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FBN1: The disease-causing gene for Marfan syndrome and other genetic disorders

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ABSTRACT

FBN1 encodes the gene for fibrillin-1, a structural macromolecule that polymerizes into microfibrils. Fibrillin microfibrils are morphologically distinctive fibrils, present in all connective tissues and assembled into tissue-specific architectural frameworks. *FBN1* is the causative gene for Marfan syndrome, an inherited disorder of connective tissue whose major features include tall stature and arachnodactyly, ectopia lentis, and thoracic aortic aneurysm and dissection. More than one thousand individual mutations in *FBN1* are associated with Marfan syndrome, making genotype–phenotype correlations difficult. Moreover, mutations in specific regions of *FBN1* can result in the opposite features of short stature and brachydactyly characteristic of Weill–Marchesani syndrome and other acromelic dysplasias. How can mutations in one molecule result in disparate clinical syndromes? Current concepts of the fibrillinopathies require an appreciation of tissue-specific fibrillin microfibril microenvironments and the collaborative relationship between the structures of fibrillin microfibril networks and biological functions such as regulation of growth factor signaling.

Contents

Abbreviations: *FBN*, fibrillin gene; MAGP, microfibril associated glycoprotein; LTBP, latent TGFβ binding protein; TGFβ, transforming growth factor β; *TGFBR*, TGFβ receptor gene; EGF, epidermal growth factor; cbEGF, calcium-binding EGF; PTC, premature termination codon; EL, ectopia lentis; H-TAD, heritable thoracic aortic disorders; BMP, bone morphogenetic protein; GDF, growth and differentiation factor.

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1. Introduction

1.1. Fibrillin microfibrils

FBN1 encodes the gene for fibrillin-1. In humans, there are three different genes (*FBN1*, *FBN2*,and *FBN3)* encoding fibrillins. Fibrillins are large (~350,000 MW) structural macromolecules that contribute to the integrity and function of all connective tissues. They are considered to be "structural macromolecules" because, like the collagens, the fibrillins form fibers that are visible in transmission electron micrographs. Unlike the collagens, fibrillins form "microfibrils" with uniform diameters (10–12 nm) that are not periodically cross-striated or "banded". Fibrillin microfibrils display a characteristic morphology consisting of light and dark or hollow areas that give the appearance of railroad tracks. Fibrillin microfibrils exist as large bundles of microfibrils, as short individual microfibrils (usually in close proximity to basement membranes, for example on the endothelial cell side of the glomerular basement membrane), or as the peripheral microfibril mantle around elastin in all elastic fibers. Typical morphological features of fibrillin microfibrils are shown in Fig. 1. In the various types of connective tissue, fibrillin microfibrils are organized to best suit the functional integrity of the tissue: for example, in skin, elastic fibers form a loose network of interconnecting highways; in the dermis, these highways run parallel to the epidermis with turn-offs coursing perpendicularly up from the deeper elastic fibers to the basement membrane at the dermal-epidermal junction, where bundles of microfibrils intersect the lamina densa; in tendons and perichondrium/periosteum, elastic fibers run parallel to the long axis; in muscular arteries, elastic fibers encircle the lumen.

Although "10 nm microfibrils" had been described as ultrastructural entities, the molecular components of these microfibrils were not known until 1986. Protocols to extract microfibrillar molecules used harsh denaturing conditions as well as disulfide bond reducing agents (Ross and Bornstein, 1969). Reductive guanidine extractions of fetal bovine nuchal ligament, an elastic fiber rich tissue, yielded a 31,000 MW glycoprotein, which was named MAGP ("microfibril associated glycoprotein") (Gibson et al., 1986). MAGP antiserum localized to elastin-associated microfibrils (Gibson et al., 1986). Today, a number of additional molecules are known to be associated with microfibrils. These molecules have been both immunolocalized to microfibrils and shown to bind directly to fibrillin. These include the fibulins (Reinhardt et al., 1996a; El-Hallous et al., 2007), the LTBPs (Latent TGFβ Binding Proteins) (Dallas et al., 1995; Isogai et al., 2003; Ono et al., 2009), and members of the Adamtslike (Tsutsui et al., 2010; Gabriel et al., 2012; Bader et al., 2012) and Adamts (Kutz et al., 2011) family of proteins.

