11.1: Proteolytic Cleavage

The most common modification is proteolytic cleavage. Some of the pre-cleavage polypeptides are immediately cleaved, while others are stored as inactive precursors to form a pool of enzymes (or other kinds of proteins) that can be activated very quickly, on a timescale of seconds to minutes, as compared to having to go through transcription and translation, or even just translation. Interestingly, though methionine (Met) is universally the first amino acid of a newly synthesized polypeptide, many proteins have that methionine cleaved off (also true for some prokaryotic f-Met).

Figure \(\PageIndex{1}\). Proteolytic processing is necessary to make biologically active insulin. (A) The linear protein contains a signal sequence, which is cleaved after the protein enters the ER, an A chain, a B chain, and a C-peptide. (B) Inside the ER, the proinsulin (insulin precursor) folds and disulfide bonds form between cysteines. (C) Finally, two cleavages release the C peptide, which leaves the A and B chains attached by the disulfide bonds. This is now active insulin.

Activation of proteins by cleavage of precursors is a common theme: the precursor protein is termed a proprotein, and
the peptide that is cleaved off of it to activate the protein is called the propeptide. Among the better known examples of proteins that are derived from proproteins are the hormone insulin, the cell death protein family of caspases, and the Alzheimer-associated neural protein β-amyloid. Insulin is an interesting example (Figure \(\PageIndex{1}\)) in mammals: preproinsulin (inactive as a hormone) is first translated from the insulin mRNA. After a cleavage that removes an N-terminal sequence, proinsulin (still inactive) is generated. The proinsulin forms some internal disulfide bonds, and when the final proteolytic action occurs, a substantial chunk (called the C-peptide) is taken out of the middle of the proinsulin. Since the protein was internally disulfide bonded though, the two end pieces remain connected to become the active insulin hormone.

Another interesting protein processing example is that of collagen assembly (Figure \(\PageIndex{2}\)). As you will read in chapter 13, collagen is a very large secreted protein that provides structure and shock absorbance for the extracellular matrix in animals. You can find it in skin, hooves, cartilage, and various connective tissues. An individual collagen protein is actually a twisted triple-helix of three subunits. The collagen subunits are made as procollagen, and propeptides are lopped off of both N- and C- termini to generate the final protein. However, they are not cleaved off until after the three subunits assemble around one another. In fact, collagen subunits that have already been processed do not assemble into triple-helical proteins. The propeptide sequences are clearly necessary for efficient assembly of the final protein complex.