils	(19)
MAGP-1	Microfibrils	(24, 25)
MAGP-2	Some microfibrils	(26, 27)
LTBP-1	Some microfibrils; also fibronectin	(28, 29)
LTBP-2	Microfibrils, elastic fibres	(30)
LTBP-3	Fibrillar structures	(29)
LTBP-4	Fibrillar structures, fibrillin	(29)
Decorin	Microfibrils, microfibril – elastic-fibre interface	(31, 32)
Biglycan	Elastic-fibre core	(31, 33)
Versican	Some microfibrils	(34)
HS	Microfibrils, elastic-fibre core	(35)
Chondroitin sulphate	Microfibrils	(31, 32, 33)
Perlecan	Microfibrils	(35)
MFAP-1	Some microfibrils	(1)
MFAP-3	Some microfibrils	(1)
MFAP-4 (MAGP-36)	Some microfibrils	(1, 36)
βIgH3	Elastic-fibre – collagen interface	(37)
Tropoelastin	Elastic-fibre core	(1)
LOX	Newly secreted tropoelastin, microfibril – elastin interface	(38)
LOXL	Microfibril – fibulin-5 – elastin interface	(38)
Fibulin-1	Elastic-fibre core	(39)
Fibulin-2	Elastin – microfibril interface	(39)
Fibulin-3	Probably associated with microfibrils	(39, 40)
Fibulin-4	Elastin – microfibril interface	(39, 41, 42, 43, 44)
Fibulin-5	Elastic-fibres	(41, 45, 46, 47, 48)
ADAMTSL-3	Probably associated with microfibrils	(49)
ADAMTSL-4	Probably associated with microfibrils	(50)
ADAMTSL-5	Probably associated with microfibrils	(51)

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Table 1. Microfibril and elastic fibre-associated molecules (updated from Ref. 1) *(continued)*

Molecule	Elastic-fibre location	Refs
ADAMTSL-6	Probably associated with microfibrils	(52)
Emilin-1	Elastin – microfibril interface	(1)
Emilin-2	Elastin – microfibril interface	(1)
Elastin-binding protein	Newly secreted tropoelastin	(53)
Vitronectin	Some microfibrils in dermal tissues	(1)
Amyloid	Some microfibrils in dermal tissues	(1)
Collagen VIII	Vascular elastic fibres	(1)
Collagen XVI	Dermal microfibrils	(1)
Endostatin (C-terminus of collagen XVIII)	Vascular elastic fibres	(1)
Collagen VI	Some microfibrils	(1)

Abbreviations: βIgH3, also known as transforming growth factor-β-inducible gene-H3 and as keratoepithelin, on chromosome 5q31; HS, heparan sulphate; LOX, lysyl oxidase; LOXL1, lysyl oxidase-like 1; LTBP, latent TGFβ-binding protein; MAGP, microfibril-associated glycoprotein; MFAP-1, microfibril-associated protein-1; ADAMTSL, a disintegrin-like and metalloprotease (reprolysin-type) with thrombospondin type-I motif-like.

absence of fibrillins-1 and -2 (Ref. 26), although depletion of fibrillin-1 disrupts its pattern of extracellular deposition (Refs 28, 57).

*ADAMTS (**a** **d**isintegrin-like **a**nd **m**etalloprotease (reprolysin-type) with **t**hrombo**s**pondin type-I motif) molecules*: Several members of this superfamily, including ADAMTS-10 and ADAMTSL 2–6, have been genetically and/or functionally implicated in microfibril biology (*see* the Assembly of elastic fibres section). The full superfamily comprises 19 zinc metalloproteases and seven noncatalytic ADAMTS-like (ADAMTSL) proteins, varying greatly in size; many members of this family play roles in morphogenesis, angiogenesis and ovulation and in ECM deposition (Ref. 58). Briefly, each ADAMTS protease has an N-terminal protease domain, containing a catalytic module, a disintegrin-like module, a cysteine-rich module and a single thrombospondin type I repeat (TSR) (Fig. 2). The C-terminal (or ancillary) domain is variable between family members, although many contain multiple TSRs and may confer substrate-binding specificity, with the N-terminal domain providing catalytic activity. ADAMTS-10 lacks an optimal furin cleavage site (necessary for activation of ADAMTS enzymes) and is unlikely to be catalytically active in vivo. ADAMTSL family members, including those implicated in microfibril biology, contain multiple TSRs but lack disintegrin-like and catalytic domains. Thus, low/no catalytic activity is a hallmark of ADAMTS family members with identified roles in microfibril biology.

MAGPs: MAGP-1 (a ~31 kDa glycoprotein) was originally detected in microfibril preparations from elastic and nonelastic tissues (Ref. 59). It has an acidic N-terminal region enriched in proline and glutamine residues, and a cysteine-rich C-terminal portion. It colocalises widely with microfibrils (Ref. 59), and has been detected in purified microfibrils by mass spectrometry (Ref. 60). Surprisingly, mice lacking the MAGP-1 gene show normal microfibrils and elastic fibre assembly (Refs 24, 61), so it is not essential for elastogenesis. Structurally related glycoprotein MAGP-2 (~25 kDa) has a cysteine-rich central region, is rich in serine and threonine and binds integrins. It colocalises with microfibrils in some tissues

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(Refs 27, 62, 63, 64). Both MAGPs can bind fibrillin and microfibrils, and may enhance the deposition of elastin on microfibrils (*see* the Assembly of elastic fibres section).

Fibulins: Fibulins are extracellular glycoproteins that are classified as Class I or II on the basis of their domain structure and length (Ref. 39). The closely related Class II (or short) fibulins (fibulins 3–5; 50–60 kDa) each comprise six cbEGF domains, including an atypical N-terminal cbEGF and a C-terminal fibulin ('FC') module (Fig. 2) and are widely expressed in developing embryos, particularly cardiovascular and skeletal tissues (Ref. 39). Fibulins-4 and -5 can bind tropoelastin and LOX or LOX-like (LOXL) cross-linking enzymes, as well as fibrillin-1; by juxtaposing these molecules, they are thought to support the cross-linking of elastin and its deposition on microfibrils.

LOX family: The five members of the LOX family (LOX, LOXL1-4) are secreted as zymogens, and are activated by removal of N-terminal propeptides by bone morphogenetic protein-1 (BMP-1) (Ref. 65). LOX especially, but also its homologue LOXL1 catalyses the oxidative deamination of peptidyl lysine residues in elastin to generate α-aminoadipic-δ-semialdehydes that then spontaneously condense to form covalent desmosine and isodesmosine cross-links, and a very stable insoluble elastin core (Ref. 65). Their C-terminal regions show sequence homology but their N-terminal 'pro' regions vary greatly, and may impart specificity to the extracellular targeting of LOX enzymes.

Assembly of elastic fibres

Microfibril formation

Assembly of fibrillin monomers into microfibrils is a complex process. 'Pro'fibrillin molecules are processed N- and C-terminally by furin/PACE proprotein convertases, either immediately before or upon secretion, thereby facilitating terminal interactions that enable linear and lateral multimerisation (Ref. 66). Homotypic N-terminal interactions are enhanced by heparan sulphate (HS) (Ref. 67), whereas C-terminal interactions may underpin bead formation (Ref. 68). In this way, microfibrils are thought to assemble at the cell surface (Fig. 3a). Microfibril formation is unlikely to be solely a self-assembly process, and there is some evidence for cellular involvement. We reported that, in fibroblasts, microfibril deposition requires fibronectin arg–gly–asp (RGD)-dependent $\alpha 5\beta 1$ integrins (Ref. 70). Fibrillin-1 can also interact with cells through integrins $\alpha 5\beta 1$ and $\alpha v\beta 3$, and $\alpha v\beta 6$ in epithelial cells (Refs 71, 72). It remains to be determined whether direct fibrillin-1 interactions with cells are necessary for microfibril assembly and/or for specific tissue-specific functions of microfibrils (and elastic fibres) such as association with smooth muscle cells in the aorta.

Assembled microfibrils comprise fibrillin monomers aligned in a head-to-tail arrangement and laterally associated (probably eight molecules in cross-section) (Refs 73, 74, 75). Fibrillin molecules within tissue microfibrils can be cross-linked by transglutaminase (Ref. 76). The 'beads-on-a-string' appearance of individual microfibrils, their untensioned periodicity (50–60 nm) in tissue sections (Refs 73, 74) and their altered structural organisation upon extension (Refs 75, 77) has given rise to unstaggered (Refs 74, 75) and staggered (Refs 78, 79) models of fibrillin alignment within microfibrils. The precise alignment of fibrillin molecules within microfibrils awaits further insights, perhaps from approaches such as experimental cross-linking.

