CARTILAGE TISSUE

Cartilage is a tough, durable form of supporting connective tissue, characterized by an **extracellular matrix** (ECM) with high concentrations of GAGs and proteoglycans, interacting with collagen and elastic fibers. Structural features of its matrix make cartilage ideal for a variety of mechanical and protective roles within the adult skeleton and elsewhere.

Cartilage ECM has a firm consistency that allows the tissue to bear mechanical stresses without permanent distortion. In the respiratory tract, ears, and nose, cartilage forms the framework supporting softer tissues. Because of its resiliency and smooth, lubricated surface, cartilage provides cushioning and sliding regions within skeletal joints and facilitates bone movements.

- Cartilage consists of cells called **chondrocytes** (Gr. *chondros*, cartilage + *kytos*, cell) embedded in the ECM which unlike connective tissue proper contains no other cell types. Chondrocytes synthesize and maintain all ECM components and are located in matrix cavities called **lacunae**.

- The physical properties of cartilage depend on electrostatic bonds between **type II collagen** fibrils, **hyaluronan**, and the sulfated GAGs on densely packed **proteoglycans**. Its semi-rigid consistency is attributable to water bound to the negatively charged hyaluronan and GAG chains extending from proteoglycan core proteins, which in turn are enclosed within a dense meshwork of thin type II collagen fibrils. The high content of bound water allows cartilage to serve as a shock absorber, an important functional role.

- All types of cartilage **lack** vascular supplies and chondrocytes receive nutrients by diffusion from capillaries in surrounding connective tissue (the perichondrium). In some skeletal elements, large blood vessels do traverse cartilage to supply other tissues, but these vessels release few nutrients to the chondrocytes. As might be expected of cells in an avascular tissue, chondrocytes exhibit low metabolic activity. Cartilage **also lacks** nerves.

- The **perichondrium** is a sheath of dense connective tissue that surrounds cartilage in most places, forming an interface between the cartilage and the tissues supported by the cartilage. The perichondrium harbors the blood supply serving the cartilage and a small neural component. Articular cartilage, which covers the ends of bones in movable joints and which erodes in the course of arthritic degeneration, lacks perichondrium and is sustained by the diffusion of oxygen and nutrients from the synovial fluid.

1. HYALINE CARTILAGE

- **Hyaline** (Gr. *hyalos*, glass) cartilage, the most common of the three types, is homogeneous and semitransparent in the fresh state. In adults hyaline cartilage is located in the articular surfaces of movable joints, in the walls of larger respiratory passages (nose, larynx, trachea, bronchi), in the ventral ends of ribs, where they articulate with the sternum, and in the epiphyseal plates of long bones, where it makes possible longitudinal bone growth. In the embryo, hyaline cartilage forms the temporary skeleton that is gradually replaced by bone.

1. HYALINE CARTILAGE

- **Hyaline cartilage matrix is produced by chondrocytes and contains three major classes of molecules.**
- Three classes of molecules exist in hyaline cartilage matrix.
- **Collagen molecules.** Collagen is the major matrix protein. Four types of collagen participate in the formation of a three-dimensional meshwork of the relatively thin (20-nm diameter) and short matrix fibrils. **Type II collagen** constitute sthe bulk of the fibrils; **type IX collagen** facilitates fibril interaction with the matrix proteoglycan molecules; **typ e X I collagen** regulates the fibril size; and **typ e X collagen** organizes the collagen fibrils into a three dimensional hexagonal lattice that is crucial to its successful mechanical function. In addition, **typ e V I collagen** is also found in the matrix, mainly at the periphery of the chondrocytes where it helps to attach these cells to the matrix framework. Because types II, VI, IX, X, and XI are found in significant amounts only in the cartilage matrix, they are referred to as **cartilage-specific collagen molecules.**

