Fibrillin and the eye

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The glycoprotein fibrillin is the principal component of the ciliary zonule and has an important role in the strength and elasticity of ocular connective tissues. Fibrillin polymers form the structural scaffold of extensible microfibrils which are present in ocular elastic tissues and are arranged in parallel bundles to form the zonular fibres. These fibrillin-rich microfibrils are morphologically identical to those which provide strength and long range elastic recoil to the connective tissues of blood vessels, lung, ligament, and dermis. In these tissues, fibrillin-rich microfibrils form a scaffold for the deposition and alignment of the elastin precursor tropoelastin during elastic fibre assembly. However, the microfibrils of the ciliary zonule as well as those of kidney glomerulus, skeletal muscle, heart, and periodontal ligament do not contain significant amounts of elastin.

Disorders which disrupt fibrillin-rich microfibril structure or function, such as Marfan’s syndrome and ectopia lentis, result in a spectrum of ocular complications. This review summarises current knowledge of fibrillin and fibrillin-rich microfibrils and their role in the eye, and discusses the pathological processes which may be involved in ocular connective tissue ageing and disease.

Fibrillin-rich microfibrils in ocular tissues

In addition to the zonules, fibrillin has been immunolocalised to the connective tissues of the anterior segment including the conjunctival, iris and ciliary body stroma, the ciliary processes, the corneal stroma and corneal epithelial basement membrane, and the endothelium of Schlemm’s canal. In the posterior segment, fibrillin has been localised to scleral stroma, lamina cribrosa, Bruch’s membrane, and choroid; beaded microfibrils are also present in vitreous. The precise role of fibrillin-rich microfibrils in all these ocular tissues is not defined, but they may regulate development and confer strength and elasticity to connective tissues. Fibrillin present in the equatorial region of the lens capsule allows anchorage of the zonular fibres.

Composition and ultrastructure of fibrillin-rich microfibrils

Fibrillin exists as two isoforms, fibrillin-1 and fibrillin-2 (Fig 1); the gene for human fibrillin-1 (FBN-1) has been localised to chromosome 15q15–21 and the gene for human fibrillin-2 (FBN-2) to chromosome 5q23–31. Fibrillin-1 and fibrillin-2 have distinct but overlapping spatiotemporal tissue distributions, and it is unclear if they form separate populations of microfibrils or if they can coexist in the same microfibril. It has been suggested that fibrillin-1 may provide force bearing structural support to tissues, whereas fibrillin-2 may play an important part in the initiation of elastogenesis. The microfibrils of the ciliary zonules (Figs 2 and 3) are almost exclusively composed of fibrillin-1.

Both fibrillin-1 and fibrillin-2 have a molecular structure of multiple protein subunits, the majority of which are epidermal growth factor (EGF)-like domains (Fig 1). Most of these EGF-like domains are capable of binding calcium which maintains the fibrillin molecule in an extended, rod-like conformation and stabilises it against degradation by proteases. Interspersed with the EGF-like domains are protein subunits containing eight cysteine residues (Fig 1). One of the most striking differences between fibrillin-1 and fibrillin-2 is in the amino acid composition of the amino terminal region which may serve as a molecular hinge and may also mediate fibrillin dimer formation during microfibril assembly. The extreme carboxy terminal region of the fibrillin molecule is cleaved off before assembly into microfibrils.

Isolated fibrillin-rich microfibrils have a diameter of 10–12 nm and a characteristic “beads on a string” appearance when imaged by rotary shadowing or scanning transmission electron microscopy (STEM) (Fig 4). The average untensioned interbead distance is 56 nm but this increases when the microfibrils are subject to tension.

The arrangement of fibrillin molecules within microfibrils...
is unknown. Recent evidence suggests that fibrillin molecules may form dimers before assembly into microfibrils,\(^2^3\),\(^2^4\) and an association between the overlapping carboxy and amino termini of adjacent fibrillin molecules allows linear growth of the microfibril, stabilised by intramolecular crosslinks.\(^3^2\),\(^3^3\) However, several other models of microfibril assembly are possible, including a parallel, unstaggered arrangement of fibrillin molecules within the microfibrils.\(^3^4\) Compaction of fibrillin molecules within microfibrils may allow microfibril extensibility, so that molecules can “unravel” in the interbead region.

