12.2: Intermediate Filaments

“Intermediate filaments” is actually a generic name for a family of proteins (grouped into 6 classes based on sequence and biochemical structure) that serve similar functions in protecting and shaping the cell or its components. Interestingly, they can even be found inside the nucleus. The nuclear filamins, which constitute class V intermediate filaments, form a strong protective mesh attached to the inside face of the nuclear membrane. Neurons have neurofilaments (class IV), which help to provide structure for axons — long, thin, and delicate extensions of the cell that can potentially run meters long in large animals. Skin cells have a high concentration of keratin (class I), which not only runs through the cell, but connects almost directly to the keratin fibers of neighboring cells through a type of cellular adhesion structure called a desmosome (described in the next chapter). This allows pressure that might be able to burst a single cell to be spread out over many cells, sharing the burden, and thus protecting each member. In fact, malformations of either keratins or of the proteins forming the desmosomes can lead to conditions collectively termed epidermolysis bullosa, in which the skin is extraordinarily fragile, blistering and breaking down with only slight contact, compromising the patient’s first line of defense against infection.

Most intermediate filaments fall between 50-100 kDa, including keratins (40-67 kDa), lamins (60-70 kDa), and neurofilaments (62-110 kDa). Nestin (class VI), found mostly in neurons, is an exception, at approximately 240 kDa.
Intermediate filaments are composed of linear subunits that wrap around each other and interact very tightly.

Structurally, as mentioned previously, all intermediate laments start from a fibrous subunit (Figure 2). This then coils around another filamentous subunit to form a coiled-coil dimer, or protofilament. These protofilaments then interact to form tetramers, which are considered the basic unit of intermediate filament construction. Using proteins called plectins, the intermediate laments can be connected to one another to form sheets and meshes. Plectins can also connect the intermediate laments to other parts of the cytoskeleton, while other proteins can help to attach the IF cytoskeleton to the cell membrane (e.g. desmoplakin). The most striking characteristic of intermediate filaments is their relative longevity. Once made, they change and move very slowly. They are very stable and do not break down easily. They are not usually completely inert, but compared to microtubules and microfilaments, they sometimes seem to be.

Epidermolysis bullosa simplex is a collection of congenital diseases caused by mutations to the keratin genes KRT5 or KRT14, or to the plectin gene PLEC1. These mutations either weaken the polymerization of keratin into filaments, or the interaction between keratin filaments. This leads to the inability of each individual cell to maintain structural integrity under pressure. Another type of EB, junctional epidermolysis bullosa (JEB), is caused by mutations to integrin receptors (b4, a6) or laminins. This includes JEB gravis or Herlitz disease, which is the most severe, often leading to early postnatal death. JEB is also related to dystrophic epidermolysis bullosa (DEB) diseases such as Cockayne-Touraine, each of which s due to a mutation in collagen type VII. The gene products involved in JEB and DEB are discussed in more detail in the next chapter. They play a role in adhering the cells to the basement membrane, and without them, the disorganization of the cells leads to incomplete connections between the epidermal cells, and therefore impaired pressure-sharing.

Some forms of Charcot-Marie-Tooth disease, the most common inherited peripheral nerve disease, are also linked to mutations of intermediate filament genes. This disease, also known as peroneal muscular atrophy or hereditary motor sensory neuropathy, is a non-lethal degenerative disease primarily affecting the nerves of the distal arms and legs. There is a broad variety of CMT types and causes, the most common being malformations of Schwann cells and the myelin sheath they form. CMT type 2 is characterized by malformations of the peripheral nerve axons, and is linked to mutations of lamin A proteins and of light neurofilaments. The causal mechanism has not yet been established; however, the neurofilaments are significant elements in maintaining the integrity of long axons.