- **Proteoglycans.** The ground substance of hyaline cartilage contains three kinds of glycosaminoglycans: **hyaluronan, chondroitin sulfate,** and **keratan sulfate.** As in loose connective tissue matrix, the chondroitin and keratan sulfate of the cartilage matrix are joined to a **core protein** to form a **proteoglycan monomer.** The most important proteoglycan monomer in hyaline cartilage is **aggrecan.** It has a molecular weight of 250 kDa. Each molecule contains about 100 chondroitin sulfate chains and as many as 60 keratan sulfate molecules. Because of the presence of the sulfate groups, aggrecan molecules have a large negative charge with an affinity for water molecules. Each linear hyaluronan molecule is associated with a large number of aggrecan molecules (more than 300), which are bound to the hyaluronan by link proteins at the N terminus of the molecule to form large **proteoglycan aggregates.**
- These highly charged proteoglycan aggregates are bound to the collagen matrix fibrils by electrostatic interactions and multiadhesive glycoproteins. The entrapment of these aggregates within the intricate matrix of collagen fibrils is responsible for the unique biomechanical properties of hyaline cartilage. Cartilage matrix also contains other proteoglycans (e.g., decorin, biglycan, and fibromodulin). These proteoglycans do not form aggregates but bind to other molecules and help stabilize the matrix.

Multiadhesive glycoproteins, also referred to as *noncollagenous* and *nonproteoglycan-linked glycoproteins*, influence interactions between the chondrocytes and the matrix molecules.

Multiadhesive glycoproteins have clinical value as markers of cartilage turnover and degeneration. Examples of such proteins are **anchorin CII** (cartilage annexin V), a small 34 kDa molecule that functions as a collagen receptor on chondrocytes, **tenascin,** and **fibronectin**, which also help anchor chondrocytes to the matrix

1.HYALINE CARTILAGE

Matrix

- The dry weight of hyaline cartilage is nearly 40% collagen embedded in a firm, hydrated gel of proteoglycans and structural glycoproteins. In routine histology preparations, the proteoglycans make the matrix generally basophilic and the thin collagen fibrils are barely discernible. Most of the collagen in hyaline cartilage is **type II**, although small amounts of minor collagens are also present.
- **Aggrecan** (250 kDa), with approximately 150 GAG side chains of chondroitin sulfate and keratan sulfate, is the most abundant proteoglycan of hyaline cartilage. Hundreds of these proteoglycans are bound noncovalently by link proteins to long polymers of hyaluronan. These proteoglycan complexes bind further to the surface of type II collagen fibrils. Water bound to GAGs in the proteoglycans constitutes up to 60%-80% of the weight of fresh hyaline cartilage.

1. HYALINE CARTILAGE

- Another important component of cartilage matrix is the structural multiadhesive glycoprotein **chondronectin**. Like fibronectin in other connective tissues, chondronectin binds specifically to GAGs, collagen, and integrins, mediating the adherence of chondrocytes to the ECM.
- Staining variations within the matrix reflect local differences in its molecular composition. Immediately surrounding each chondrocyte, the ECM is relatively richer in GAGs than collagen, often causing these areas of **territorial matrix** to stain differently from the intervening areas of interterritorial matrix

1. Hyaline Cartilage

Chondrocytes

- Cells occupy relatively little of the hyaline cartilage mass. At the periphery of the cartilage, young chondrocytes or **chondroblasts** have an elliptic shape, with the long axes parallel to the surface. Deeper in the cartilage, they are round and may appear in groups of up to eight cells that originate from mitotic divisions of a single chondroblast and are called **isogenous aggregates**. As the chondrocytes become more active in secreting collagens and other ECM components, the aggregated cells are pushed apart and occupy separate lacunae.
- Cartilage cells and matrix may shrink slightly during routine histologic preparation, resulting in both the irregular shape of the chondrocytes and their retraction from the matrix. In living tissue chondrocytes fill their lacunae completely.

