Cartilage diseases

Yamini Krishnan [a] **and Alan J. Grodzinsky** [b, c, d]

***a* - Department of Chemical Engineering,** *MIT, Cambridge, MA 02139, USA*
***b* - Department of Biological Engineering,** *MIT, Cambridge, MA 02139, USA*
***c* - Department of Mechanical Engineering,** *MIT, Cambridge, MA 02139, USA*
***d* - Department of Electrical Engineering and Computer Science,** *MIT, Cambridge, MA 02139, USA*

Correspondence to Alan J. Grodzinsky *at: Department of Biological Engineering, MIT, Cambridge, MA 02139, USA.*
alg@mit.edu
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Abstract

Hyaline cartilages, fibrocartilages and elastic cartilages play multiple roles in the human body including bearing loads in articular joints and intervertebral discs, providing joint lubrication, forming the external ears and nose, supporting the trachea, and forming the long bones during development and growth. The structure and organization of cartilage's extracellular matrix (ECM) are the primary determinants of normal function. Most diseases involving cartilage lead to dramatic changes in the ECM which can govern disease progression (e.g., in osteoarthritis), cause the main symptoms of the disease (e.g., dwarfism caused by genetically inherited mutations) or occur as collateral damage in pathological processes occurring in other nearby tissues (e.g., osteochondritis dissecans and inflammatory arthropathies). Challenges associated with cartilage diseases include poor understanding of the etiology and pathogenesis, delayed diagnoses due to the aneural nature of the tissue and drug delivery challenges due to the avascular nature of adult cartilages. This narrative review provides an overview of the clinical and pathological features as well as current treatment options available for various cartilage diseases. Late breaking advances are also described in the quest for development and delivery of effective disease modifying drugs for cartilage diseases including osteoarthritis, the most common form of arthritis that affects hundreds of millions of people worldwide.

Introduction: cartilage structure and function

Cartilage is an avascular, aneural, alymphatic connective tissue found in the synovial joints, spine, ribs, external ears, nose, and airways, and in the growth plates of children and adolescents. There are three major types of cartilage found in humans: hyaline, fibrous and elastic [1] (see Fig. 1). All three types have a low density of cells (chondrocytes) [2] that synthesize and secrete the major components of the extracellular matrix (ECM) [3]. In order to perform the biomechanical functions of providing structural support and resistance to deformation, cartilage ECM contains a unique family of proteoglycans enmeshed within a highly hydrated collagen fibrillar network. Chondrocyte-mediated synthesis and assembly of this matrix is aided, in turn, by synthesis of dozens of additional non-collagenous proteins, proteoglycans and glycoproteins. The abundance, distribution and types of collagens and proteoglycans are different in each of the three types of cartilage, which gives rise to differences in appearance and biomechanical properties.

Hyaline cartilage has a glassy appearance and is the most common form of cartilage in the human body. It is found in the articulating surfaces of bones in synovial joints, and in the ribs, nose, trachea, bronchi, larynx, and growth plates. Articular hyaline cartilage enables joint movements by providing a lubricating surface with an extremely low coefficient of friction on