An increasing number of other proteins have been identified in association with fibrillin containing microfibrils in addition to fibrillin-1 and fibrillin-2. In most instances, it is unclear whether the protein is an integral structural component of the microfibril or is just adherent to its surface. The relative proportions of most of these proteins varies between tissues, and they may thus contribute to the tissue specific structural and functional characteristics of fibrillin-rich microfibrils. Microfibril associated glycoprotein-1 (MAGP-1), also designated microfibril associated protein-2 (gene symbol MFAP-2),\(^3^5\) has been shown by immunoelectron microscopic techniques to be associated with the bead regions of zonular and vitreous microfibrils.\(^3^6\) Microfibril associated protein-1 (MFAP-1) has been immunolocalised to microfibrils of chick aorta, bovine nuchal ligament, and human ocular zonules.\(^3^7\) Emilin (elastin microfibril interface located protein) is a glycoprotein which is abundant at the elastin-microfibril interface and has been immunolocalised in the eye to the zonules, to elastin-free microfibrils of the cornea and to Descemet's membrane.\(^3^8\) Microfibril associated molecules

![Figure 2](http://bjo.bmj.com/) Environmental scanning electron microscopy of normal hydrated human zonules. (A) Zonular fibres arising from ciliary processes. (B) Branching of a zonular fibre.

![Figure 3](http://bjo.bmj.com/) Transmission electron microscopy (TEM) of human zonular microfibrils, and effects of matrix metalloproteinase treatment. Normal human zonular specimens from a 54 year old were incubated for 3 hours at 37°C in the presence of 10 mM calcium chloride and hyaluronidase to remove adherent vitreous, with and without MMP-13, before fixation and TEM with uranyl acetate and lead citrate stains. (A) and (B) are untreated zonules which consist of dense and regular, parallel striated microfibrils. (C) and (D) are MMP-13 treated zonules. The zonular microfibrils are fragmented and irregularly and loosely arranged. Magnification: (A) and (C) ×20 000; (B) and (D) ×68 000.
may mediate cell adhesion to microfibrils and may stabilise the interactions of microfibrils with other structural elements of the extracellular matrix.

Ocular conditions associated with abnormalities in fibrillin-rich microfibrils

Microfibril abnormalities occurring as a result of mutations in the gene for fibrillin-1 are manifest as a spectrum of disease phenotypes ranging from severe, lethal neonatal Marfan’s syndrome to “simple” ectopia lentis. There is no clear correlation between genotype and phenotype, with the exception of a clustering of fibrillin-1 mutations associated with severe neonatal Marfan’s syndrome. Approximately 60% of patients with Marfan’s syndrome have ectopia lentis. Familial ectopia lentis also occurs in patients in whom the clinical criteria for Marfan’s syndrome are not fulfilled, although some of these patients have systemic features such as arachnodactyly or tall stature.

The structural consequences of microfibrillar abnormalities have been demonstrated by examination of ocular tissues from patients with ectopia lentis and Marfan’s syndrome. Ectopia lentis zonular fibres have been shown to be reduced in number, thin, stretched, and irregular in diameter, and inelastic and easily broken when compared with normal controls. The insertion of zonular fibres onto the lens capsule has also been noted to shift progressively anteriorly with age, suggesting that the ageing zonules undergo remodelling. Other factors may contribute to this shift, however, such as the changing curvature of the lens and contraction of the anterior capsule.

Proteolytic degradation of fibrillin-rich microfibrils in ocular ageing and disease

The extent of physiological zonular degradation during development and ageing is unknown although the zonular insertion onto the lens capsule has been observed to shift progressively anteriorly with age, suggesting that the ageing zonules undergo remodelling. Other factors may contribute to this shift, however, such as the changing curvature of the lens and contraction of the anterior capsule.

Proteolytic damage to zonular microfibrils potentially contributes to these observed ageing changes as well as to the pathogenesis of zonular dysfunction in patients with Marfan’s syndrome and ectopia lentis.

The zonules have been known for many years to be susceptible to degradation by serine proteases as demonstrated by the use of chymotrypsin for zonulysis during intracapsular cataract surgery. The serine proteases are a large group of enzymes which are secreted by inflammatory cells and whose activity is regulated by inhibitors such as α1 antitrypsin in the plasma and tissue thrombospondin.

The zonules are normally exposed to low levels of serine proteases in the aqueous and, potentially, to proteases released by inflammatory cells. Both fibrillin-1 molecules and fibrillin-rich microfibrils are susceptible to degradation by serine proteinases such as neutrophil elastase, chymotrypsin, and trypsin. Calcium binding stabilises fibrillin against such proteolytic degradation.

Mutations in fibrillin-1 that affect calcium binding may therefore increase fibrillin-1 susceptibility to proteolytic degradation by reducing calcium binding affinity and inducing conformational changes which expose cryptic protease cleavage sites.

Matrix metalloproteinases are another important class of proteases which are widely expressed in ocular tissues and which may be involved in ocular development, physiological remodelling, and wound healing. They are secreted by a wide range of cell types including mesenchymal...
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Fibrillin assembly: dimer formation

Regulation of fibrillin carboxy-

Matrix metalloproteinases and their

characterization of the human gene

A novel sequence variation affecting a

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Immunisation with undenatured

Characterization of the human gene

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Matrix metalloproteinases and their

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