Tissue Physiology

Connective tissue is one of the most abundant and widely distributed tissues in the body. It forms our bones, surrounds our organs, allows for the integrity of our neural and vascular system, cushions and lubricates our joints, and connects the muscles to our skeleton.

Connective tissue serves multiple functions. It provides the organism with shape and mechanical support. Also, it modulates cell migration, growth, and differentiation. The following are major features of connective tissue: structural and mechanical, defense, nutrition and transport of molecules and storage.

Connective tissue supports the shape of cells, tissues, and organs interacting with the cytoskeleton. The most obvious structural connective tissue is bone, comprising the skeleton and supporting the entire organism. It contains cells and metabolites important in immune function, such as inflammation, and in tissue repair after injury. Blood and blood vessels are connective tissue, which transports substances throughout the body. The nervous system is housed within connective tissue. Components in connective tissue regulate movement of nutrients between cells. Adipose tissue is a unique connective tissue, providing storage of energy and insulation.

Connective tissue function is mediated by its different components, most of which are macromolecules that interact with one another and with the cells. Varying the proportions and the arrangement of the individual components determines the function of the particular tissue. Nutrient deficiencies may disrupt regulation of tissue synthesis and degradation.

Connective tissue is metabolically active and serves many functions. The tissue consists of three basic components: fibers, ground substance, and cells. Outside the cell the fibers and ground substance form the extra cellular matrix. This matrix separates and protects cells, allows weight bearing, creates a tension and protects cells. Connective tissue on the whole is sparsely innervated and vascularized.

Three main types of fibers appear in connective tissue: collagen, elastic and reticular fibers. Tissues contain one or more types of collagen and different proportions of collagen and elastic fibers. These fibers associate with other elements of the extra cellular matrix to form specialized connective tissue (ex. bone).

Collagen is the most abundant protein in our body comprising up to 30% of the total. There are perhaps nineteen different types of collagen we humans have. All share a common structure, varying in their chemical composition, macromolecular organization, tissue distribution and function.

Patterns between collagen types and orientation differ between various connective tissues and even between species. In general, collagen fibers are inelastic, but have great tensile strength giving a combination of flexibility and strength to the tissues. The diameter and orientation of the fibers constitutes the tensile strength of the tissue.

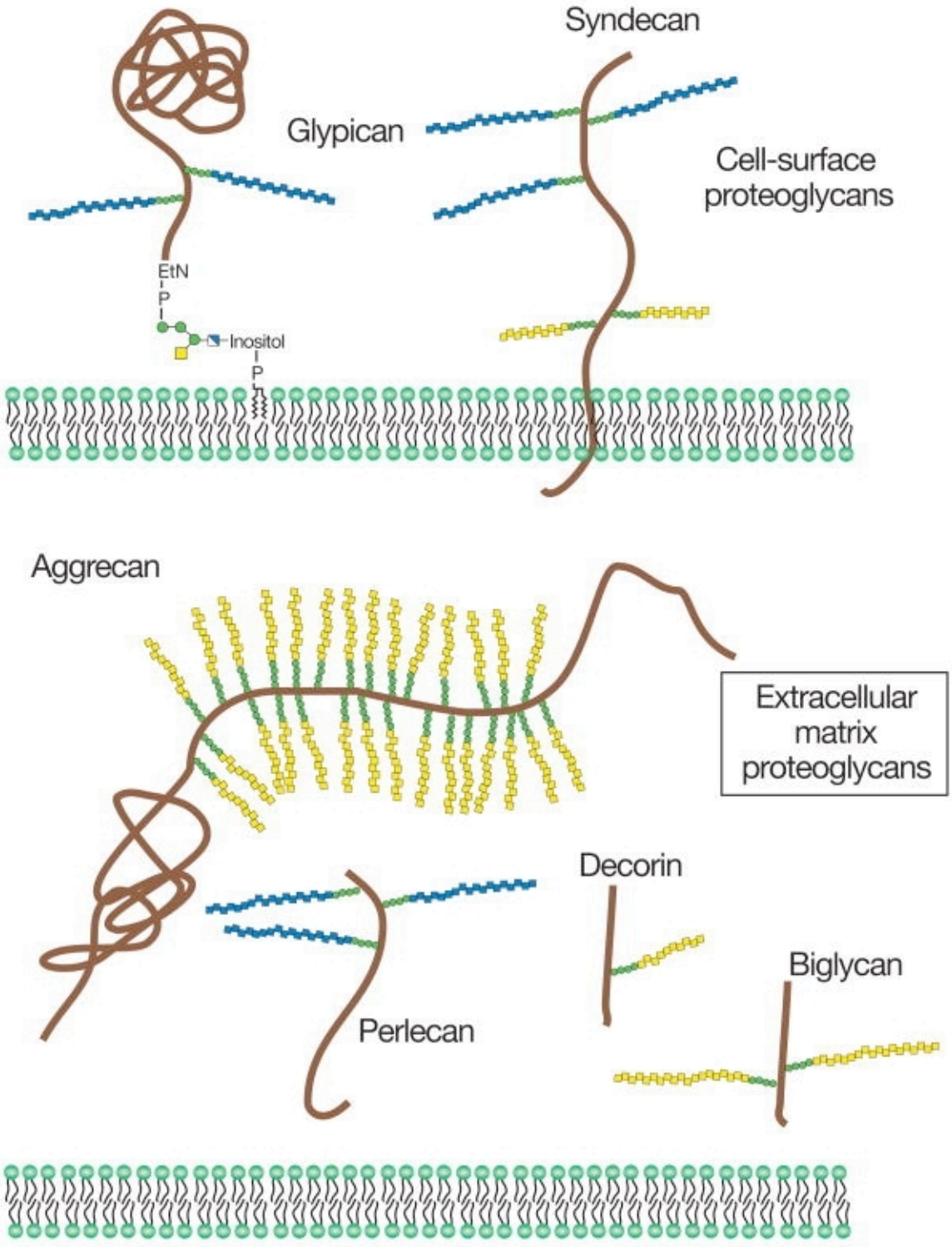
Elastic fibers predominate in tissues subject to stretching.