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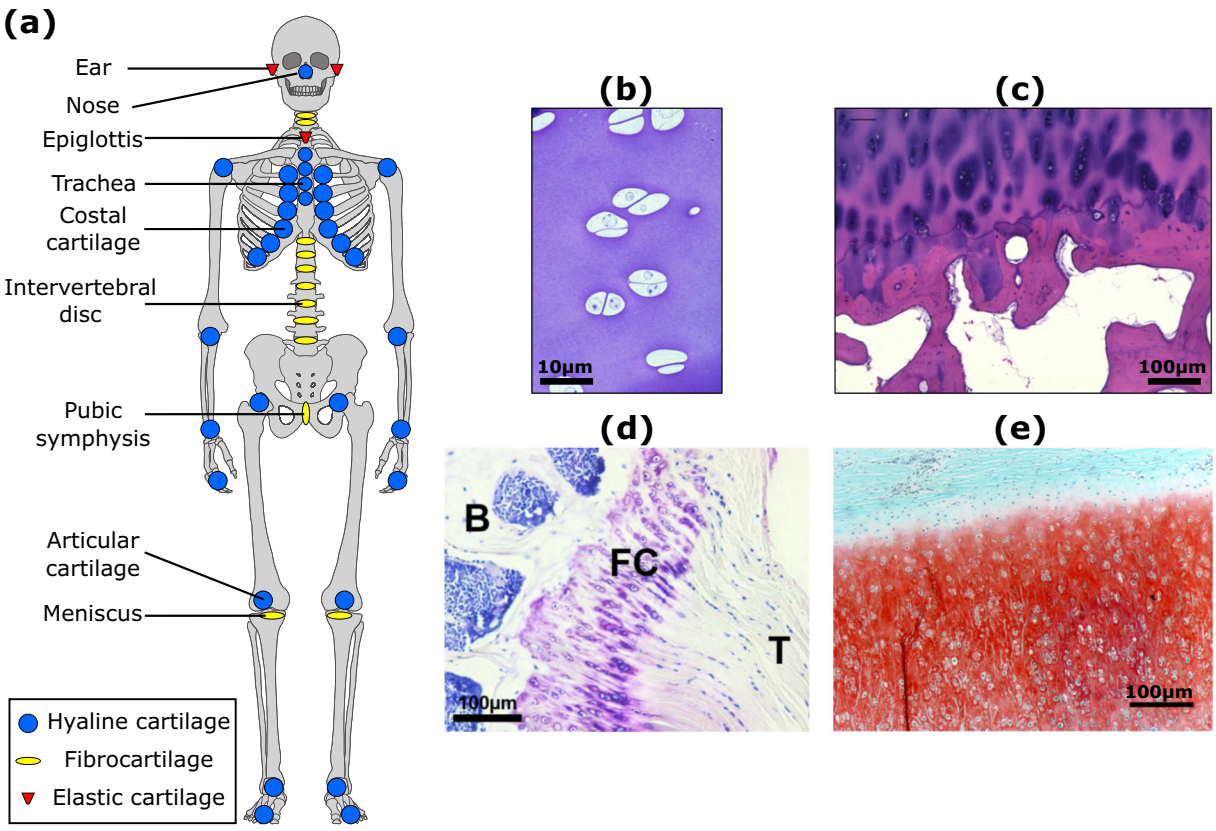

Fig. 1. Anatomical locations and microscopic structure of cartilage (a) Locations of hyaline cartilage (blue), fibrocartilage (yellow) and elastic cartilage (red) in the human body; (b) Immature bovine articular cartilage; (c) Human adult articular cartilage (83 year old male donor distal femur) showing chondrocyte clustering near the tidemark, typical of osteoarthritis; (d) Murine fibrous cartilage (FC) at the interface of the supraspinatus tendon (T) and the humeral head of the humerus bone (B); (e) Elastic cartilage of neonatal bovine ear; elastin fibers appear as unstained lines between the safranin-O staining for GAGs. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the order of 0.001–0.01 [4–7]. Water accounts for 60 to 85% of the wet weight of the tissue [8,9]. Many different types of collagen molecules are expressed in articular cartilage, but the backbone type II collagen fibrillar network is described by Eyre et al. as a heteropolymeric structure with collagen IX molecules covalently linked to the surface of collagen II and collagen XI forming the inner filamentous template of the fibril as a whole [10]. This network accounts for 60 to 70% of the dry weight [9], with a hydrated spacing of ~100 nm between fibrils [11,12], thereby providing the tissue with tensile and shear strength. The basic NC4 domain of collagen IX is thought to enable interactions between other collagen fibrils as well as other matrix macromolecules [13]. Type VI collagen is found in the pericellular matrix and enables chondrocytes to sense changes in the surrounding matrix and respond to them [14,15]. Other collagens found in articular cartilage include type III, type X, type XI, type XII and type XIV [10].

The dominant proteoglycan in hyaline cartilage is aggrecan, comprised of a core protein substituted with over 100 chondroitin sulfate glycosaminoglycan (GAG) chains and a lower number of keratan sulfate chains, forming a bottle-brush structure [16–18]. The G1 globular domain at the N-terminus of the core protein binds non-covalently to hyaluronan (stabilized by adjacent binding of link protein) to form large aggrecan aggregates containing over 100 aggrecan monomers [16,19]. These aggregates can achieve molecular weights as high as 350 MDa. The GAG chains of each aggrecan monomer are located between the G2 and G3 globular domains [18], giving each aggrecan a net negative charge of approximately −10,000 [20]. Visualized by atomic force microscopy, the protein core of aggrecan in immature and adult cartilage can range from 400 to 500 nm long, while the GAG chains range from 30 to 50 nm in length [21–22]. Importantly, with respect to biomechanical and biophysical function of aggrecan, the spacing between

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