13.2: Collagen

The largest and most prominent of the extracellular matrix proteins, constituting a quarter of the dry mass of the human body, are the members of the collagen family. Collagens are polymers that can be categorized into fibrillar (e.g. collagens I, II, III) and non fibrillar (e.g. collagen IV) types. The fibrillar collagens are made up of triple helical monomers of either identical (homotrimer) or different (heterotrimer) subunits. These monomers are then associated in an offset parallel interaction with other collagen monomers, leading to the formation of long fibers. Electron microscopic examination of these long fibers shows a banding pattern, which is indicative of the slight gap between monomers along the same parallel.

Figure \(\PageIndex{2}\). Collagen is a triple-helical protein consisting of three fibrillar subunits. Some of the amino acids are hydroxylated, and the protein is also glycosylated (represented by purple hexagons).
Like all secreted proteins, collagen I is processed in the ER (Figure \(\PageIndex{2}\)), but not completely assembled there: the three pro-α-chains are assembled into a procollagen triple helix, which is secreted. Extracellularly, they must then be cleaved at both termini to form the active collagen protein, which is completely fibrillar. Other collagen types do not have the same cleavage, and may have globular domains at the ends of the fibrils. Collagens are also interesting for their unusual amino acid makeup. They contain a high proportion of hydroxylated amino acids, mostly prolines and lysines (Figure \(\PageIndex{3}\)). This hydroxylation is necessary for the extensive hydrogen bonding that occurs between subunits and between monomers. The fibrils are associated with high tensile strength. An example of this would be the long collagen fibers that run parallel to the long axis of tendons and ligaments. These high-stress-bearing structures (connecting bone to muscle, and bone to bone, respectively) require the resilience that collagen fibers can provide.

![Collagen amino acids](https://bio.libretexts.org/Bookshelves/Cell_and_Molecular_Biology/Book%3A_Cells_-_Molecules_and_Mechanisms_(Wong)/1…)

Conversely, conditions that adversely affect collagen formation can lead to serious disease conditions. In fact, a form of epidermolysis bullosa (the heritable skin blistering disease introduced in the previous chapter) is caused by mutation in collagen VII which is primarily produced by epidermal keratinocytes and secreted into the dermal-epidermal basement membrane layer. A variety of chondrodysplasias as well as bone malformations such as osteogenesis imperfecta (which can be perinatally lethal) have been linked to mutations in various collagen genes. Finally, several symptoms of scurvy are due to malformation of collagen in the ECM: weak blood vessel walls, bleeding gums and loose teeth, and fragile bones. Scurvy is a disease of ascorbic acid (vitamin C) deficiency, and the effect on ECM is due to the need for ascorbic acid as a cofactor for enzymes that hydroxylate the prolines and lysines of collagen.

Collagen is a major component of the basement membrane and basal lamina. The basal lamina is strong and flexible, able to serve as structural support for the epithelial sheets attached to it, as well as providing a semi-permeable matrix/filter that allows the passage of water and smaller molecules, but excludes larger macromolecules. The two major protein components to the basal lamina are collagen IV and laminin. Collagen IV has both long fibrillar, alpha-helical domains as well as globular domains that can interact in different orientations to form the meshwork that sets up the basement membrane. The laminin network is connected to the collagen network through entactin (nidogen) linker proteins.

An interesting application of collagen fibrils is in the cornea, the protective clear covering of the eye. The cornea is the primary protection against eye injury, and must be tough. The central layer (stroma, or substantia propria) is composed of approximately 200 layers of tightly packed, regularly spaced parallel collagen fibrils, with adjacent layers arranged so that the collagen fibrils lie perpendicularly from one layer to the next. This kind of laminar structure is used in a variety of man-made construction materials (including the ubiquitous building material, plywood) and provides great strength in a relatively small mass. Somewhat amazingly, and quite unlike plywood, the cornea is transparent. That property is thought to come from the regularity of the collagen lattice, which allows for cancellation of scattered light from one fibril.
by destructive interference from the scattered light of another fibril. Somewhat counterintuitively, it actually gets cloudy (due to refraction) when it absorbs fluid from the aqueous humor, and has active mechanisms to pump any such fluid back out of the cornea. This is why the cornea thickens and becomes translucent after death — the pump mechanism no longer has energy to run, and the aqueous humor diffuses into the cornea.

The reasoning behind the use of glucosamine and chondroitin sulfate supplements by people with joint problems is that they are two of the sugars found in proteoglycans of cartilaginous tissue such as the meniscus of the knee, and in other joints. Chondroitin sulfate in particular is the major sugar in articular cartilage proteoglycans. Both are thought to stimulate GAG synthesis, and limited documentation of protease inhibitory and collagen synthesis effects have been noted. Data from rabbit models (but potential conflict of interest, Lippiello et al, 2000) suggests a therapeutic benefit from such supplements. However, human studies have so far shown no significant improvement in patients already suffering from moderate to severe arthritis and other joint-related ailments (Clegg et al, 2006). A secondary survey analysis suggested that there was some promise with regard to effects on mild to moderate cases, but the data was not significant.