Reticular fibers are thin and branch to form an extensive network in organs, smooth muscle, adipose tissue and bone marrow. These fibers consist of collagen protein associated with glycoproteins and proteoglycans. During inflammation and wound healing, most connective tissue have abundant reticular fibers, which are subsequently replaced by regular collagen fibers.

The ground substance fills the spaces in between the cells and fibers. Its viscosity acts as a lubricant due to the high water content. Soluble precursors of the fibrous proteins, proteoglycans, glycoproteins, and other molecules secreted by cells are abundant in the ground substance. These synthesizing cells include fibrocytes, smooth muscle cells and nerve cells. The two major components of the ground substance are the proteoglycans and the structural glycoproteins, which trap water molecules and lend strength, rigidity and resiliency to the extra cellular matrix.

Proteoglycans are large molecules formed by many linear chains of polysaccharide units called glycosaminoglycans (GAGs). Proteoglycan monomers are grouped according to the length and type of GAG chains attached to a protein core. These GAG chains radiate out from the core like bristles of a bottle brush. Sulfation of the GAGs determine their biological activity. Proteoglycan monomers may combine further with a chain of hyaluronic acid and unsulfated GAG to form larger proteoglycan complexes. There are six main types of glycosaminoglycans; hyaluronic acid, chondroitin 6 sulphate, chondroitin 4 sulphate, dermaton sulphate, keratan sulphate, heparan sulphate, and heparin.

Proteoglycans act as a molecular sieve moderating the movement of cells, and nutritive and inflammatory substances. They are also responsible for attracting and maintaining water balance within the tissue. The long chains of GAGs are negatively charged due to the carboxylic and sulphate groups of the amino sugars. **The high density of negative charges attracts and binds water molecules.** Depending on the structure and types of GAGs proteoglycans can trap as much as 50x their weight in water.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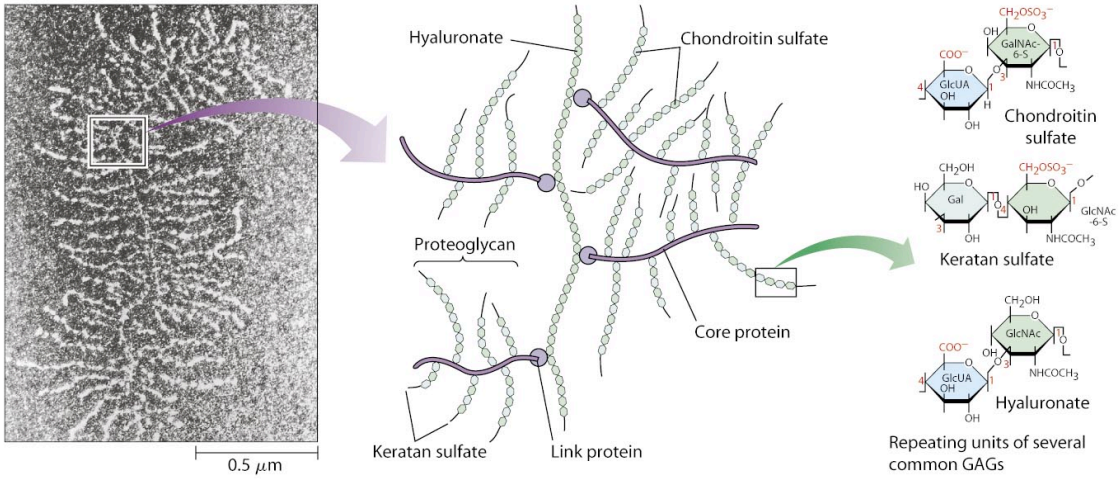