Role for fibronectin

In mesenchymal cultures, fibronectin is an essential prerequisite for microfibril formation (Refs 26, 70, 79). This relationship is surprising because fibrillin microfibrils arose in early metazoans and fibronectin-like molecules only in chordates (Refs 3, 4, 80). Fibronectin is able to bind several regions of fibrillin-1, as well as fibrillin multimers, whereas newly deposited microfibrils and fibronectin networks show initial colocalisation (Refs 70, 79, 81). It has been suggested that fibronectin could act as a template for microfibril deposition (Refs 70, 79); however fibrillin microfibrils occur in many lower organisms that lack fibronectin (Ref. 82), and in fibronectin-null cultures (Ref. 83), implying that fibronectin enhances rather than underpins microfibril assembly.

Role for HS

The glycosaminoglycan HS is strongly implicated in microfibril and elastic fibre assembly. It is a component of syndecan and glypican receptors, and of the basement membrane molecule perlecan. Supplementation of cell cultures with heparin effectively ablates microfibril assembly

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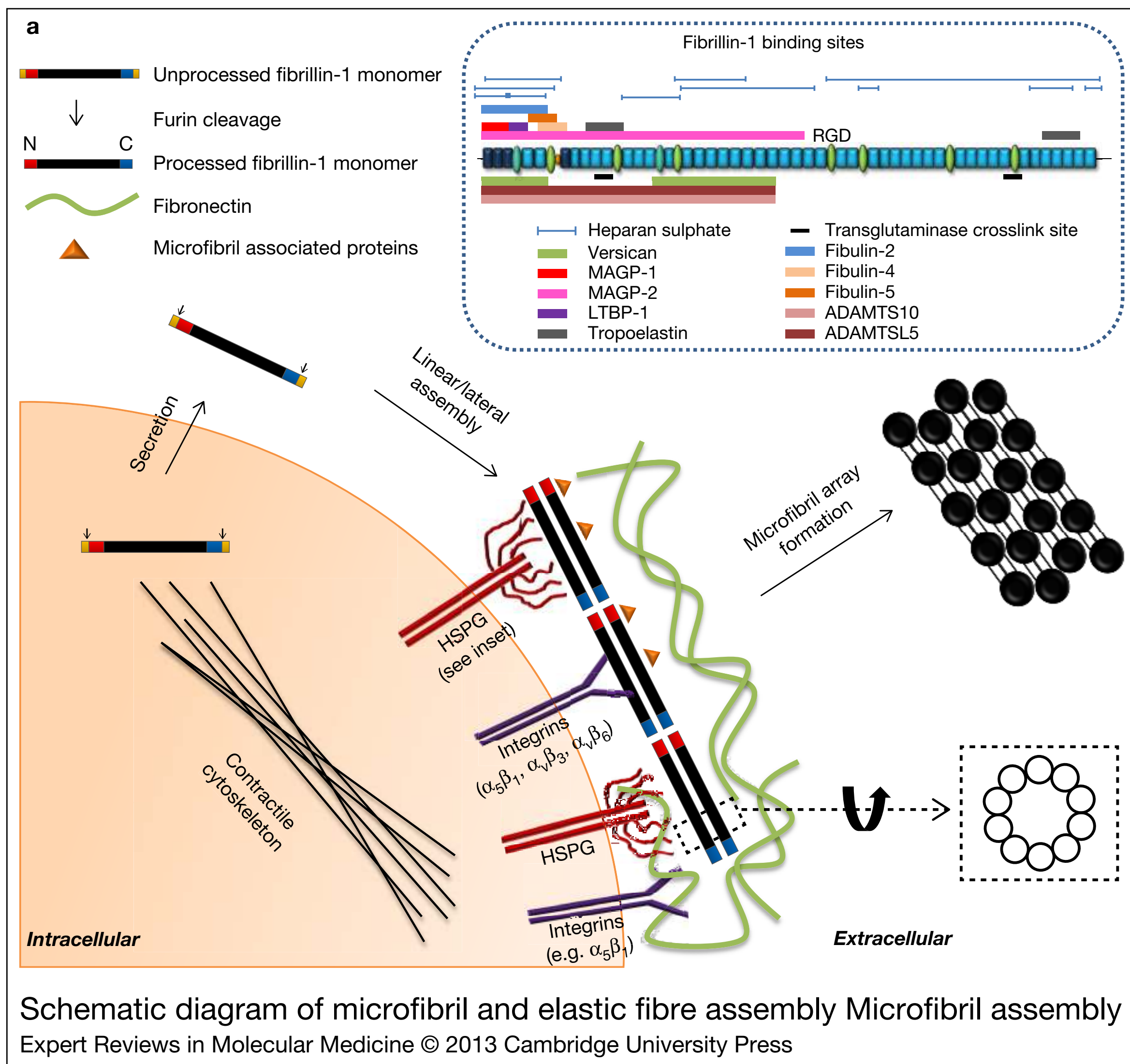

Schematic diagram of microfibril and elastic fibre assembly Microfibril assembly
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Figure 3. Schematic diagram of microfibril and elastic fibre assembly: elastin assembly. (a) **Microfibril assembly** occurs pericellularly, and requires fibronectin, integrins and heparan sulphate proteoglycans (HSPG). Fibrillin molecules are secreted and, after processing N- and C-terminally by furin, interact homotypically at N- and C-termini leading to axial and lateral assembly to form microfibrils. Beads may arise from folding of terminal regions. Microfibrils may be stabilised by transglutaminase cross-links. The reason why fibronectin is needed for microfibril deposition is unclear, but it may act as a template for assembly and/or it may stimulate cytoskeletal tension through the α5β1 integrin, thereby facilitating assembly at fibrillar adhesions. Fibrillin-1 also interacts with α5β1, αvβ3 and αvβ6 integrins; however, it is not known whether these interactions are essential for microfibril assembly. Heparin inhibits microfibril assembly, and HSPGs may contribute by facilitating cell surface fibrillin-1 interactions. (b) **Elastin assembly** occurs pericellularly on 'microassembly' and on microfibrils 'macroaggregates' (Ref. 69). Secreted tropoelastin forms globules at the cell surface which become cross-linked by lysyl oxidase; this process may involve αvβ3 integrin interactions with tropoelastin, and integrin interactions with heparan sulphate proteoglycans (HSPGs) which can interact with tropoelastin. Fibulin-4 and fibulin-5 contribute to elastin cross-linking by lysyl oxidase, and probably direct the deposition of elastin globules onto preformed fibrillin microfibrils, to form elastic fibres. Microfibrils and elastic fibres are important matrix storage sites for BMPs and latent TGFβ1.

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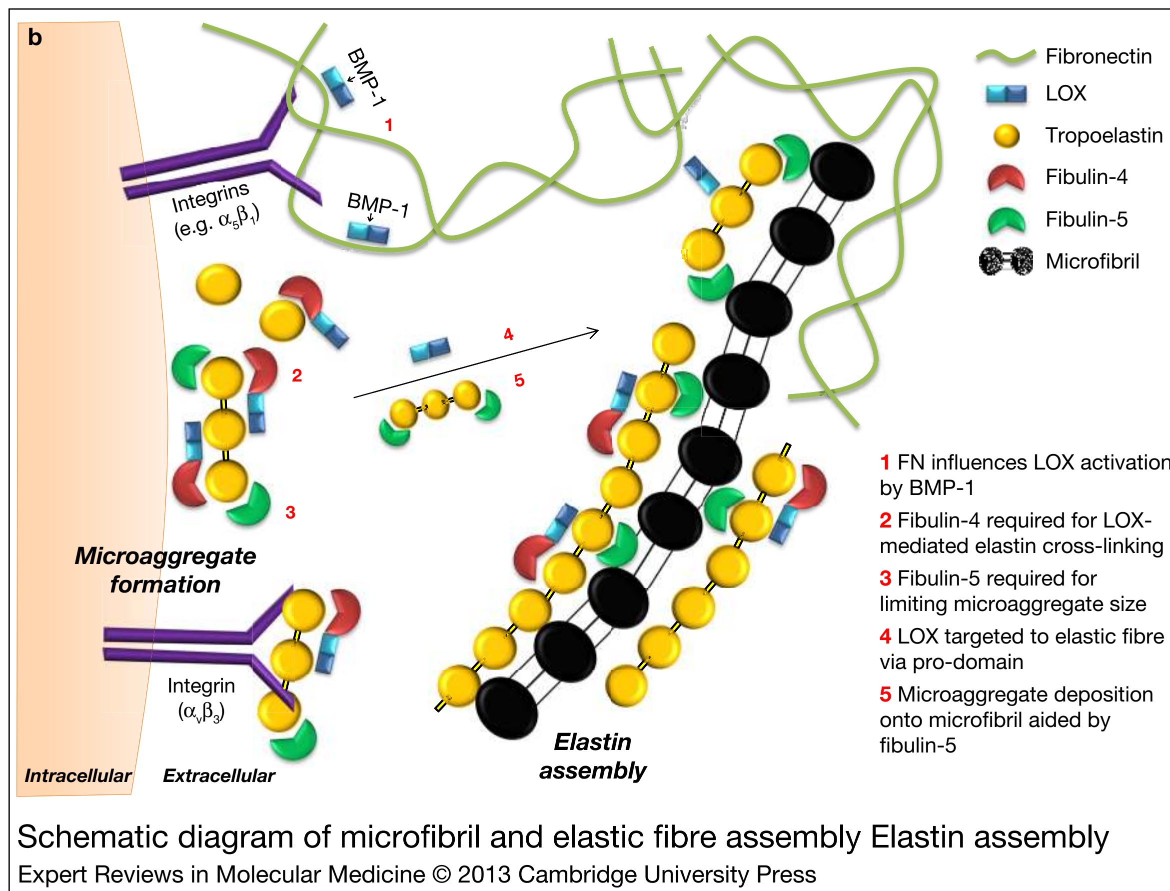

Schematic diagram of microfibril and elastic fibre assembly Elastin assembly

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Figure 3. (continued).

