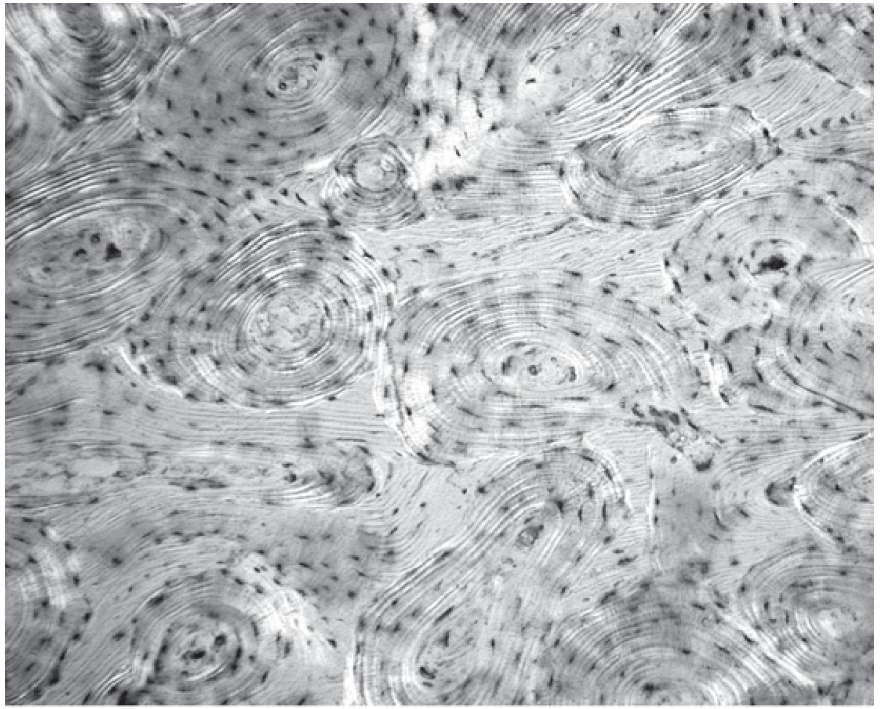
ANIMAL CONNECTIVE TISSUES

COLLAGEN & OTHER ECM MOLECULES

CONNECTIVE TISSUES AND COLLAGEN – A BRIEF INTRODUCTION

- Four major types of tissues in animals: connective, epithelial, nervous, and muscular.
- In connective tissues, extracellular matrix is plentiful and carries the mechanical load.
- In other tissues, such as epithelia, extracellular matrix is scanty, and the cells are directly joined to one another and carry the mechanical load themselves. We discuss connective tissues first.
- Animal connective tissues are enormously varied. They can be tough and flexible like tendons or the dermis of the skin; hard and dense like bone; resilient and shock-absorbing like cartilage; or soft and transparent like the jelly that fills the interior of the eye.
- In all of these tissues, the tensile strength is chiefly provided by a fibrous protein: collagen.

