Extracellular microfibrils in development and disease.
Child Health Institute of New Jersey, Robert Wood Johnson Medical School, 89 French Street, New Brunswick, NJ 08901 USA, *Corresponding author ramirefr@umdnj.edu

RAMIREZ FRANCESCO*, CARTA LUCA, NISTALA HARIKIRAN,. LEE-ARTEAGA SUI, AND LIU CATHERINE

Fibrillins 1 and 2 are the main structural components of extracellular microfibrils and the defective gene products in Marfan syndrome (MFS) and congenital contractural arachnodactyly (CCA), respectively. MFS is a pleiotropic disorder of the connective tissue with wide variation in clinical severity, whereas CCA is a rare condition akin to MFS but with major manifestations confined to the skeletal system. Fibrillins can form homo- or heteropolymetric microfibrils and interact with integrins, growth factors, several other matrix components, and latent TGFβ-binding proteins (LTBPs). Recent analyses of genetically targeted mouse lines have provided insights into the differential roles of fibrillin proteins in organ formation and homeostasis. One of the studies has focused on the cardiovascular phenotype of a newly created strain of mice that completely lack fibrillin-1 and the consequences of combined deficiency of fibrillins 1 and 2 on tissue formation. The results have demonstrated that involvement of fibrillin-2 in the initial assembly of the aortic matrix overlaps in part with fibrillin-1, and that continued fibrillin-1 deposition is absolutely required for the maturation and function of the vessel during neonatal life. These findings have important implication for our understanding of aneurysm progression and rupture in MFS. The study of the skeletal phenotype in mice lacking fibrillin-2 or underexpressing fibrillin-1 has demonstrated overlapping roles of the fibrillins in this organ system as well. Reduced bone mass in these mutant animals is in fact accounted for by distinct cellular abnormalities. Whereas osteopenia in fibrillin-2 null mice was associated with reduced osteoblast activity both in vivo and in vitro, this phenotype in fibrillin-1 underexpressing mice was instead associated with both reduced bone formation and increased bone resorption. These results validate the long-held belief that osteopenia/osteoporosis is indeed part of the MFS phenotype, in addition to providing mechanistic insights into the underpinning of reduced bone mass in this condition and in CCA as well.