(Refs 84, 85). At least six high affinity-binding sites between heparin and fibrillin-1 have been identified (Refs 67, 84, 85, 86), some of which direct N-terminal multimerisation during microfibril assembly (Ref. 67) or interactions with cell surface HS (Ref. 71). Although it is not known precisely how HS contributes to microfibril deposition, these HS-directed interactions may be essential. Heparin does not disrupt N- and C-terminal fibrillin-1 interactions and so these interactions are compatible with microfibril assembly (Ref. 86), and may directly support these homotypic interactions. Murine perlecan (recombinant fragment or molecules isolated from Engelbreth-Holm-Swarm (EHS) sarcoma; Ref. 35) or human perlecan expressed by ARPE-19 retinal epithelial cells (Ref. 60) binds fibrillin-1 through protein and HS interactions, and directs microfibril-basement membrane interactions. HS competes with MAGP-1 and tropoelastin (Ref. 67) to bind fibrillin-1; hence, it may regulate elastin deposition onto microfibrils. HS can also mediate smooth muscle cell interactions with tropoelastin, thus influencing cell phenotype (Ref. 87). It also directly influences elastin multimerisation (Ref. 88).

Roles for microfibril-associated molecules

LTBP-1 co-localises with microfibrils in some tissues (Ref. 82). This juxtaposition, together with the ability of LTBPs (Refs 1, 3, 4) to form large latent TGFβ complexes, and to bind fibrillin-1 (Ref. 89), implicates microfibrils in TGFβ sequestration. Recently, it was shown that fibrillins are needed for matrix deposition of LTBP-3, but not LTBP-1 (Ref. 26). LTBP-1 deposition in the ECM is however, such as fibrillin-1, dependent on fibronectin and LTBP-1 colocalises with microfibrils but not fibronectin

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over time in culture (Refs 26, 82). Fibronectin is also required for LTBP-4 deposition (Ref. 90). However, incorporation of LTBP-2, which does not bind TGFβ, as well as LTBP-3 and LTBP-4, into ECM is dependent on microfibrils (Refs 26, 91). LTBP-2 also competes with LTBP-1 to interact with the N-terminal region of fibrillin-1 (Ref. 92). Thus, while none of the LTBPs is necessary for fibrillin microfibril assembly, microfibrils and fibronectin both profoundly influence the extracellular deposition of LTBPs.

Several members of the ADAMTS superfamily are genetically and functionally implicated in microfibril biology (Ref. 93). ADAMTS-10, which causes autosomal recessive WMS (*see* the Elastic fibre disorders section) may not be physiologically cleaved by furin and is probably not an active enzyme in vivo. ADAMTSL-5 binds both fibrillin-1 and -2, as well as heparin, and co-localises with microfibrils (Ref. 51). ADAMTSL-6 binds to the N-terminal region of fibrillin-1, whereas the conditioned medium-containing recombinant ADAMTSL-6 suggested potential to promote fibrillin-1 matrix assembly (Ref. 52), and it enhanced microfibrils in an MFS mouse model (Ref. 94). ADAMTSL-3 is implicated in a molecular pathway involving fibrillin-1 and ADAMTS-10 (Ref. 49); it can bind fibrillin-1 and may participate in microfibril biogenesis (Ref. 95). Supplementation with recombinant ADAMTSL-4 accelerated fibrillin-1 deposition in culture, and co-localisation with microfibrils (Ref. 50). It is interesting to speculate that inactive ADAMTS-10 and the ADAMTSL 3–6 molecules could act as 'decoys' to protect fibrillins from active ADAMTS enzymes.

MAGP-1 can interact with elastin and may contribute to elastin deposition on microfibrils (Refs 25, 96). It strongly binds an N-terminal sequence of fibrillin-1, thereby inhibiting N- and C-terminal fibrillin-1 interactions (Ref. 25), and thus has the potential to fine-tune fibrillin multimerisation. MAGP-1 can also bind TGFβ and BMP-7 (Ref. 61), and can activate pSmad2 signalling in culture (Ref. 28), so it may contribute to regulating TGFβ growth factors in association with microfibrils (Ref. 61). Intracellular MAGP-1 can modulate expression of versican (Ref. 97), which interacts with microfibrils (Ref. 34) and is a regulator of matrix. MAGP-1 can also bind fibronectin (Ref. 98) and could influence fibronectin-mediated microfibril deposition. None of these putative functional contributions to elastic fibre formation can be essential since MAGP-1 null mice have functional elastic fibres (Ref. 24). MAGP-2 can interact with fibrillins-1 and -2, has covalent periodic association with isolated microfibrils and co-localises with microfibrils in certain tissues (Refs 27, 63, 64). MAGP-2 expression peaks during elastic fibre assembly; evidence shows that its overexpression increases elastic fibre formation and that it can stimulate elastic fibre assembly, probably by targeting elastin onto microfibrils (Ref. 27).

Elastic fibre formation

Tropoelastin has the propensity to self-assemble through a process termed coacervation, which involves rapid molecular association, at increasing temperatures (Ref. 99). Exposed hydrophobic domains interact in an entropically-driven process, resulting in lysine residues aligning in readiness for LOX-mediated cross-linking. In vitro, the sizes and properties of coacervation 'droplets', and the rate at which coacervation and maturation processes proceed, are dependent on tropoelastin concentration, pH, temperature and solution conditions (Ref. 100), as well as the presence of accessory proteins. Fibulin-5 and also fibulin-4, limit aggregation of tropoelastin and slows the maturation phase (Ref. 101). The N-terminal region of fibrillin-1 and MAGP-1 both increase maturation velocity and induce clustering of elastin droplets, and the fibrillin-1 fragment induces 'strings' of linear droplets (Ref. 100).

In culture and tissues, elastin can self-associate pericellularly into globules that become cross-linked prior to deposition onto microfibrils (Refs 69, 102, 103) (Fig. 3b). This initial stage in elastic fibre assembly, termed 'microassembly', may involve interaction of the C-terminal region of tropoelastin with $\alpha_v\beta_3$ integrin (Ref. 12) and HS (Refs 87, 104). Certainly, this region of elastin is critical for elastic fibre assembly (Ref. 7). In culture, pericellular globule aggregation is coupled with cell motion (Ref. 102), with globule size probably limited by accessory proteins (Ref. 69) and biophysical constraints (Ref. 100). Once transferred to the microfibril scaffold, the globules coalesce and are stabilised by formation of cross-links facilitated by LOX or LOXL1, probably facilitated by fibulins-4 or -5 (see below), thus forming the insoluble elastin

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core in a process termed 'macroassembly' (Fig. 3b) (Refs 99, 100).