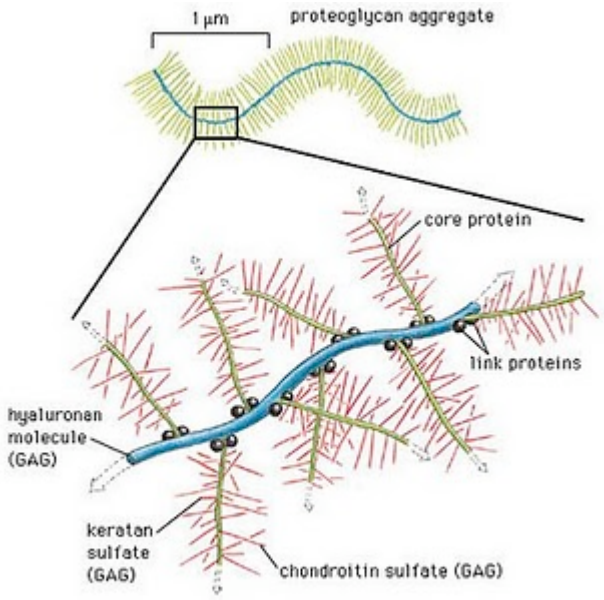

Glycoproteins are similar to proteoglycans. In contrast, the protein fraction predominates over the carbohydrates, which are branched structures. The primary glycoproteins are fibronectin, laminin, and chondronectin. Their role in the ground substance is the migration and adhesion of cells to their substrates. For example, fibronectin connects fibroblasts to collagen and bind to proteoglycans. These compounds contribute to the scaffolding on connective tissue to provide support and influence movement of cells.

The various cells in connective tissue store vital metabolites and synthesize fibrous proteins and other components of the extra cellular matrix. They play important roles in immune and inflammatory responses as well as in tissue repair. Many cells are indigenous to the connective tissue. These include fibroblasts, chondroblasts, and osteoblasts. Some originate in the bone marrow but are constantly present in the tissue.

Some examples are macrophages and mast cells. Other cells migrate from blood vessels in response to tissue injury, inflammation and repair. Plasma cells, neutrophils, monocytes and basophils would be included in this category. The extra cellular matrix greatly influences function and differentiation of the cells. Tensile forces also influence cell function.

To understand how connective tissue is influenced by activities and trauma one should understand some basic physiology of these structures. Synthesis and degradation of connective tissue are a continual process and are integral parts of tissue remodeling and turnover. Many modulators can affect these processes. Each of the intracellular and extracellular events involved in macromolecular synthesis is subject to alteration or biochemical modification. Changes in gene transcription and in events after translation of macromolecules can alter distribution and deposition of tissue proteins and proteoglycans. For example, **the concentration of proteoglycans in tendinopathies can be 40x greater than normal** .

Remodeling of tissues is the process of changing and replacing of tissue components with others. Normal remodeling during growth or repair requires a proper balance of synthesis and degradation of tissue components. Proteoglycans in the extra cellular matrix appear to regulate remodeling of connective tissue by influencing collagen formation during the repair process. Remodeling is also regulated by mechanical stimulation (end-range loading, for example). Mechanical tension and compression modify bone and cartilage remodeling, where tissues such as these depend on diffusion of nutrients for maintenance since they have no direct blood supply. However, **after injury angiogenesis and neurogenesis often take place in these tissues.**

Turnover rate of various connective tissue components varies. Elastin may take months to years for renewel. Collagen is also a stable protein and renewal is slow. Replacement of mature collagen can require weeks to several months. Collagen turnover rates vary in different structures. Tendon collagen renewal is very slow, whereas the collagen of loose connective tissue that surrounds our organ is renewed more rapidly (perhaps due to a lack of blood supply to the tendons). Proteoglycans turn over rapidly: 2-4 days for hyaluronic acid and 7-10 days for the sulphated proteoglycans.