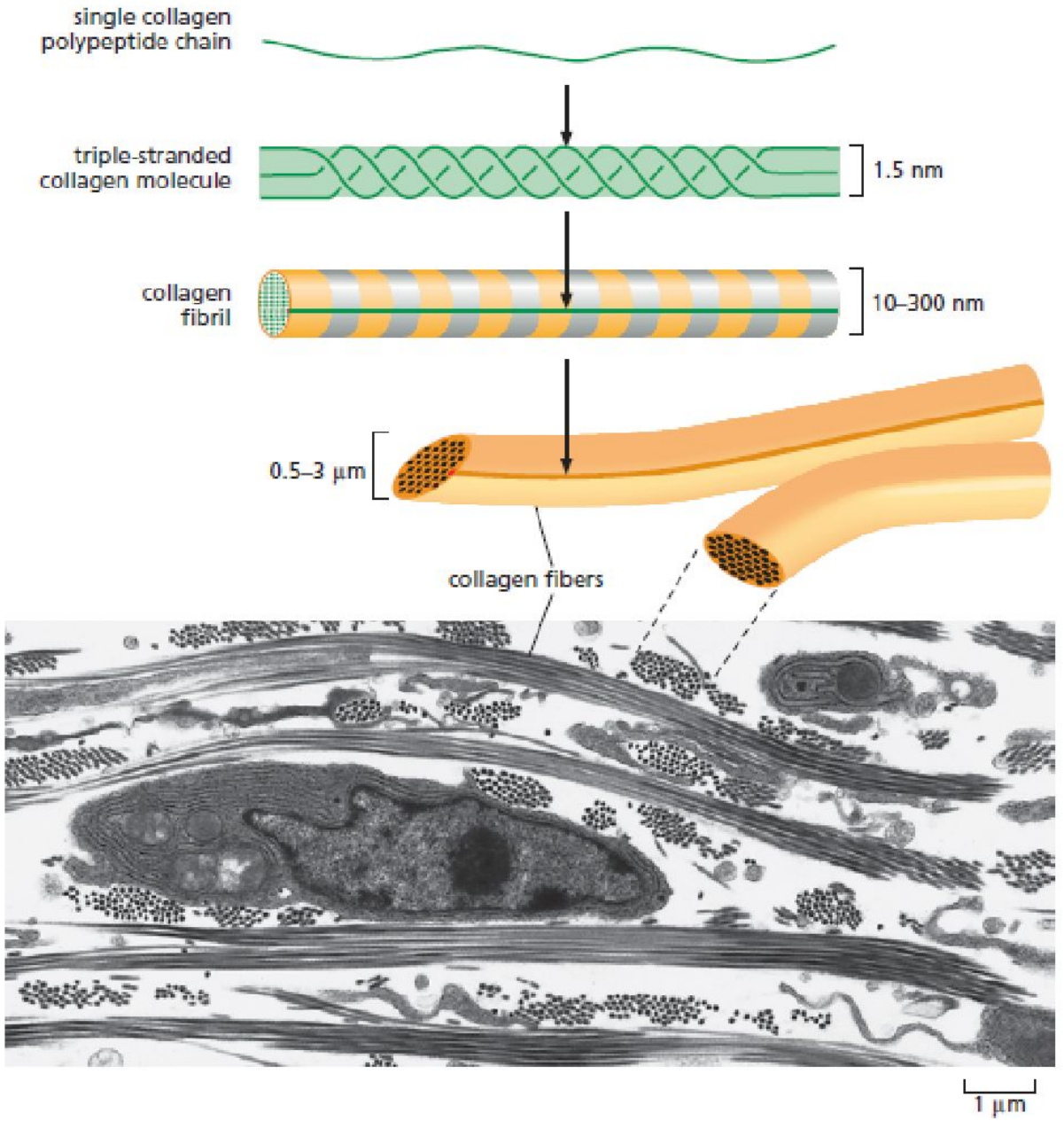
Extracellular matrix is plentiful in connective tissue such as bone. In this micrograph, cells in a cross section of bone appear as small, dark, antlike objects embedded in the bone matrix, which occupies most of the volume of the tissue and provides all its mechanical strength. The alternating light and dark bands are layers of matrix containing oriented collagen fibrils (made visible with the help of polarized light). Calcium phosphate crystals (not visible) filling the interstices between the collagen fibrils make bone matrix resistant to both compression and tension, like reinforced concrete.



ABOUT COLLAGEN

- Collagen is a protein found in all animals, and it comes in many varieties.
- Mammals have about **20 different collagen genes**, coding for the variant forms of collagen required in different tissues.
- **They constitute 25% of the total protein mass in a mammal—more than any other type of protein**.