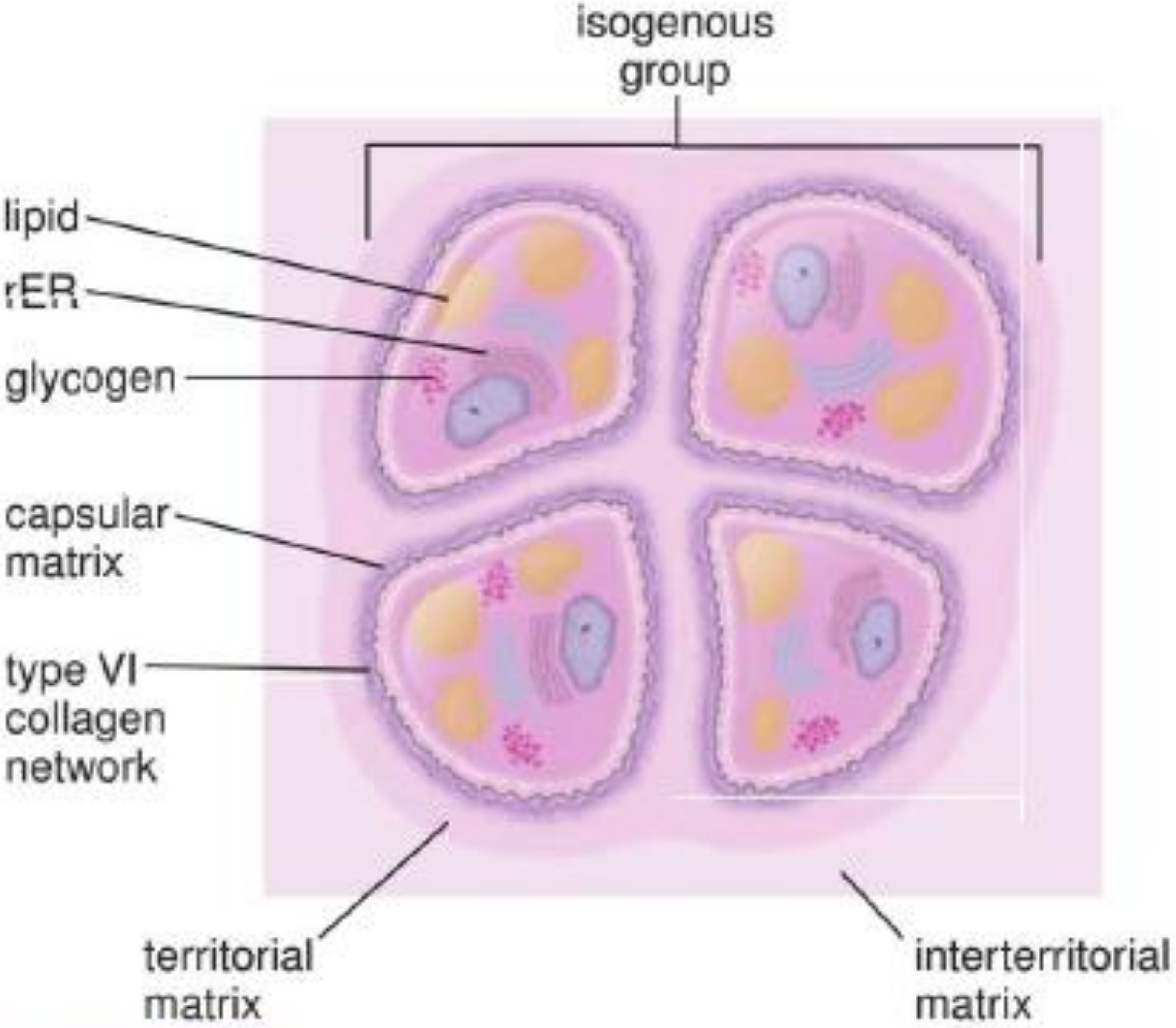


FIGURE 7.7 ▲ Diagram of cartilage matrices. Note the areas of capsular, territorial, and interterritorial matrices. The characteristics of each are described in the text above.