Roles for fibulins

The homologous small fibulins (3–5) are critical regulators of elastic fibre assembly (Refs 39, 41). Fibulin-4 colocalises with microfibrils (Ref. 41), and binds fibrillin-1 in vitro (Ref. 42). Fibulin-4 depletion decreases elastic fibre formation but not microfibrillogenesis (Ref. 43). Its involvement in the pathogenesis of the disease CL (*see* the Elastinopathies section) identifies it as an essential element of elastic fibre formation. Fibulin-4 null mice, which die perinatally, have a drastic reduction in desmosine cross-links and grossly impaired elastic fibre formation (Ref. 43). Fibulin-4 can bind LOX concurrently with tropoelastin (Ref. 42) and influence LOX-tropoelastin interactions (Ref. 44). Thus, it is considered that fibulin-4 is essential for LOX-mediated elastin cross-linking, probably by forming complexes that juxtapose LOX and elastin (Refs 42, 44). Fibulin-4 may also play a, as yet poorly defined, role in the sequestration of LTBPs (and thus latent TGFβ) within the ECM (Ref. 89). Fibulin-5 null mice exhibit a less dramatic elastic fibre phenotype than fibulin-4 null mice, with only 16% decrease in desmosine levels; mice survive well into adulthood but have loose skin (Refs 45, 46). Fibulin-5 localises at the interface between the elastin core and microfibrils (Ref. 41). It can interact with LOXL enzymes, and it enhances tropoelastin self-association and elastic fibre formation (Ref. 47). Fibulin-5 is also capable of integrin-mediated cell attachment, but does not activate $\alpha5\beta1$ integrin (Ref. 48). Fibulin-5 may act as a molecular adapter that directs the deposition of elastin microaggregates onto microfibrils (Refs 42, 69, 105, 106). Indeed, fibulin-5 knockdown in culture-altered elastin aggregates (Ref. 42). Like its homologues, fibulin-3 null mice exhibit elastic fibre deficiencies in some tissues as well as herniation (Ref. 40). A fibulin-3 point mutation (R345W) caused malattia leventinese, a dominantly inherited macular degenerative disease with sub-retinal pigment epithelial deposits (Refs 107, 108) with similarities to age-related macular degeneration (ARMD).

The different severities and tissue defects induced by depletion of fibulins 3–5 may reflect, in part, their tissue-specific expression patterns. It is also likely that some evolutionary diversification of their roles in elastic fibre assembly has occurred, e.g. fibulin-4 preferentially interacts with LOX and fibulin-5 with LOXL enzymes (Refs 42, 44, 47).

Elastic fibre disorders

Inherited and acquired diseases of elastic fibres are also reviewed in Ref. 1 (updated in Table 2).

Fibrillinopathies

Heritable connective tissue disorders termed fibrillinopathies arise from mutations in fibrillin genes. Fibrillin-1 disorders include MFS, ectopia lentis, MASS (mitral valve prolapse, aortic enlargement, skin and skeletal findings) syndrome, Shprintzen–Goldberg syndrome, Stiff skin syndrome, autosomal dominant WMS and acromicric and geleophysic dysplasias (AD, GD) (Refs 6, 109, 116, 115). Fibrillin-1 is also implicated in the pathogenesis of homocystinuria, which exhibits MFS-like symptoms (Ref. 83). Congenital contractural arachnodactyly (CCA; Beal's syndrome) arises from mutations in fibrillin-2, and polycystic ovary syndrome is associated with mutations in fibrillin-3 (Ref. 113). In addition, mutations in LTBP-2 and the ADAMTS family members ADAMTS-10, ADAMTS-17, ADAMTSL-2 and ADAMTSL-4 are associated with the fibrillin-related disorders WMS, a Weill–Marchesani-like syndrome, acromicric and GD and ectopia lentis, demonstrating genetic and functional links between these proteins and fibrillin microfibrils (Refs 9, 147, 148, 149).

MFS and related pathologies

MFS (OMIM 154700) is the most prevalent fibrillinopathy, with an incidence of 2–3 per 10,000 people. A complex and phenotypically heterogeneous systemic disorder, MFS is characterised by severe cardiovascular, skeletal and ocular abnormalities, with symptoms ranging from isolated features through progressive classical MFS to severe early onset and rapidly progressive MFS (associated with early childhood mortality). Disease symptoms can reflect both elastic fibre deficiencies and perturbed TGFβ activity (Refs 6, 109). A life-threatening complication of MFS is aortic rupture due to dilation of the ascending aorta.

Although commonly inherited as an autosomal dominant trait, 25% of cases arise from de novo

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Table 2. Heritable disorders of elastic fibres (updated from Ref. 1)

Disease	Affected molecule	Clinical effects	Genotype to phenotype
MFS and related fibrillinopathies (Ref. 6)	Fibrillin-1 (15q21.1) Over 1000 mutations associated with MFS	A range of effects comprising vascular disease (including aortic aneurysms and dissections), skeletal and ocular defects	Microfibril and elastic fibre defects stemming from altered secretion, decreased expression, structural defects and increased proteolytic susceptibility of mutant fibrillin-1 proteins. Enhanced TGFβ signalling is a predominant phenotype, and clinical target (Refs 109, 110)
MFS-II, Loeys–Dietz syndrome, familial thoracic aortic aneurysms and dissections, Furlong syndrome (Ref. 111)	TGFβ receptor II (TGFβ RII) (3p24-p25)	Severe vascular disease (including familial aortic aneurysms and dissections), ocular, skeletal, craniofacial and neurocognitive abnormalities	Enhanced TGFβ signalling, defective elastogenesis and increased expression of collagen
Homocystinuria (Ref. 83)	CBS (21q22.3)	MFS-like symptoms including ocular and skeletal abnormalities	Elevated homocysteine levels cause modifications to the structure, function and degradation of fibrillin-1
Autosomal dominant WMS, acromicric and GD	Fibrillin-1 (15q21.1)	Short stature, thickened skin, ocular and joint defects	Reduced or abolished fibrillin-1 binding to HS, disruption of functional relationship between fibrillin-1, ADAMTS and ADAMTSL proteins. Increased TGFβ activity is associated with acromicric and GD (Refs 49, 91, 112)
Recessive WMS (Ref. 113)	ADAMTS-10 (19p13.2)	Short stature, thickened skin, ocular and joint defects	Disrupted growth and skin, lens, and heart development; and disrupted microfibril biogenesis (Refs 91, 114)
Weill-Marchesani like syndrome (Ref. 109)	ADAMTS-17 (15q26.3)	Short stature, ocular defects and no joint involvement.	Disruption to connective tissue formation and crystalline ciliary lens zonules.
WMS 3 (Ref. 115)	LTBP-2 (14q24.3)	Cardiovascular, ocular and joint defects	Disrupted ECM and microfibrillar network in skin

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Table 2. Heritable disorders of elastic fibres (updated from Ref. 1) ***(continued)***

Disease	Affected molecule	Clinical effects	Genotype to phenotype
Geleophysic dysplasia (Ref. 113)	ADAMTSL-2 (9q34.2)	Short stature, thickened skin, skeletal and joint defects	Indistinguishable from geleophysic dysplasia associated with fibrillin-1 mutations
Beal's syndrome/CCA (Ref. 6)	Fibrillin-2 (5q23)	Some MFS symptoms (skeletal problems, aortic enlargement) but no ocular involvement. Joint contractures and abnormally shaped ears	Altered fibrillin-2 expression, secretion and/or microfibril and elastic fibre assembly
Polycystic ovary syndrome (PCOS) (Ref. 116)	Fibrillin-3 (19p13.2)	Endocrine and reproductive abnormalities	Loss of fibrillin-3 during folliculogenesis. Contribution to metabolic features of disorder (maintenance of basal glucose homoeostasis)
SVAS OMIM 185500 (Refs 117, 118, 119, 120, 121)	Elastin (7q11.2) heterozygous loss-of-function mutations	Narrower, thicker, less flexible and resilient ascending aorta. Severe forms may lead to congestive heart failure	Elastin haploinsufficiency because of unstable mRNA or dominant-negative effect of the truncated elastin cause thinner and disorganised elastic lamellae and smooth muscle cell hyper-proliferation
WBS OMIM 194050 (Refs 112, 114, 122, 123, 124)	Hemizygous deletion/ duplication of 1.5–1.8 Mb region (7q11.23); usually includes elastin gene	Multisystem developmental disorder associated with connective tissue, cardiovascular and metabolic abnormalities	Elastin haploinsufficiency associated with cardiovascular (SVAS) and connective tissue abnormalities; Other gene deletions in the region may be associated with cognitive and cytoskeletal abnormalities
PXE OMIM 264800 (Refs 125,126,127,128,129, 130)	ABCC6 (16q13.1) – a putative transmembrane transporter	Loss of skin elasticity and appearance of yellow papule, angioid streaks and neovascularisation of the eye, early onset of arteriosclerosis and cardiac failure. Papillary dermal elastolysis is a rare PXE-like condition that is associated with elastolytic papules on the neck and supraclavicular sites (Ref. 130)	Progressive ectopic mineralisation and fragmentation of elastic fibres. Circulatory factors that normally prevent aberrant mineralisation may be affected by the ABCC6 mutations

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Table 2. Heritable disorders of elastic fibres (updated from Ref. 1) *(continued)*