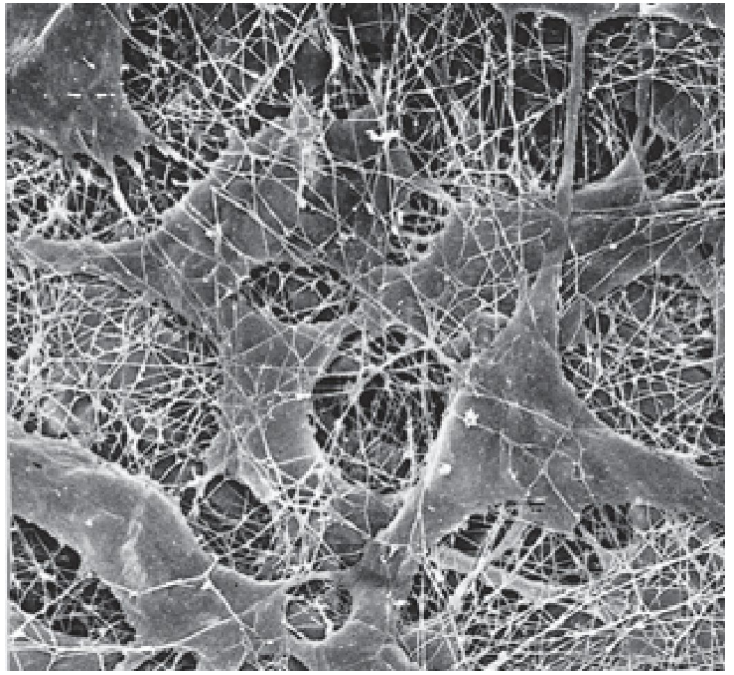
Collagen fibrils are organized into bundles. The drawings show the steps of collagen assembly, from individual polypeptide chains to triple-stranded collagen molecules, then to fibrils and, finally, fibers. The electron micrograph shows fully assembled collagen in the connective tissue of embryonic chick skin. The fibrils are organized into bundles (fibers), some running in the plane of the section, others approximately at right angles to it. The cell in the micrograph is a fibroblast, which secretes collagen and other extracellular matrix components.



COLLAGEN PRODUCTION

- The connective-tissue cells that manufacture and inhabit the extracellular matrix go by various names according to the tissue:
- In skin, tendon, and many other connective tissues, they are called **fibroblasts**, in bone, they are called **osteoblasts**.
- They make both the collagen and the other macromolecules of the matrix. Almost all of these molecules are synthesized intracellularly and then secreted in the standard way, by exocytosis.