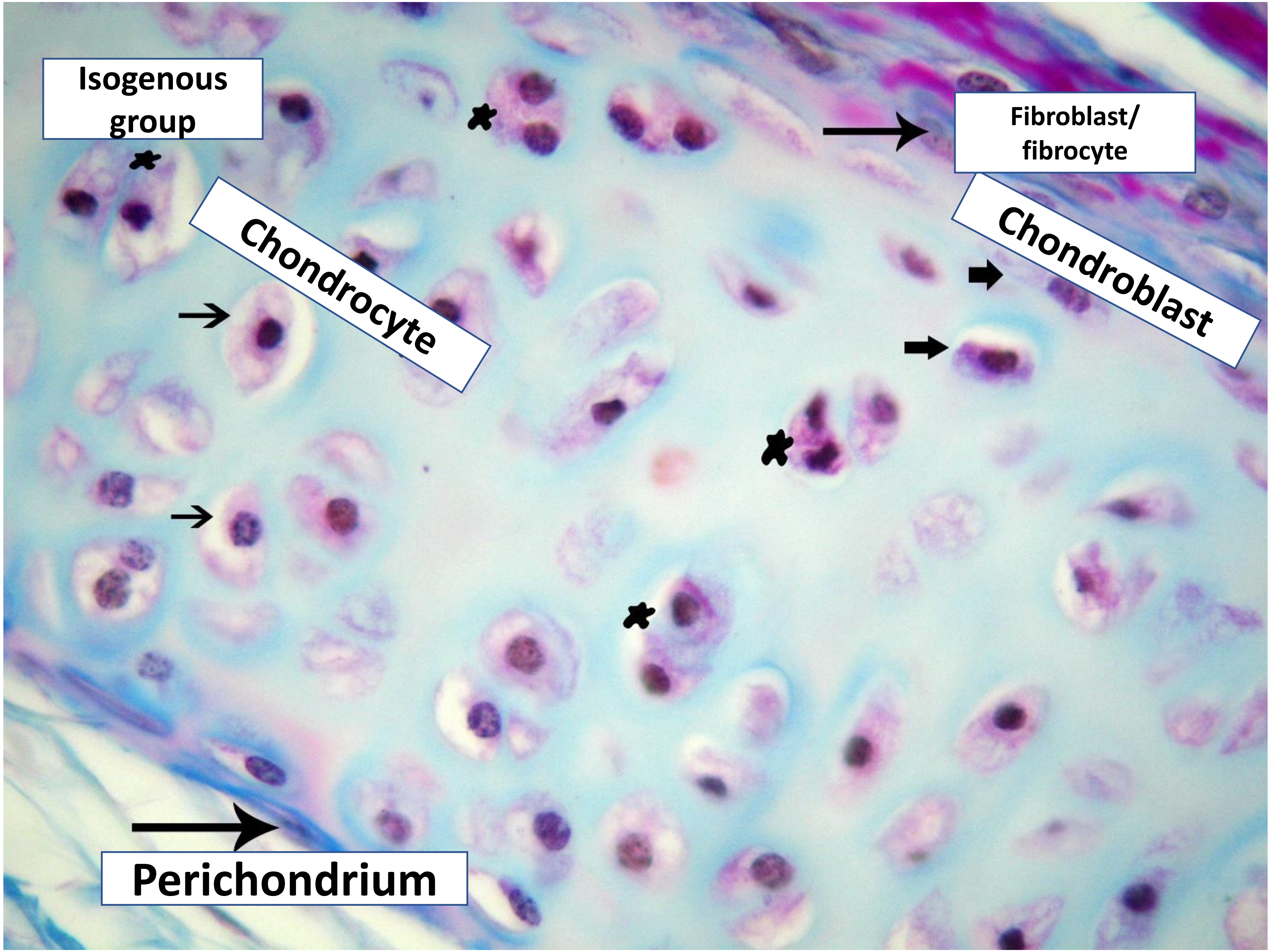
1. HYALINE CARTILAGE

- Because cartilage matrix is avascular, chondrocytes respire under low-oxygen tension. Hyaline cartilage cells metabolize glucose mainly by anaerobic glycolysis. Nutrients from the blood diffuse to all the chondrocytes from the cartilage surface, with movements of water and solutes in the cartilage matrix promoted by intermittent tissue compression and decompression during body movements. The limits of such diffusion define the maximum thickness of hyaline cartilage, which usually exists as small, thin plates.
- Chondrocyte synthesis of sulfated GAGs and secretion of proteoglycans are accelerated by many hormones and growth factors. A major regulator of hyaline cartilage growth is the pituitary-derived protein called growth hormone or **somatotropin**. This hormone acts indirectly, promoting the endocrine release from the liver of insulin-like growth factors, or somatomedins, which directly stimulate the cells of hyaline cartilage.

1. HYALINE CARTILAGE

Perichondrium

- Except in the articular cartilage of joints, all hyaline cartilage is covered by a layer of dense connective tissue, the **perichondrium**, which is essential for the growth and maintenance of cartilage. The outer region of the perichondrium consists largely of collagen type I fibers and fibroblasts, but an inner layer adjoining the cartilage matrix also contains mesenchymal stem cells which provide a source for new chondroblasts that divide and differentiate into chondrocytes.