Connective tissue trauma is a major source of physical discomfort and disability. During inflammation and repair, the number of fibroblasts increase within some connective tissues. Injury to connective tissues involves damage to the cells and structural components of the tissue. Several responses are triggered and a sequence of events begins to repair the tissue. The reaction to injury includes vascular, cellular and biochemical responses. Three phases of the repair process can be applied to the general healing of connective tissue. These phases, however, may overlap. These responses prevent the spread of damaging agents to nearby tissues, dispose of damaged cells, and replace damaged tissue with newly synthesized components.

The initial inflammatory stage involves several vascular and cellular reactions to initiate the response. The process begins with the release of chemical mediators from cells into

the extra cellular fluid. The initial tissue damage stimulates release of histamine from mast cells which causes dilation of blood vessels in the local area and increases vascular permeability. Increased blood flow and fluids and proteins that leak from the permeable blood vessels cause edema in the tissue and consequent swelling. Cells migrate from nearby blood vessels and cause release of more inflammatory mediators such as kinins and prostaglandins (PGs). Local tissue pressure and some of these mediators act on nearby nerves to cause pain. These events lead to the classical signs of inflammation: rubor, tumor, dolar and calor. The primary purpose of inflammation is to rid the site of damaged tissue cells and set the stage for tissue repair. Acute inflammation generally lasts about a week then subsides as the repair process progresses. Many of the events that occur during this time initiate tissue repair. PGs are considered important mediators of inflammation and are often the target of intervention with anti-inflammatory agents. However PGs may also have a significant role in tissue repair. Many immigrant cells also have significant roles in tissue remodeling. White blood cells accumulate within the damaged tissue along with resident macrophages. Enzymes released from these cells help digest necrotic cells and degrade matrix molecules; neutrophils and macrophages engulf cell debris. Blood platelets release growth factors that stimulate new fiber and matrix molecule synthesis. Also during this early stage of repair angiogenesis and neurogenesis takes place.

The matrix and cellular proliferation phase, the stage of regeneration, involves chemical mediators released by inflammatory cells. These stimulate migration and proliferation of fibroblasts, which participate in the repair process. Fibroblasts secrete fibronectin, proteoglycans and small diameter Type III collagen fibers. In addition to these fibers, newly formed capillary channels, clotting proteins, platelets and freshly synthesized matrix molecules form granulation tissue. However, this granulation tissue has little tensile strength.

The remodeling phase reshapes and strengthens damaged tissues by removing and reforming the matrix and replacing cells. As repair progresses inflammatory cells disappear and the number of blood vessels and the density of fibroblasts decrease. The proportion of Type I collagen to Type III collagen and the matrix organization increases. Collagen fibers are reoriented in the direction of loading, especially in ligament repair. Collagen matures and elastin forms; tensile strength increases. However, the remodeled tissue may not completely resemble the original and thus the mechanical capabilities of that tissue may be altered.

In my opinion, the inflammatory/healing response is not perfect. Far too much proteoglycan may be produced by the involved nerves and their connective tissue housing. This causes edema different from the inflammatory response. This edema is due to diffusion of surrounding liquid towards the hydrophilic proteoglycans. Consequently, the hydrostatic pressure rises and even with angiogenesis, the blood doesn't flow into these vessels as the host's systolic pressure is less than that in the injured area. Oxygen and blood elements can't get to interstitial nerves and their vasomotor activity is then subverted. This condition becomes chronic. Cells die and collagen degrades.

In my opinion this nerve and associated connective tissue synthesis of too many macromolecules also occurs with ‘sub clinical’ trauma. I believe a stress to the nerves will cause this scenario. The resulting symptoms and disability the patient experiences will depend on which nerves are affected. For example, repetitive stress of the lateral epicondyle resulting in Tennis Elbow or too much walking on hard surfaces resulting in an Achilles tendinopathy.