- Outside the cell, they assemble into huge, cohesive aggregates.
- If assembly were to occur prematurely, before secretion, the cell would become choked with its own products.
- In the case of collagen, the cells avoid this catastrophe by secreting collagen molecules in a precursor form, called **procollagen**, with **additional peptide extensions** at each end that **obstruct premature assembly into collagen fibrils**. **Extracellular enzymes**—called **procollagen proteinases**—cut off these terminal extensions to allow assembly only after the molecules have emerged into the extracellular space.

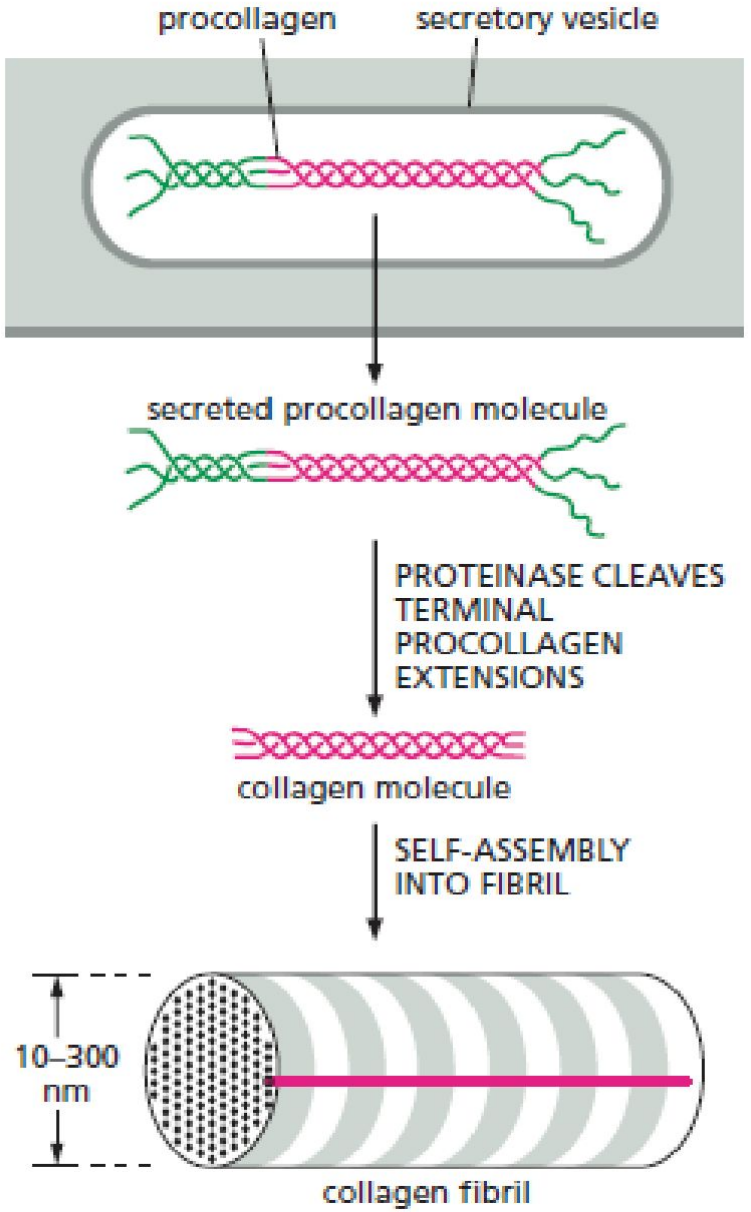
A scanning electron micrograph showing fibroblasts and collagen fibers in connective tissue from the cornea of a rat. Other components that normally form a hydrated gel filling the spaces between the collagen fibrils and fibers have been removed by enzyme and acid treatment.