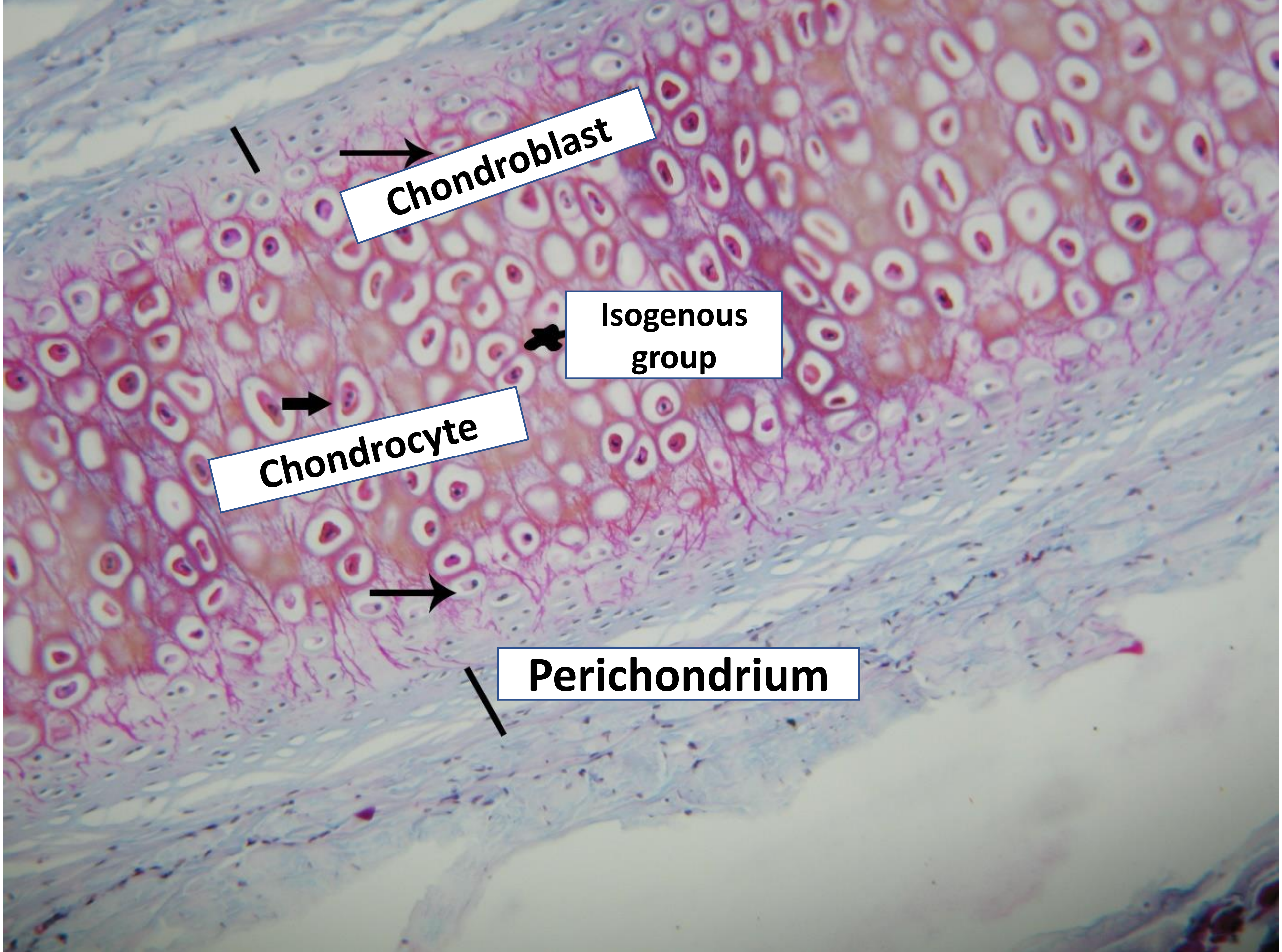

Isogenous group
Chondrocyte
Fibroblast/ fibrocyte
Chondroblast
Perichondrium

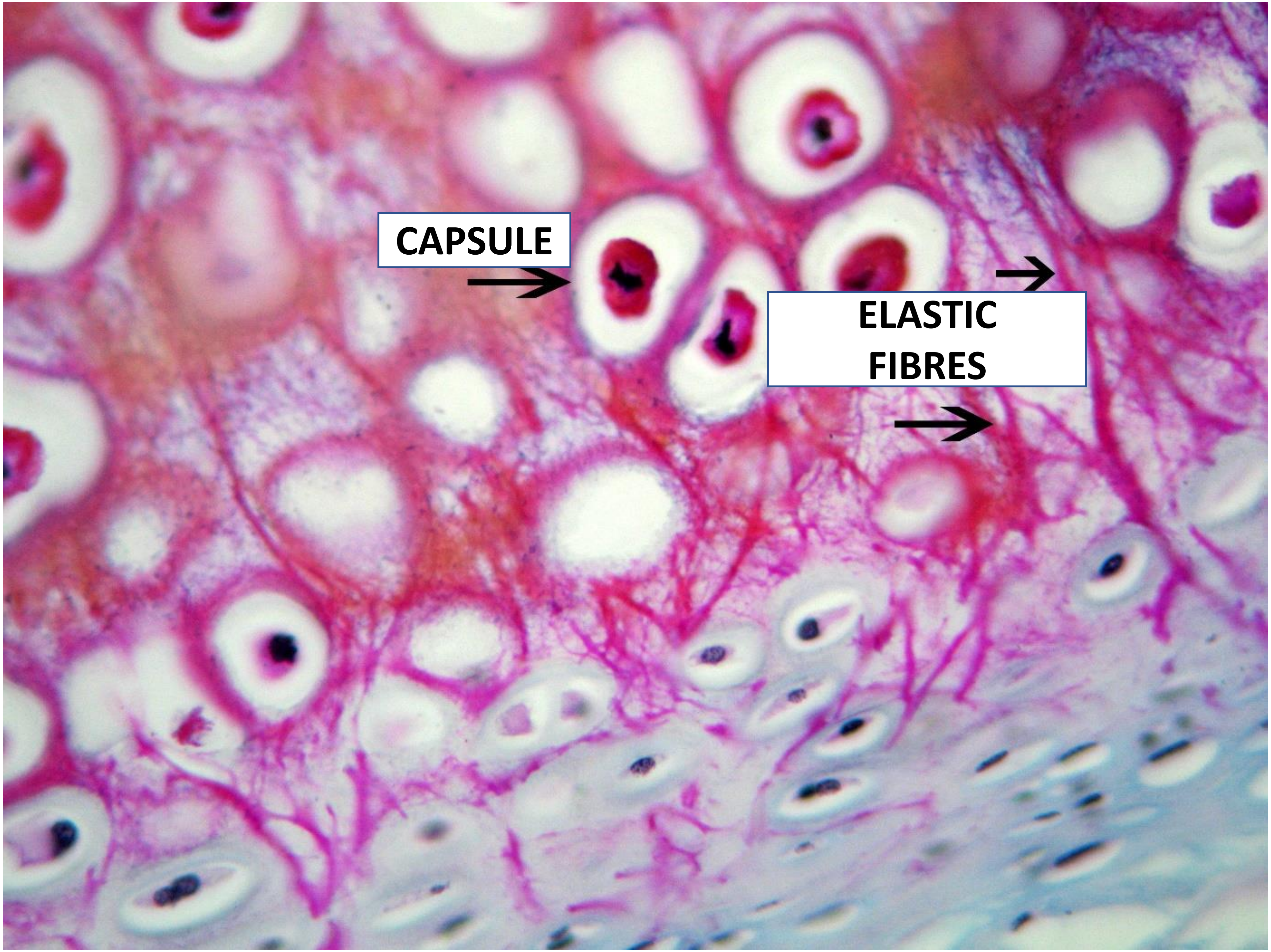
2. Elastic Cartilage

- **Elastic cartilage** is essentially similar to hyaline cartilage except that it contains an abundant network of elastic fibers in addition to a meshwork of collagen type II fibrils, which give fresh elastic cartilage a yellowish color. With appropriate staining the elastic fibers usually appear as dark bundles distributed unevenly through the matrix.

2. Elastic Cartilage

- More flexible than hyaline cartilage, elastic cartilage is found in the auricle of the ear, the walls of the external auditory canals, the auditory (Eustachian) tubes, the epiglottis, and the upper respiratory tract. Elastic cartilage in these locations includes a perichondrium similar to that of most hyaline cartilage. Throughout elastic cartilage the cells resemble those of hyaline cartilage both physiologically and structurally.


Chondroblast
Isogenous group
Chondrocyte
Perichondrium


CAPSULE
ELASTIC
FIBRES

3. FIBROCARTILAGE

- **Fibrocartilage** takes various forms in different structures but is essentially a mingling of hyaline cartilage and dense connective tissue. It is found in intervertebral discs, in attachments of certain ligaments, and in the pubic symphysis—all places where it serves as very tough, yet cushioning support tissue for bone.