	Disease	Affected molecule	Clinical effects	Genotype to phenotype
ARCL	Type IA/B OMIM 219100 (Refs 131, 132, 133, 134, 135)	Fibulin-4 (11q13) Fibulin-5 (14q32.1)	Redundant inelastic skin. Fibulin-4 mutations lead to a more severe phenotype that includes emphysema, vascular tortuosity and aortic aneurisms	Fragmented elastic fibres because of disruption to the process of elastic fibre assembly in which fibulin-4 and -5 play vital roles
	Type IIA/B OMIM 219200 (Refs 136, 137)	ATP6VOA2 (12q24.31) – vesicular proton pump	Cutis laxa, abnormal growth and facial features developmental delay and skeletal abnormalities typical for type II. Ocular abnormalities and aged appearance characteristic of type III	Elastin haploinsufficiency because of the accumulation of tropoelastin within Golgi as a result of abnormal vesicular trafficking
	Type III (De Barsy Syndrome) OMIM 219150 (Ref. 138)	PYCR1 (17q25.3) – mitochondrial enzyme involved in proline metabolism		
	Urban-Rifkin-Davis syndrome OMIM 613177 (Ref. 8)	LTBP-4 (19q13.2)	Severe phenotype that includes developmental, craniofacial and fatal pulmonary defects	LTBP-4 haploinsufficiency causes increased TGFβ activity and abnormal elastic fibre assembly
	MACS syndrome OMIM 613075 (Ref. 139)	RIN2 (20p11.21-p11.23) – guanine exchange factor for Rab5, and Fibulin-5 (14q32.1)	Multitude malformations including MACS	Connective tissue abnormalities associated with decreased expression of fibulin-5
Arterial tortuosity syndrome OMIM 208050 (Ref. 140)		SLC2A10 (20q13.1) – encodes glucose transporter GLUT10	Elongated and tortuous arteries, accompanied by cutis laxa	Abnormal TGFβ activity leads to induced smooth muscle cells proliferation. Aberrant collagen and elastin metabolism
XLCL and Menkes disease OMIM 304150 and 309400 (141)		ATP7A (Xq21.1) – copper transporting enzyme	Menkes disease is more severe and commonly lethal; includes neurological defects	Lower functionality of copper dependant LOX affects collagen and elastin deposition

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Table 2. Heritable disorders of elastic fibres (updated from Ref. 1) *(continued)*

Disease	Affected molecule	Clinical effects	Genotype to phenotype
ADCL OMIM 123700 (Refs 142, 143)	Elastin (7q11.2)	Milder phenotype compared with the recessive form. May include cardiovascular abnormalities such as stenosis, dilatation and tortuosity. Mutations in ALDH18A1, encoding P5CS have overlapping symptoms with ADCL (143)	Structure of elastic fibres is perturbed because of the dominant-negative effect on elastin deposition
ARMD OMIM 603075 (Refs 144, 145, 146)	Complement factor H (1q31.3), and Fibulin-5 (14q32.1)	Progressive loss of vision	Neovascularisation of macula and deposition of proteins and lipids within the elastic structure of Bruch's membrane

Abbreviations: ADAMTSL, a disintegrin-like and metalloprotease (reprolysin-type) with thrombospondin like; ADCL, autosomal dominant cutis laxa; ARCL, autosomal recessive cutis laxa; ARMD, age-related macular degeneration; CCA, congenital contractural arachnactyly; ECM, extracellular matrix; GD, geleophysic dysplasias; HS, heparan sulphate; LOX, lysyl oxidase; LTBP, latent TGFβ-binding protein; MACS, macrocephaly, alopaecia, CL and scoliosis; MFS, Marfan syndrome; P5CS, Δ^1-pyrroline-5-carboxylate synthase; PXE, pseudoxanthoma elasticum, SVAS, supravalvular aortic stenosis; TGFβ, transforming growth factor β; WBS, Williams-Beuren syndrome; WMS, Weill-Marchesani syndrome; XLCL, X-linked cutis laxa.

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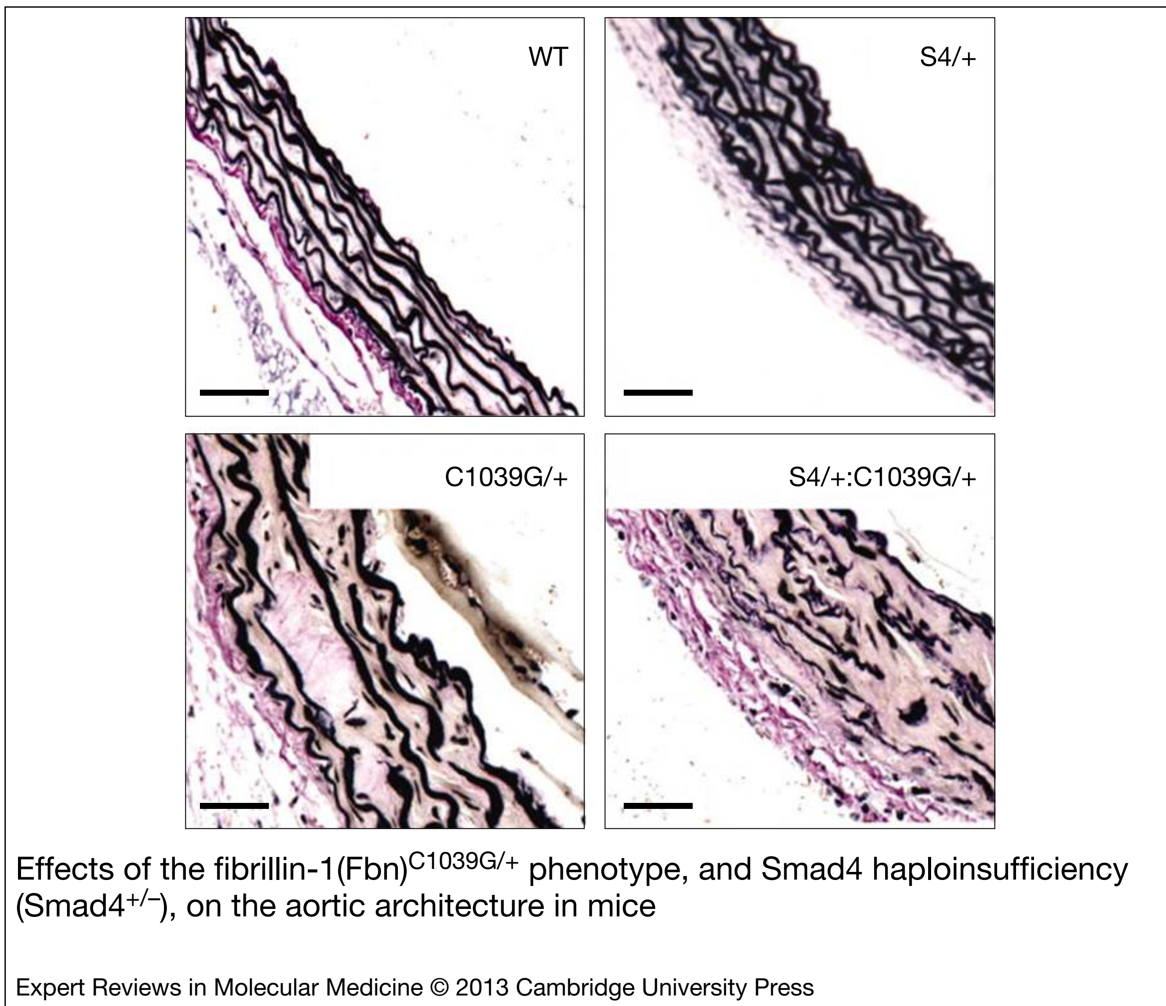

Figure 4. Effects of the fibrillin-1(Fbn)$^{C1039G/+}$ phenotype, and Smad4 haploinsufficiency (Smad4$^{+/-}$), on the aortic architecture in mice. Verhoeff-Van Giesen staining revealed architectural abnormalities in the ascending aorta of these mutant mice. Compared with wild-type littermates, Fbn$^{C1039G/+}$ mice had medial thickening and elastic fibre fragmentation. These defects were enhanced in Smad4$^{+/-}$: Fbn$^{C1039G/+}$ mice. Figure taken from Ref. 111 (with permission from the corresponding author and the publisher).

mutations; well over 1000 causative fibrillin-1 mutations have been identified. Mutations often affect disulphide bond patterns or calcium-binding consensus sequences within cbEGF domains, resulting in structural alterations that alter assembly and/or integrity of microfibrils and elastic fibres (Ref. 6). There is no single mechanism from fibrillin-1 mutation to disease; mouse models and recombinant fibrillin-1 studies have shown that altered secretion, decreased expression, structural defects and increased proteolytic susceptibility of mutant fibrillin-1 proteins and perturbations in TGFβ activity can all contribute to MFS phenotypes (Refs 6, 109, 150, 151, 152, 153).