PROCOLLAGEN TO COLLAGEN FIBRIL

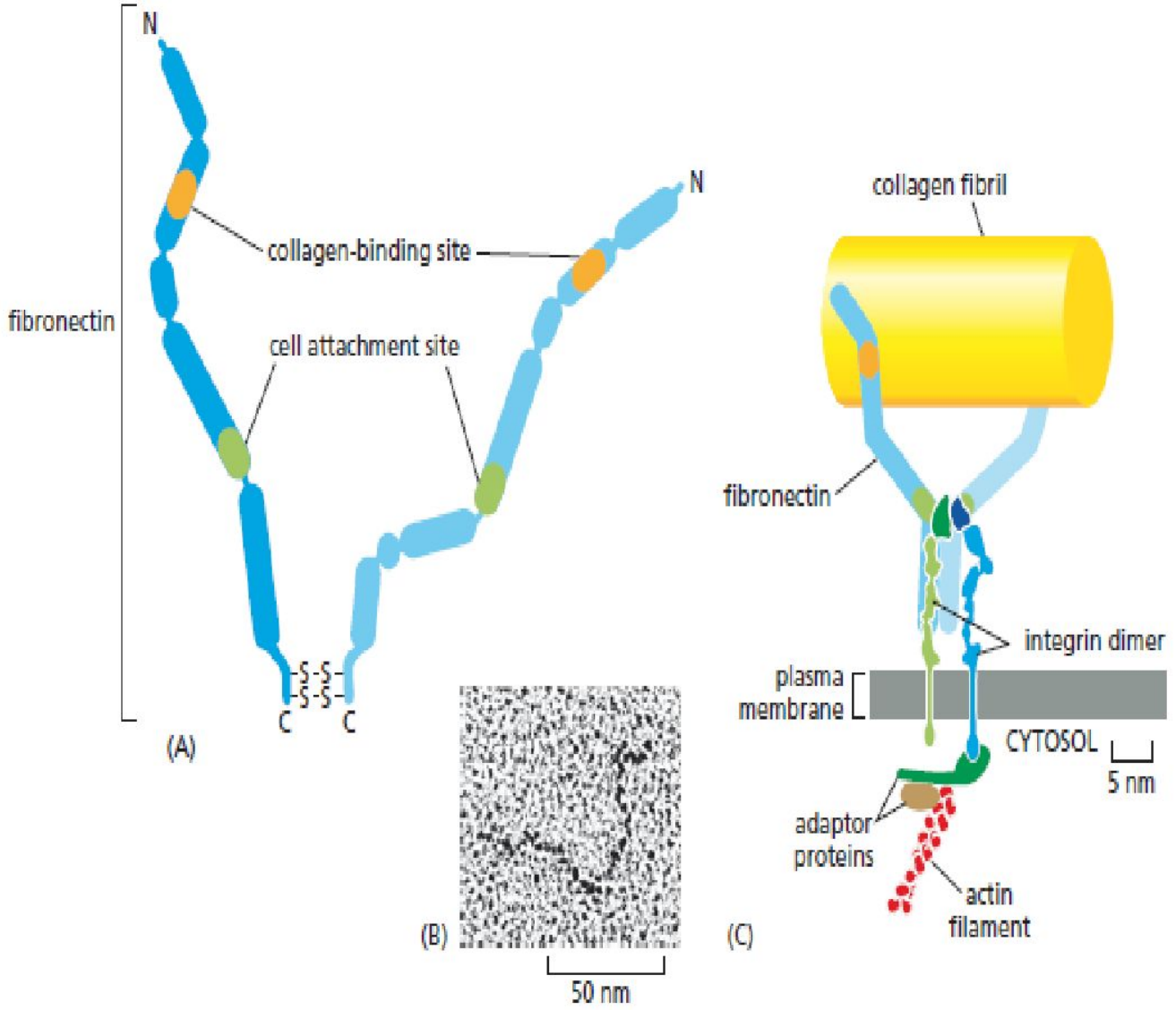
- Procollagen precursors are cleaved to form mature collagen outside the cell. Collagen is synthesized as a procollagen molecule that has unstructured peptides at either end. These peptides prevent collagen from assembling into a fibril inside the fibroblast. When the procollagen is secreted, an extracellular enzyme removes its terminal peptides, producing mature collagen molecules. These molecules can then self-assemble into ordered collagen fibrils

