6.5: Glycogen Synthesis

Although glucose is the primary fuel for cells, it is not an efficient molecule for long-term storage in complex (i.e. greater than single-celled) organisms. Therefore, in both plants and animals, the glucose molecules are linked together to form polysaccharides known as glucans. In animals, the glucan formed is glycogen, which consists of glucose molecules linked by α(1->4) glycosidic bonds, and branching α(1->6) bonds approximately between 8 to 14 residues apart. The average size of a glycogen unit is a cytoplasmic granule containing over 100000 glucose molecules. The addition of a glucose-1-phosphate to another (or to a glycogen chain) is energetically unfavorable, so it must be coupled with a sufficiently exergonic reaction to proceed.

Glycogen synthesis begins with UDP-glucose phosphorylase, which combines the nucleotide uridine triphosphate (UTP) with glucose-1-phosphate to release pyrophosphate (PP\(_i\)) and form UDP-glucose.

The phosphoenolpyruvate exchange reaction catalyzed by UDP-glucose phosphorylase is minimally exergonic. However, the pyrophosphate released is quickly hydrolyzed by inorganic pyrophosphatase, a ubiquitous cytosolic enzyme, in a highly exergonic reaction. This pyrophosphate hydrolysis is a mechanism utilized in many biosynthetic pathways to provide energy for otherwise endergonic reactions.
In the next step, glycogen synthase attaches the UDP-glucose to the pre-existing glycogen chain with an α(1->4) linkage. It cannot join two individual glucoses together, only add to a pre-existing chain. This means that there must be some workaround for the first two glucoses: glycogenin is an enzyme that catalyzes the addition of UDP-glucose to itself, and can do so for up to seven UDP-glucose molecules, thus forming a short primer for glycogen synthase to work with. Furthermore, glycogen synthase can only add glucoses with an α(1->4) link. For branching to occur, a branching enzyme (specifically, amylo-(1,4->1,6)-transglycosylase is needed. This enzyme can transfer terminal chain segments to the 6-carbon hydroxyl of any glucose in a glycogen chain. However, the branches can only be added if there are at least 4 glucose residues between them, and if the originating chain was at least 11 residues in length.

Oligosaccharide Synthesis

Like glycogen synthesis, oligosaccharide synthesis also requires the initial step of coupling the sugar with a nucleotide. In mammals, a major disaccharide is lactose, which is the linkage of a galactose and a glucose, and the formation is catalyzed by lactose synthase. However, before the lactose synthase is able to act, the galactose must first be in the form of a UDP-galactose. Similarly, in plants, the major disaccharide is sucrose, formed by the linkage of UDP-glucose and fructose-6-phosphate. This results in sucrose-6-phosphate, which is then readily dephosphorylated to sucrose. These kinds of mechanisms are also used in the glycosylation of proteins and lipids, which will be discussed primarily in the protein processing and trafficking chapter.

Mutation of galactose-1-phosphate uridylyltransferase or mutations of other enzymes in this pathway (uridylyl transferase mutations are most common and usually most severe) can lead to galactosemia, a human genetic disease whose symptoms begin in infancy and may include mental retardation, liver damage, jaundice, vomiting, and lethargy. The cause of these symptoms is generally a buildup of galactose-1-phosphate, especially in the liver and nervous tissue. Fortunately, with early diagnosis, the symptoms can be prevented by avoiding milk products (lactose).

The major hexose species besides glucose are fructose, mannose, and galactose. Interconversion between these hexoses can occur via intermediates, as demonstrated in glycolysis (glucose-6-P to fructose-6-P). Mannose-6-P can be converted to fructose-6-P by phosphomannose isomerase. Galactose can be converted similarly, to galactose-1-P and then to glucose-1-P. The galactose to glucose conversion can also take place by epimerization of UDP-Glucose to UDP-galactose via intermediate redox using NAD⁺/NADH.