Fibrillin-1 is highly susceptible to proteolytic degradation, and increased proteolytic susceptibility appears to play a significant role in the pathogenesis of MFS (Refs 6, 152, 153). Murine models of MFS (e.g. C1039 G heterozygote; Ref. 154) have revealed gross disruption to the elastic lamellar structure of the aorta (Fig. 4). Matrix metalloproteinases (MMPs) -1, -2, -3 and -9 that can cleave fibrillin-1 are upregulated in thoracic aortas from MFS patients and MMPs-2 and -9 are upregulated in an MFS mouse model (Ref. 155). MMP-1 up-regulation has been associated with a fibrillin-1 fragment containing an elastin-binding protein recognition sequence (Ref. 156). Recombinant

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fibrillin-1 fragments harbouring mutations associated with severe neonatal MFS showed enhanced susceptibility to physiological and non-physiological proteases. In addition, cathepsins K and V can cleave fibrillin-1 at multiple sites and thus may play a role in the pathogenesis of MFS (Ref. 152).

TGFβ is known to control smooth muscle cell differentiation, matrix synthesis and vascular morphogenesis, and perturbed TGFβ signalling has been identified as a primary causative feature of MFS aortic disease progression (Refs 109, 157) (Fig. 4). Mouse studies have shed further light on the complex contribution of TGFβ to disease progression. For example, mice with a fibrillin-1 deletion showed increased TGFβ activity in lung sections compared with wild-type littermates, coupled with impairment in alveolar septation (158). Increased TGFβ activity also contributed to defective mitral valvulogenesis in a murine model of MFS. Cultured vascular smooth muscle cells from thoracic aortas of fibrillin-1 null mice showed constitutively active Smad2/3 signalling (Ref. 159). Non-canonical (non-Smad-mediated) TGFβ signalling also enhances aortic defects in Marfan mice (Ref. 111) (Fig. 4).

Enhanced TGFβ activity is associated with other fibrillinopathies including Stiff skin syndrome (Ref. 116), and acromicric and GD that can be caused by fibrillin-1 or ADAMTSL2 mutations (Refs 149, 160). These diseases highlight the central role of fibrillin-1 microfibrils in regulating TGFβ bioavailability. Other MFS-like diseases with perturbed TGFβ include MFS2 caused by mutations in the TGFβ receptor II, and Loeys–Dietz syndrome (Refs 109, 161), familial aortic aneurysm (Ref. 162) and Furlong syndrome (Ref. 163), which are caused by mutations in TGFβ receptors I or II. The rare disorder arterial tortuosity syndrome, which causes arterial elastic fibre fragmentation, might result from altered TGFβ activity as a consequence of mutations in the gene encoding the glucose transporter GLUT10 (Ref. 164). Mutations in the TGFβ repressor SKI cause the Shprintzen–Goldberg syndrome, which has many overlapping features with MFS and Loeys–Dietz syndrome (Ref. 165).

MFS patients are routinely prescribed beta blockers to reduce haemodynamic stress on the aorta (Ref. 109). In recent years, uncovering the link between increased TGFβ activity and MFS pathogenesis has led to the development of advanced therapeutic strategies that reduce TGFβ signalling. In particular, treatment with the angiotensin II type I receptor antagonist losartan was shown in MFS mice (Ref. 110) to prevent aortic aneurysm and to improve non-cardiovascular symptoms (such as alveolar septation and muscle repair) (Fig. 5). Several clinical trials have since been assessing the benefits of losartan treatment for MFS patients. In a clinical trial of patients with severe and rapidly progressive MFS, losartan treatment reduced both the rate of aortic root growth to 10% of pretreatment levels (Refs 109, 166). A multicentre losartan trial is in progress (Ref. 117), alongside a trial that studies the combined effects of β-blockers and losartan in MFS patients (Ref. 118). Angiotensin II-receptor blockers are also being assessed for their potential to modulate pathological progression of mitral valve prolapse in MFS patients (Ref. 119). Levels of circulating TGFβ are elevated in MFS mice and patients; thus circulating TGFβ may prove to be a valuable prognostic marker for MFS (Ref. 109). Doxycycline has also been shown to delay aneurysm rupture through inhibition of MMPs-2 and -9 (Ref. 120). A recent study has also revealed that treatment of MFS mice with antagonists to the elastin-binding protein motif (GxxPG) can reduce several abnormalities characteristic for MFS, suggesting a potential new method of treatment for cardiovascular manifestations of MFS (Ref. 121).

WMS and acromicric and GD

WMS is characterised by short stature, brachydactyly (short digits), eye abnormalities and joint stiffness. Both autosomal (WMS2; OMIM 608328) and recessive (WMS1; OMIM 277600) forms of WMS exist (Ref. 115). Clinical manifestations of the acromicric (AD; OMIM 102370) and GD (OMIM 231050) include short stature, joint defects and thickened skin (Ref. 160).

Mutations causing autosomal dominant WMS, AD and GD are located within the TB5 domain of fibrillin-1 (Refs 108, 157). This WMS-associated mutation abolishes binding of the TB5 domain to heparin, whereas six tested mutations associated with AD and GD reduce binding (Ref. 112). A second N-terminal fibrillin-1 mutation associated with dominant WMS results in an in-frame deletion, abolishing a

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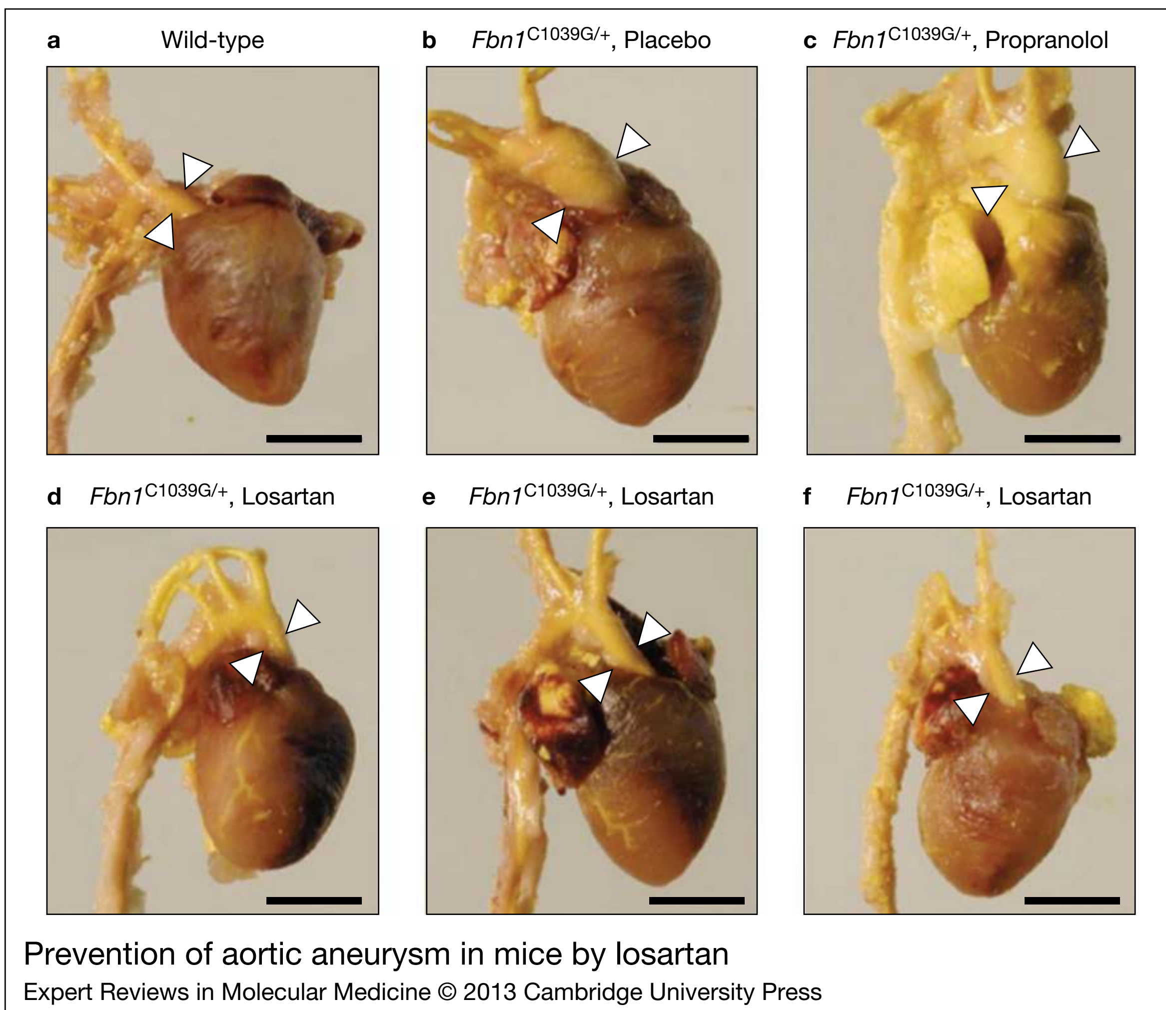