Cells in tissues have to be able to degrade matrix as well as make it. This ability is essential for tissue growth, repair, and renewal; it is also important where migratory cells, such as macrophages, need to burrow through the thicket of collagen and other extracellular matrix polymers. Matrix proteases that cleave extracellular proteins play a part in many disease processes, ranging from arthritis, where they contribute to the breakdown of cartilage in affected joints, to cancer, where they help cancer cells invade normal tissue.



FIBRONECTIN & INTEGRIN-ACCESSORY ECM PROTEINS

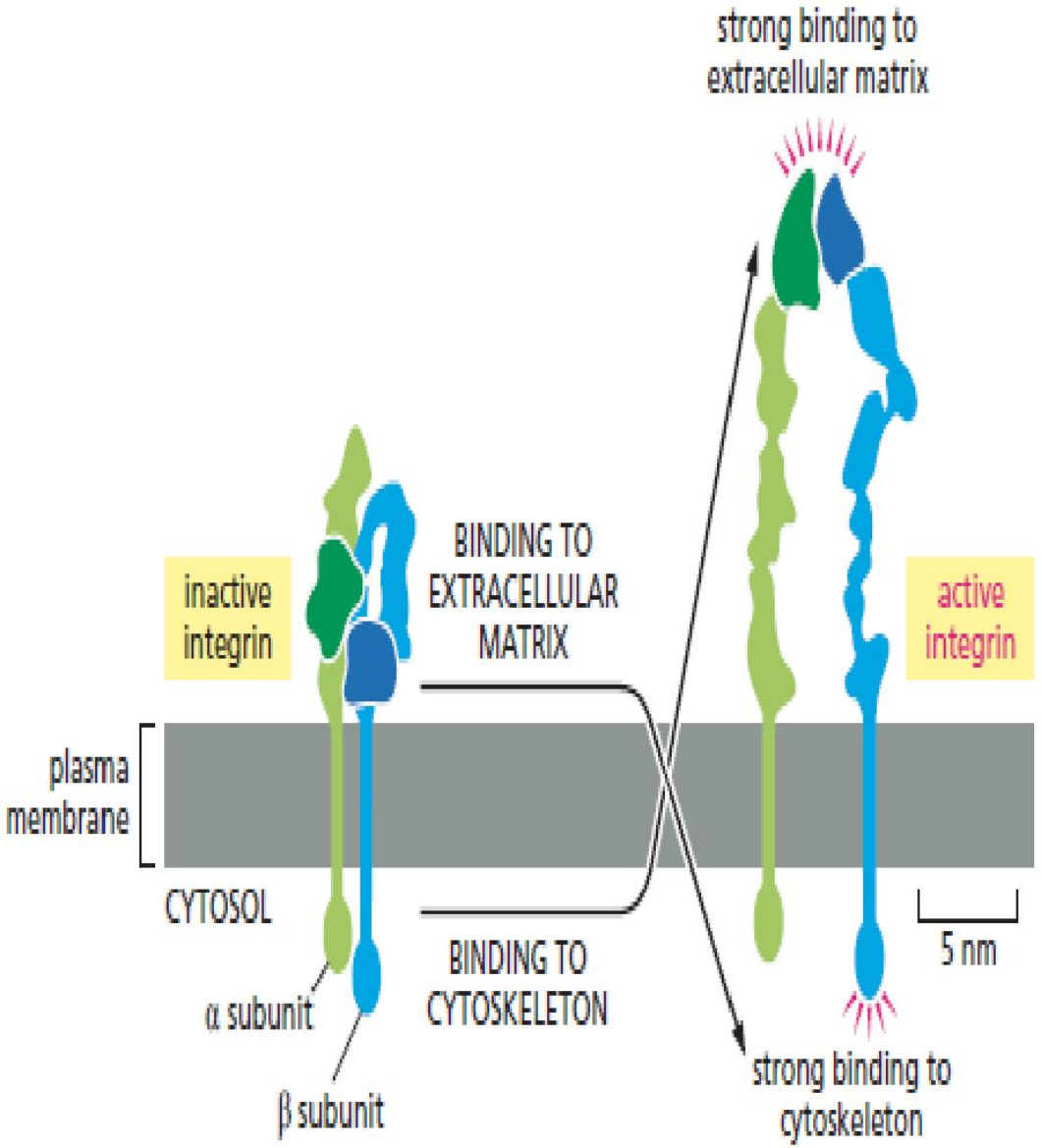
- Fibronectin and integrin proteins help attach a cell to the extracellular matrix. Fibronectin molecules outside the cell bind to collagen fibrils. Integrins in the plasma membrane bind to the fibronectin and tether it to the cytoskeleton inside the cell. (A) Diagram and (B) electron micrograph of a molecule of fibronectin.
- (C) The transmembrane linkage mediated by an integrin protein (blue and green dimer). The integrin molecule transmits tension across the plasma membrane: it is anchored inside the cell via adaptor proteins to the actin cytoskeleton and externally via fibronectin to other extracellular matrix proteins, such as the collagen fibril shown.
- The integrin shown here links fibronectin to an actin filament inside the cell. Other integrins can connect different extracellular proteins to the cytoskeleton (usually to actin filaments, but sometimes to intermediate filaments).



