

to extracellular matrix structure, a major role for fibrillins in TGF- β signaling was emphasized by the discovery of mutations in genes coding for proteins involved in canonical TGF- β signaling in patients with Marfan-like manifestations, including thoracic aortic aneurysm.

Proteoglycans The resiliency to compression of connective tissues such as cartilage or the aorta is largely explained by the presence of proteoglycans. Proteoglycans are composed of a core protein to which are attached a large series of negatively charged polymers of disaccharides (largely chondroitin sulfates). At least 30 proteoglycans have been identified. They vary in their binding to collagens and other components of matrix, but specific functions have not been assigned to most. The major proteoglycan of cartilage, called aggrecan, has a core protein of 2000 amino acids that is decorated with ~ 100 side chains of chondroitin sulfate and keratan sulfate. The core protein, in turn, binds to long chains of the polymeric disaccharide hyaluronan to form proteoglycan aggregates, one of the largest soluble macromolecular structures in nature. Because of its highly negative charge and extended structure, the proteoglycan aggregate binds large amounts of water and small ions to distend the three-dimensional arcade of collagen fibers found in the same tissues. It thereby makes the cartilage resilient to pressure.

SPECIFIC DISORDERS

■ OSTEOGENESIS IMPERFECTA

OI is a phenotypically and genetically heterogeneous generalized connective tissue disorder. The hallmark features of OI are increased susceptibility to skeletal fractures, bone deformity, and growth deficiency. Bone fragility is based on decreased bone mass and increased bone brittleness due to defective mineralization.

Secondary features of OI are highly variable even within a type and include blue sclerae, dentinogenesis imperfecta, hearing loss, basilar invagination, pulmonary function impairment, cardiac valve abnormalities, and ligamentous laxity. Most patients have defects in the structure or quantity of type I collagen.