Figure 5. Prevention of aortic aneurysm in mice by losartan. Representative murine ascending aortae (arrowheads), after therapy, are: (a) wild-type mice; (b–f) mice heterozygous for Marfan-causing fibrillin-1 mutation C1039 G ($Fbn^{C1039G/+}$), treated with placebo (b), propanolol (c) or losartan (d–f). Scale bars = 4 mm. Figure taken from Ref. 110 (with permission from the corresponding author and the publisher).

specific binding site in fibrillin-1 for ADAMTSL-2, -3, -6 and the ADAMTSL papilin (Ref. 49). It was recently demonstrated that ADAMTS-10 can bind fibrillin-1 (Ref. 95), and recessive WMS is associated with ADAMTS-10 mutations (Ref. 9). Mutations in ADAMTS-17 and ADAMTSL-2 cause a Weill-Marchesani-like syndrome (WMS-like; OMIM 613195) and GD, respectively (Refs 148, 149). These closely related genetic disorders suggest a functional relationship between ADAMTSL (-2,-4), ADAMTS (-10,-17) and fibrillin-1. It has been hypothesised that ADAMTSL-3, ADAMTS-10 and fibrillin-1 might form a ternary complex and that these interactions may influence integrin interactions with fibrillin-1 because of the proximity of the fibrillin-1 binding sites to an RGD motif (Ref. 49). ADAMTS molecules are also implicated in TGFβ sequestration and activation (Ref. 114); although the underlying mechanism is unknown, ADAMTS molecules could influence stable deposition of LTBP-containing large latent TGFβ complexes with fibrillin microfibrils. In addition, a mutation in LTBP-2 has recently been associated with WMS (WMS3; OMIM 614819) (Ref. 147).

Elastinopathies

Mutations in elastin and elastic fibre-associated proteins cause disease through loss or gain of

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function, and increased susceptibility to inflammatory or proteolytic damage of elastic fibres (Refs 122, 123).

Supravalvular aortic stenosis (SVAS; OMIM 185500) occurs in 1 in 20 000 live births, is inherited in an autosomal dominant manner but can also occur sporadically and is characterised by narrowing or obstruction of the ascending aorta. Other defects include obstruction of pulmonary, coronary, carotid and renal arteries. Severe SVAS may lead to dyspnoea, angina, systolic murmur, left ventricular hypertrophy ultimately leading to congestive heart failure. Although congenital non-syndromic forms of SVAS exist, SVAS is typically associated with Williams–Beuren syndrome (WBS), a complex developmental disorder (below).

The spectrum of heterozygous loss-of-function mutations in the elastin gene reflects diverse SVAS phenotypes (Ref. 124). Point mutations, translocations and partial deletions of the elastin gene lead to premature stop codons and unstable mRNA. The most widely accepted underlying mechanism of SVAS is elastin haploinsufficiency (Ref. 125), where smooth muscle cells of large vessels generate half normal levels of elastin, leading to thinner and disorganised elastic lamellae (Ref. 117). That ELN gene haploinsufficiency is an underlying cause of nonsyndromic SVAS was confirmed by the identification of seven novel elastin gene mutations in 31 SVAS patients with familial and sporadic non-syndromic SVAS (Ref. 126). Apart from its structural role, elastin inhibits smooth muscle cell proliferation and promotes organisation of actin filament bundles. In SVAS, smooth muscle cells hyper-proliferate, become hypertrophic and collagen levels increase, leading to thicker, narrower and less flexible and resilient arteries.

Human induced pluripotent stem (iPS) cells from SVAS patients, which exhibit SVAS characteristics, have been generated to study pathogenesis and patient-specific interventions (Ref. 127). They reveal that affected smooth muscle cells have fewer organised networks of smooth muscle alpha-actin filament bundles compared with control cells. They also predict therapeutic inhibition of smooth muscle cell overproliferation by decreasing ERK1/2 signalling. Another SVAS therapy by simple sliding aortoplasty has been reported (Ref. 128).

Williams–Beuren Syndrome (WBS; OMIM 194050) is a rare multisystem developmental genetic disorder that has a prevalence of 1 in 7500 and usually occurs sporadically (Refs 129, 167). Characteristics associated with WBS include intellectual deficit, connective tissue defects, cardiovascular abnormalities (SVAS, also peripheral pulmonary aortic stenosis and arterial hypertension), dimorphic facial features, short stature and metabolic defects (infantile hypocalcaemia and abnormal glucose intolerance). Mitral valve disease is also associated with WBS, with a prevalence of approximately 40%.

WBS results from a hemizygous deletion (1.5–1.8 megabase), and less frequently duplication, of 26–28 genes, including elastin, that localise to the Williams syndrome region of the chromosome 7q11.23 (Ref. 131). These deletions arise as a consequence of meiotic misalignment of repetitive sequences that flank the WBS chromosome region (Ref. 132). Deletions cause the phenotypes outlined above, whereas duplications typically result in milder phenotypes (Refs 131, 132).

Deletion of one copy of elastin gene is the most common and most recognised genetic rearrangement known in WBS, as it occurs in over 96% of WBS patients, and elastin haploinsufficiency underlies the cardiovascular manifestations in WBS, most prominently SVAS. Smooth muscle cells of WBS patients produce reduced levels of elastin (Ref. 124). Treatments for the vascular symptoms of WBS commonly involve reparative surgery of aortic stenosis and individualised hypertension treatment (Ref. 133).

Pseudoxanthoma elasticum (PXE; OMIM 264800) is a heritable autosomal recessive disorder with a prevalence of approximately 1 in 25 000–100 000 (Refs 134, 135). PXE is characterised by progressive ectopic mineralisation and fragmentation of elastic fibres that leads to ocular, cutaneous and cardiovascular abnormalities. PXE becomes initially evident when the accumulation of calcium/phosphate complexes in the skin causes the appearance of yellow papule and loss of elasticity. In the eyes, these complexes cause angioid streaks and neovascularisation, leading to gradual loss of vision. Early onset of arteriosclerosis and cardiac failure are the most serious complication. PXE is caused by loss-of-function mutations in the ABCC6 gene, which encodes a putative transmembrane transporter, especially abundant in the liver (Ref. 136). The

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dysfunctional transporter may affect levels or activity of circulatory factors, such as fetuin-A and matrix Gla-protein, responsible for prevention of aberrant mineralisation in normal conditions (Ref. 137). Therapies for the ocular symptoms of PXE focus on treating neovascularisation of the eye by intravitreal injections of vascular endothelial growth factor (VEGF) inhibitors (Ref. 138). Other approaches such as supplementation of diet with magnesium, introduction of anti-mineralising factors, regeneration of the liver and stem-cell therapy are being assessed.

Cutis laxa (CL) comprises inherited (Ref. 8) and acquired disorders that are characterised by abnormal elastic fibres and loose sagging skin that often gives an aged appearance. CL can be inherited in ADCL, ARCL or X-linked forms (XLCL). Based on different mutations and phenotypic manifestations, autosomal recessive types can be further divided into type I (A and B), II (A and B) and III (De Barsy syndrome), Urban-Rifkin-Davis syndrome, macrocephaly, alopaecia, CL and scoliosis (MACS) syndrome and arterial tortuosity syndrome. Recessive forms of CL tend to be more severe, often resulting in childhood mortality (Ref. 8).

ARCL type I (OMIM 219100) is caused by mutations in the genes encoding fibulin-4 (subtype A) or fibulin-5 (subtype B) (Refs 139, 140, 141, 142). Fibulin-4 mutations usually cause more severe and often lethal phenotypes with emphysema, tortuosity, aortic aneurysms and joint laxity. Fibulin-4 mutations were previously thought to be rare, but recently, in a small population, a novel fibulin-4 mutation has been identified in 22 infants suffering from severe arteriopathy syndrome (Ref. 168).

The two subtypes of *ARCL type II* (OMIM 219200) are both associated with loss-of-function mutation in the ATP6VOA2 gene, which encodes a vesicular proton pump, thus affecting vesicular trafficking. The mutation indirectly leads to tropoelastin accumulation within the Golgi and thereby significantly reduced deposition of mature elastin (Ref. 143). Mutations in the PYCR1 gene, which encodes for a mitochondrial enzyme involved in proline biosynthesis (pyrroline-5-carboxylate reductase 1), have also been associated with this form of CL (Ref. 169).