INTEGRIN DEFICIENCIES

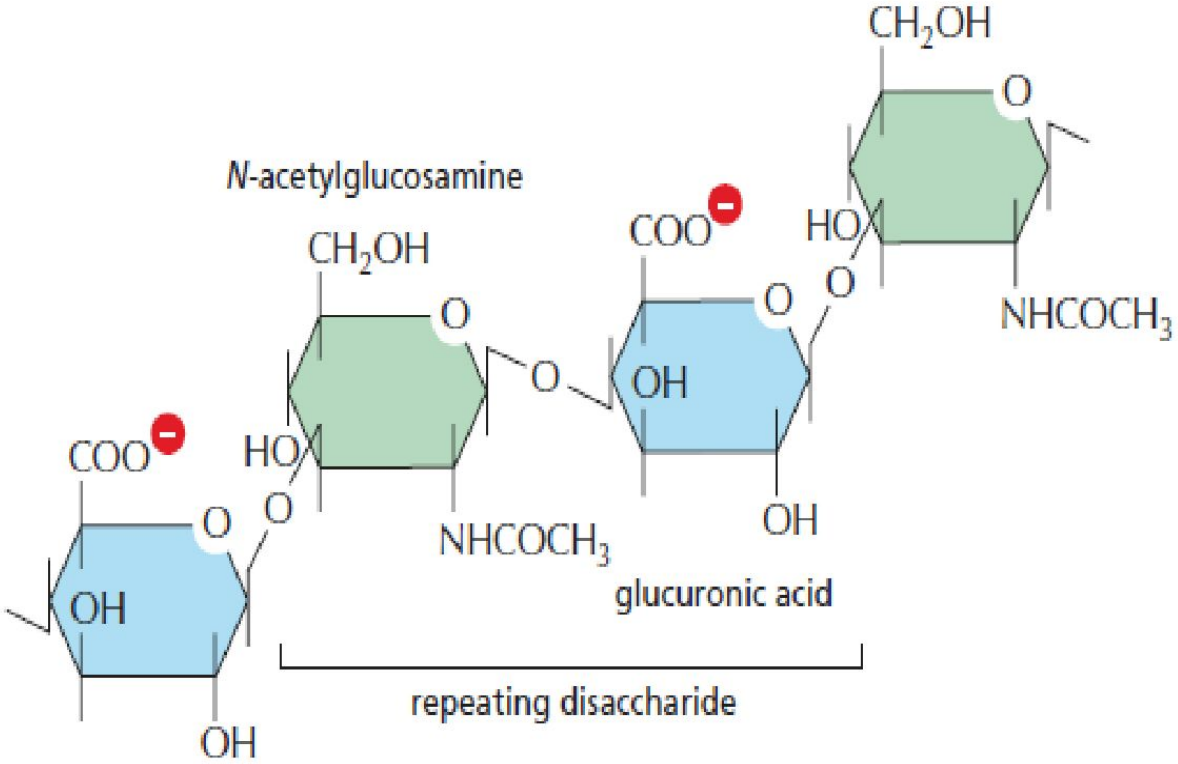
- Humans make at least 24 kinds of integrins, each of which recognizes distinct extracellular molecules and has distinct functions, depending on the cell type in which it resides.
- **The integrins on white blood cells help the cells crawl out of blood vessels at sites of infection so as to deal with marauding microbes. People who lack this type of integrin develop a disease called leucocyte adhesion deficiency and suffer from repeated bacterial infections.**
- **A different form of integrin is found on blood platelets, and individuals who lack this integrin bleed excessively because their platelets cannot bind to the necessary clotting factor in the extracellular matrix.**

An integrin protein switches to an active conformation when it binds to molecules on either side of the plasma membrane. An integrin protein consists of two different subunits, α (green) and β (blue), which can switch between a folded, inactive form and an extended, active form. The switch to the activated state can be triggered by binding to an extracellular matrix molecule (such as fibronectin) or to intracellular adaptor proteins that then link the integrin to the Cytoskeleton. In both cases, the conformational change alters the integrin so that its opposite end rapidly forms a counterbalancing attachment to the appropriate structure. In this way, the integrin creates a mechanical linkage across the plasma membrane.