3. FIBROCARTILAGE

Fibrous cartilage is characterized by abundant type I and II collagen fibers as well as the matrix material of hyaline cartilage. The relative scarcity of proteoglycans overall makes fibrocartilage matrix more acidophilic than that of hyaline or elastic cartilage. There is no distinct surrounding perichondrium in fibrocartilage.

Intervertebral discs of the spinal column are composed primarily of fibrocartilage and act as lubricated cushions and shock absorbers preventing damage to adjacent vertebrae from abrasive forces or impacts.

	Hyaline Cartilage	Elastic Cartilage	Fibrocartilage
Main features of the extracellular matrix	Homogeneous, with type II collagen and aggrecan	Type II collagen, aggrecan, and darker elastic fibers	Type II collagen and large areas of dense connective tissue with type I collagen
Major cells	Chondrocytes, chondroblasts	Chondrocytes, chondroblasts	Chondrocytes, fibroblasts
Typical arrangement of chondrocytes	Isolated or in small isogenous groups	Usually in small isogenous groups	Isolated or in isogenous groups arranged axially
Presence of perichondrium	Yes (except at epiphyses and articular cartilage)	Yes	No
Main locations or examples	Many components of upper respiratory tract; articular ends and epiphyseal plates of long bones; fetal skeleton	External ear, external acoustic meatus, auditory tube; epiglottis and certain other laryngeal cartilages	Intervertebral discs, pubic symphysis, meniscus, and certain other joints; insertions of tendons
Main functions	Provides smooth, low-friction surfaces in joints; structural support for respiratory tract	**Provides flexible shape and support** of soft tissues	Provides cushioning, tensile strength, and resistance to tearing and compression

CARTILAGE FORMATION, GROWTH, & REPAIR

- All cartilage forms from embryonic mesenchyme in the process of **chondrogenesis**. The first indication of cell differentiation is the rounding up of the mesenchymal cells, which retract their extensions, multiply rapidly, and become more densely packed together. In general the terms "chondroblasts" and "chondrocytes" respectively refer to the cartilage cells during and after the period of rapid proliferation. At both stages the cells have basophilic cytoplasm rich in RER for collagen synthesis. Production of the ECM encloses the cells in their lacunae and then gradually separates chondroblasts from one another. During embryonic development, the cartilage differentiation takes place primarily from the center outward; therefore the more central cells have the characteristics of chondrocytes, whereas the peripheral cells are typical chondroblasts. The superficial mesenchyme develops as the perichondrium.

CARTILAGE FORMATION, GROWTH, & REPAIR

- **Chondrogenesis,** the process of cartilage development, begins with the aggregation of chondroprogenitor mesenchymal cells to form a mass of rounded, closely apposed cells. In the head, most of the cartilage arises from aggregates of ectomesenchyme derived from neural crest cells. The site of hyaline cartilage formation is recognized initially by an aggregate of mesenchymal or ectomesenchymal cells known as a **chondrogenic nodule.** Expression of **transcription factor SOX-9** triggers differentiation of these cells into **chondroblasts,** which then secrete cartilage matrix (expression of SOX-9 coincides with secretion of type II collagen). The chondroblasts progressively move apart as they deposit matrix. When they are completely surrounded by matrix material, the cells are called **chondrocytes.** The mesenchymal tissue immediately surrounding the chondrogenic nodüle gives rise to the perichondrium.

CARTILAGE FORMATION, GROWTH, & REPAIR

- Once formed, the cartilage tissue enlarges both by **interstitial growth**, involving mitotic division of preexisting chondrocytes, and by **appositional growth**, which involves chondroblast differentiation from progenitor cells in the perichondrium. In both cases, the synthesis of matrix contributes greatly to the growth of the cartilage. Appositional growth of cartilage is more important during postnatal development, interstitial growth in cartilaginous regions within long bones is important in increasing the length of these structures. In articular cartilage, cells and matrix near the articulating surface are gradually worn away and must be replaced from within, because there is no perichondrium to add cells by appositional growth.
- Except in young children, damaged cartilage undergoes slow and often incomplete **repair**, primarily dependent on cells in the perichondrium which invade the injured area and produce new cartilage. In damaged areas the perichondrium produces a scar of dense connective tissue instead of forming new cartilage. The poor capacity of cartilage for repair or regeneration is due in part to its avascularity and low metabolic rate.

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