The genetic cause of the *De Barsy syndrome*/CL-corneal clouding-mental retardation syndrome (OMIM 219150) is currently unknown; however, because of the significant overlap with the phenotypic characteristics of type II ARCL, mutations in ATPVOA2 and PYCR1 seem to be the likely underlying cause of this syndrome (Ref. 170).

Urban-Rifkin-Davis syndrome (OMIM 613177) is a newly characterised type of ARCL that is caused by mutations in LTBP-4 (Ref. 171). A severe phenotype including developmental, craniofacial and fatal pulmonary abnormalities is common. Haploinsufficiency of LTBP-4 is likely to cause increased TGFβ activity and abnormal elastic fibre assembly.

MACS syndrome (OMIM 613075) is a multitude malformation syndrome that includes macrocephaly, alopaecia, CL and scoliosis. It is caused by mutations in RIN2, which is a guanine exchange factor for Rab5, which in turn controls endocytic trafficking. It is unlikely that these mutations underlie the connective tissue abnormalities, which more probably are attributable to fibulin-5 deficiency, which MACS patients exhibit (Ref. 172).

Arterial tortuosity syndrome (OMIM 208050) is characterised by elongated and tortuous arteries, along with CL. Mutations in the SLC2A10 gene that encodes the glucose transporter GLUT10 are associated with this syndrome. Although previously thought that the mutation may lead to abnormal TGFβ activity, stimulating smooth muscle cell proliferation, it has also been suggested that the loss of GLUT10 rather results in aberrant collagen and elastin metabolism (Ref. 173).

XLCL (OMIM 304150) and *Menkes disease* (OMIM 309400) are both caused by mutations in the ATP7A gene that encodes for a copper-transporting enzyme. Defects in this enzyme reduce functionality of copper-dependent enzymes such as LOX, affecting elastin and collagen deposition. Although both disease forms have overlapping phenotypic manifestations, XLCL tends to be milder. Severe and commonly lethal Menkes disease is associated with neurological defects. Although neonatal diagnosis and early treatment with copper can improve survival, some residual activity of ATP7A is essential (Ref. 8). Recently, gene replacement therapy has been suggested as a therapeutic approach to alleviate Menkes disease (Ref. 130).

ADCL (OMIM 123700) is generally defined as a milder form of the inherited CL spectrum,

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typically characterised by aged facial appearance. Systemic manifestations are less common and may involve gastrointestinal abnormalities, hernias, pulmonary aortic stenosis, tortuosity, emphysema and aortic root dilatation (Ref. 174). ADCL-causing mutations do not lead to elastin haploinsufficiency, in contrast to SVAS, but rather have a dominant-negative effect on elastin deposition. Indeed, mutant elastin has abnormal binding to fibrillin-1 and enhanced self-association of elastin, which caused decreased mature elastin deposition (Ref. 174). Increased endoplasmic reticulum stress, induced apoptosis and increased TGFβ signalling are also reported (Ref. 144). Mutations in ALDH18A1, encoding Δ^1-pyrroline-5-carboxylate synthase (P5CS) have overlapping symptoms with ADCL, with altered elastic fibre ultrastructure (Ref. 145).

Buschke–Ollendorff syndrome (OMIM 166700) is a rare autosomal dominant condition, which includes skin lesions containing elastic fibres, and osteopoikilosis, and is caused by mutations in the LEMD3 gene, which encodes a protein involved in bone and connective tissue morphogenesis (Ref. 146). The encoded protein can antagonise TGFβ signalling at the inner nuclear membrane.

Acquired elastic fibre disorders

Acquired elastic fibre disorders arise wherever elastic fibre structure and function are compromised, including tissues such as skin, blood vessels and lungs. Some examples are highlighted below.

Acquired CL usually develops in adulthood. Characteristic secondary destruction of elastic fibres occurs because of dermal inflammation caused by other medical conditions or reactions to medicines. Systemic manifestations, which often lead to fatal outcomes, may include emphysema, hernias and vascular dilatation (Ref. 175).

Marshall syndrome is a type of acquired CL typically affecting children after suffering neutrophilic dermatosis (Sweet's syndrome) (Ref. 176).

Solar/actinic elastosis is a result of a prolonged exposure to sunlight, leading to degeneration of the elastic tissue of the dermis and consequently to premature ageing of the skin. Deposition of the elastotic material and decreased collagen synthesis lead to rough, inelastic, wrinkled and hyperpigmented skin. Current therapy of choice is a skin-rejuvenating photodynamic therapy in which photosensitisers and diverse light sources have been successfully used to reverse the effects of photodamage (Ref. 177).

Acquired PXE is characterised by cutaneous mineralisation and fragmentation of elastic fibres leading to lax inelastic skin. Unlike the heritable PXE, the acquired PXE is non-systemic and is limited to the skin only. Exposure to chemicals such as calcium–ammonium–nitrate salts, mechanical stress and abnormal calcium–phosphate metabolism has been implicated in the development of this disease (Ref. 178). There are no generally accepted therapies for the acquired PXE. Papillary dermal elastolysis is a rare condition, similar to PXE, which usually affects elderly women, and is associated with elastolytic papules on the neck and supraclavicular sites (Ref. 179).

Ageing changes to blood vessels and lungs: loss of elastic fibre integrity and elastic recoil are common features of ageing changes to blood vessels especially the elastic arteries, whereas pulmonary emphysema is associated with loss of elasticity and pathological alveolar remodelling (Ref. 180).

ARMD (OMIM 603075) is one of the most frequent causes of loss of vision and is characterised by progressive deposition of extracellular aggregates and neovascularisation in the macula region of the eye. A multitude of genes have been associated with this disease, with mutations in complement factor H being the most common cause of the disease (Ref. 181). Mutations in fibulins, and especially fibulin-5, have also been implicated in ARMD. Fibulin-5 mutations lead to haploinsufficiency which may cause the observed phenotype by altering the structure of the elastic Bruch's membrane of the macula (Ref. 182). Anti-VEGF-A therapy has been successfully used to alleviate neovascularisation in the ARMD. A recent review has highlighted other possible therapeutic approaches, and stressed the importance of supporting the coping mechanisms of the retinal pigment cells of the macula (Ref. 183).

Elastosis perforans serpiginosa (EPS; OMIM 130100) is a rare degenerative skin disease, which exhibits loss of elastic fibres in the upper dermis, following extended treatment with D-penicillamine that chelates copper and inhibits cross-linking of elastin by copper-dependent lysyl oxidase (Ref. 184).

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Research in progress and outstanding research questions

Recent progress in treating MFS and related diseases with losartan and other therapies that target TGFβ activity have led to improved patient outcomes. However, further understanding of the biology of elastic fibres and their assembly is urgently needed to advance the therapeutic prospects for elastic fibre diseases. Current research on elastic fibres aims to define how cells and their integrin and heparan sulphate proteoglycans (HSPG) receptors direct the assembly of microfibrils and elastic fibres, how fibronectin and the ADAMTS and ADAMTSL molecules influence microfibril deposition and how pericellular processing (by furin/PACE enzymes) and cross-linking (by LOX and tissue transglutaminase enzymes) regulate elastic fibre deposition. New insights into how LTBPs are deposited in the matrix, and how active TGFβ and BMPs are released from these complexes are needed to resolve precisely how TGFβ growth factor bioavailability is controlled. All this information is critical for elucidating how defects in microfibrils and elastic fibres cause distinct genetic and acquired diseases by perturbing different stages in their assembly, their structural integrity or their susceptibility to proteolytic attack. We also need to understand much better how inflammatory enzymes cause elastic fibre remodelling and loss of both microfibril and elastic fibre functional integrity in disease and ageing. There is a need to identify biomarkers of elastic fibre damage to enable early diagnosis and treatment. Much recent progress has been made in the engineering of vascular constructs based on elastin and elastic fibre components, and this approach offers great promise for the repair of damaged elastic tissues. Such advances will provide mechanistic targets to prevent elastic fibre degeneration and to encourage de novo elastic fibre formation in regenerating tissues.

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Features associated with this article

Figures

Figure 1. Evolutionary analysis of fibrillin.
Figure 2. Domain structures of elastic fibre molecules.
Figure 3. Schematic diagram of microfibril and elastic fibre assembly: elastin assembly.
Figure 4. Effects of the fibrillin-1(Fbn)$^{C1039G/+}$ phenotype, and Smad4 haploinsufficiency (Smad4$^{+/-}$), on the aortic architecture in mice.

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Features associated with this article *(continued)*

Figure 5. Prevention of aortic aneurysm in mice by losartan.

Tables
Table 1. Microfibril and elastic fibre-associated molecules (updated from Ref. 1).
Table 2. Heritable disorders of elastic fibres (updated from Ref. 1).

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