PROTEOGLYCANS

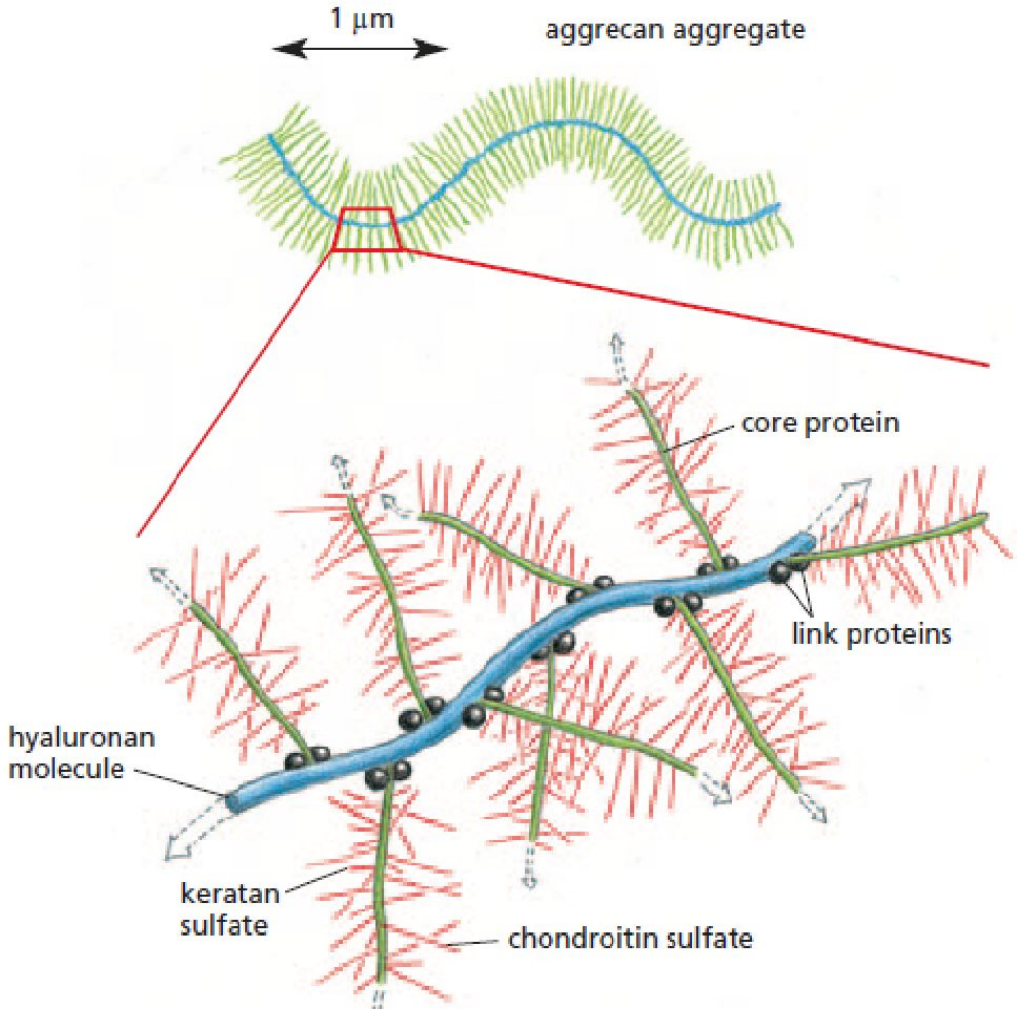
- Resist compression.
- Composed of glycosaminoglycans (GAGs), negatively charged polysaccharide chains made of repeating disaccharide units
- GAGs are usually covalently linked to core proteins to form proteoglycans, which are extremely diverse in size, shape, and chemistry.
- Typically, many GAG chains are attached to a single core protein, which may in turn be linked at one end to another GAG, creating an enormous aggregate resembling a bottlebrush, with a molecular weight in the millions.
- In dense, compact connective tissues such as tendon and bone, the proportion of GAGs is small, and the matrix consists almost entirely of collagen.
- At the other extreme, the jellylike substance in the interior of the eye consists almost entirely of one particular type of GAG, plus water, with only a small amount of collagen.



Glycosaminoglycans (GAGs) are built from repeating disaccharide units. Hyaluronan, a relatively simple GAG, is shown here. It consists of a single long chain of up to 25,000 repeated disaccharide units, each carrying a negative charge (red). As in other GAGs, one of the sugar monomers (green) in each disaccharide unit is an amino sugar. Many GAGs have additional negatively charges, often from sulfate groups (not shown).

GAGS - FUNCTIONS

- GAGs are strongly hydrophilic and tend to adopt highly extended conformations, which occupy a huge volume relative to their mass. Thus GAGs act as effective “space fillers” in the extracellular matrix of connective tissues.
- their multiple negative charges attract a cloud of cations, such as Na+, that are osmotically active, causing large amounts of water to be sucked into the matrix. This gives rise to a swelling pressure, which is balanced by tension in the collagen fibers interwoven with the proteoglycans. When the matrix is rich in collagen and large quantities of GAGs are trapped in its meshes, both the swelling pressure and the counterbalancing tension are enormous. Such a matrix is tough, resilient, and resistant to compression. The cartilage matrix that lines the knee joint, for example, has this character: it can support pressures of hundreds of kilograms per square centimeter.
- They can form gels of varying pore size and charge density that act as filters to regulate the passage of molecules through the extracellular medium.
- They can bind secreted growth factors and other proteins that serve as extracellular signals for cells.
- They can block, encourage, or guide cell migration through the matrix.



Schematic drawing of the giant aggregate showing how it is built up from GAGs (red and blue) and proteins (green and black). The mass of such a complex can be 108 daltons or more, and it occupies a volume equivalent to that of a bacterium.