Initially, it was thought that the main function of microfibrils is to serve as the scaffold for elastic fiber formation. This function was based on morphological studies of developing elastic tissues, which documented that microfibrils appeared first in the embryo, followed by the deposition of amorphous elastin onto the microfibril scaffold (Fahrenbach et al., 1966). Biochemical investigations as well as genetic evidence from both humans and mice have uncovered many more functions of fibrillin microfibrils. Today we know that fibrillin microfibrils perform important tissue-specific architectural functions, beyond serving as scaffolds for elastin deposition. For example, fibrillin microfibrils are specifically required for the structural integrity of both the aortic wall (which contains elastin) and the suspensory ligament of the lens (which does not contain elastin). In addition, over the last decade, a novel and highly significant function of fibrillin microfibrils has emerged: fibrillin microfibrils target and sequester members of the TGFβ superfamily of growth factors. Because this superfamily of growth factors includes >30 different members, this function diversifies the biological roles performed by fibrillin microfibrils, even though the microfibrils themselves are ubiquitous elements of all connective tissues. Using tissue-specific architectures, fibrillin microfibrils pattern the targeting and sequestration of a variety of growth factors and contribute to organ formation and repair. In this manner, the structures of fibrillin microfibrils collaborate with biological functions to shape and maintain connective tissues, and mutations in fibrillins exert powerful, even opposing, forces on tissue growth and homeostasis.

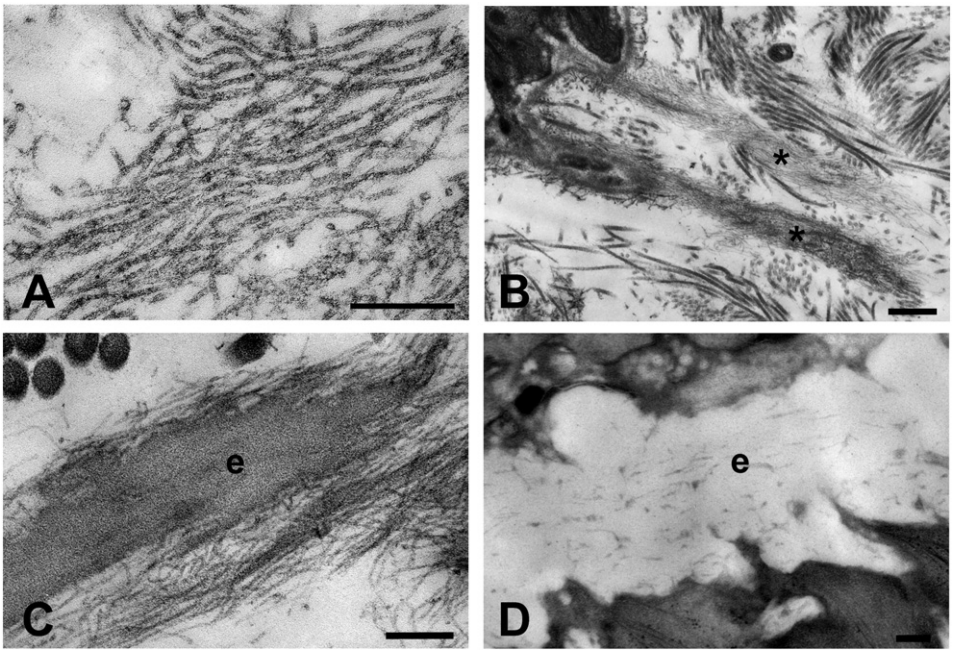

Fig. 1. Ultrastructure of fibrillin microfibrils. A. High magnification images of fibrillin microfibrils in human amnion show fibrils of uniform diameter with alternating hollow and filled (light and dark) regions. B. Fibrillin microfibrils exist in bundles (*), especially in close proximity to basement membranes. Here are two bundles of microfibrils intersecting the lamina densa at the dermal-epidermal junction in human skin. C. Fibrillin microfibrils surround amorphous elastin (e) in all elastic fibers. Shown here is an elastic fiber in human skin. D. In the aorta, elastic fibers are organized circumferentially in lamellae around the lumen of the vessel. Using high pressure freezing techniques, cell processes are seen directly adjacent to and even within the elastic fiber. In the mouse aorta, microfibrils are barely visible around the amorphous elastin. Scale bars = 200 nm (A, C, D); 500 nm (B).