4.2: Insulin

Insulin is a polypeptide that is naturally synthesized by the pancreas. Insulin is comprised of two polypeptide chains called Chain A (21 amino acids) and Chain B (30 amino acids) with a combined molecular weight of ~6 kDa. Additionally, there are three critical di-sulfide linkages within insulin:

- Intramolecular: Cys6 (Chain A) and Cys11 (Chain A)
- Intermolecular: Cys7 (Chain A) with Cys7 (Chain B)
- Intermolecular: Cys20 (Chain A) and Cys19 (Chain B)

Insulin is biosynthesized as a single polypeptide chain in the β-cells of the pancreas. The ribosomes generate the polypeptide with four continuous segments which is called **preproinsulin**. (Figure 4.5) The N-terminal segment contains the signal sequence for the excretory pathway, and it is cleaved from the main protein segment in the rough endoplasmic reticulum (the polypeptide is now called **proinsulin**). This enables the protein to fold over on itself and form the three characteristic di-sulfide bridges. In the trans-Golgi network, the proinsulin peptide is cleaved at two sites to give the final insulin molecule. This is the version of the protein that is excreted by the pancreas beta cells and travels through the blood stream.

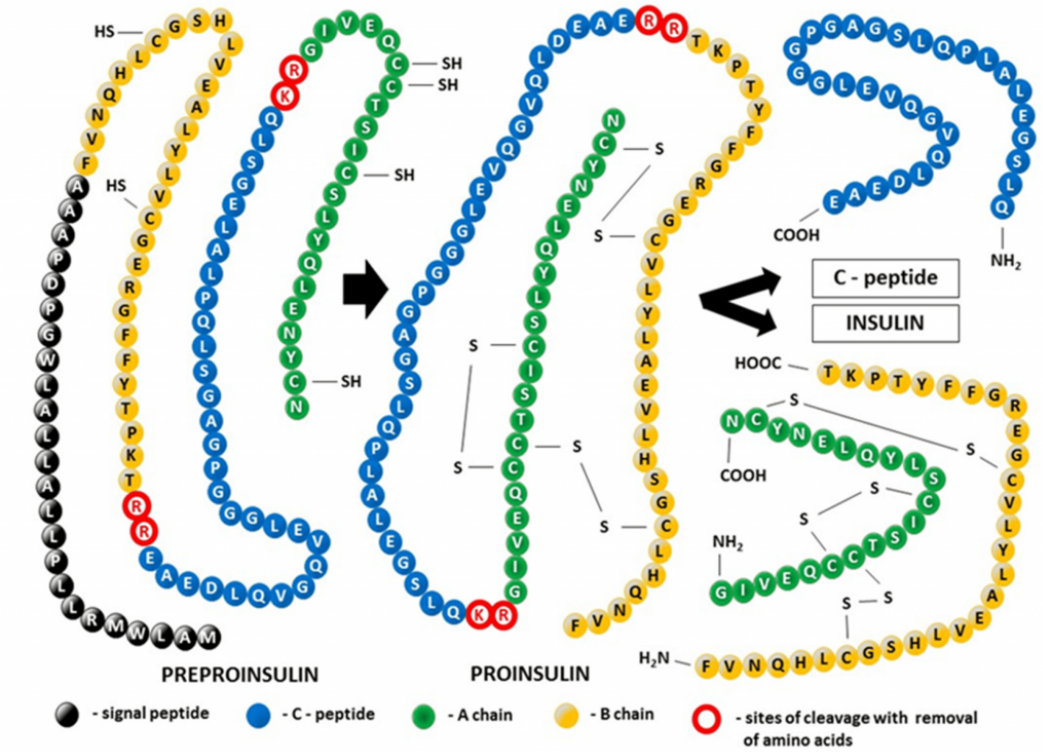

Figure 4.5 Multiple cleavage steps of preproinsulin lead to the active insulin signalling protein. Image source: (Fig 1) by Dariusz Szukiewicz is used under a CC-BY 4.0 license.

Insulin biosynthesis occurs in the pancreas, and results in very high intracellular concentrations. β-Cells also maintain a relatively high concentration of Zn^{2+} ions and, coupled to the high concentration of insulin, this causes the insulin peptides to crystallize around the Zn^{2+} ions. The crystals exhibit a 3-fold symmetry. There are two Zn^{2+} ions at the centre of the polymer along with 6 insulin molecules surrounding these ions (i.e. a trimer of dimers). Specific histidine residues from chain B on insulin coordinate the Zn^{2+} ions. (Figure 4.6)

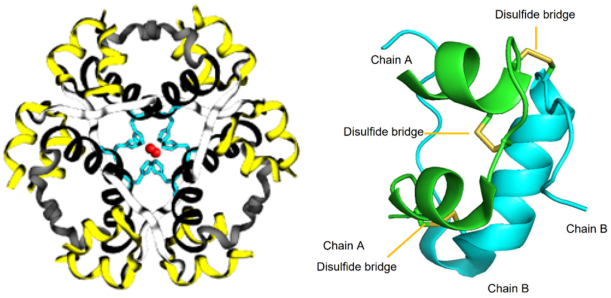

Figure 4.6 Insulin monomers combine to form insulin hexamers that coordinate a central zinc ion. Image Source: (Fig 1) by Beatrice Rosetti and Silvia Marchesan is used under a CC-BY 4.0 license & (Fig 2) by Harish Vashisth has been modified (cropped) and is used under a CC-BY 4.0 license.

These hexamers become extremely important pharmacologically. In particular, the insulin hexamers are inactive and cannot perform their natural biological function in this state. However, when the pancreas releases insulin into the blood stream, the concentration of Zn^{2+} is substantially diluted, and the hexamers rapidly dissociate into monomers and become active. Therefore, the equilibrium and transition from insulin hexamers to monomers is critical. The cellular vessels that store insulin are also quite acidic which further reduces the solubility and increases the crystalline packing of insulin. Insulin has a very short half-life in the blood (~3-10 min) and is rapidly degraded. Therefore, the effects of insulin are short-lived but extremely potent.
