6.3: The Pentose Phosphate Pathway

NADPH is found not only in plants, but in animal cells as well. Although our first discussion of NADPH was in the context of photosynthesis, it is also a general reducing agent in any cell. It is also crucial to note that though introductory texts often consider NAD⁺/NADH and NADP/NADPH similarly as high energy electron carriers, and although they are structurally differentiated only by a phosphate group (on the 2'-OH of adenosine), they are not interchangeable in the metabolic pathways of a cell. NADP/NADPH is used in reductive metabolic pathways, whereas NAD⁺/NADH is used in oxidative pathways. With such an important role in biosynthesis, it is no surprise that its production is part of a major metabolic pathway, the pentose phosphate pathway (figure 7), also called the phosphogluconate pathway, and the hexose monophosphate shunt.

In step 1 of this pathway, glucose-6-phosphate and NADP⁺ are bound to glucose-6-phosphate dehydrogenase, which transfers a hydride ion from glucose-6-phosphate to NADP⁺ to form 6-phosphoglucono-d-lactone and NADPH.

In step 2, the 6-phosphoglucono-d-lactone is hydrolyzed to 6-phosphogluconate using 6-phosphogluconolactonase. This reaction actually proceeds fairly quickly even without the enzyme.
In step 3, the 6-phosphogluconate is decarboxylated by 6-phosphogluconate dehydrogenase, in the process producing more NADPH, as well as the five-carbon sugar, ribulose-5-phosphate. This metabolite is used by the cell as the basis for nucleotide synthesis. This concludes the NADPH-producing portion of the pentose phosphate pathway.

However, it is useful, in the context of this chapter, to also consider the fate the Ru5P, which is converted to ribose-5-P by ribulose-5-P isomerase or it is converted to xylulose-5-phosphate using ribulose-5-P epimerase. The ribose-5-phosphate is used in nucleotide synthesis, so plays an important role in not only nucleic acid production, but general metabolism (e.g. for ATP).

Ribulose-5-phosphate and NADPH are the most significant products of this pathway. As mentioned earlier, NADPH is important as a general reducing agent. The mechanism for this involves glutathione and glutathione reductase. Glutathione is the primary scavenger of reactive oxygen species such as oxides and peroxides, and the key regulator of cellular oxidative stress. The reduced form of the glutathione tripeptide (Glu-Cys-Gly) dimerizes with another glutathione via disulfide bond as they donate electrons to oxidizers, and is regenerated by glutathione reductase. NADPH is a necessary cofactor for glutathione reductase activity, providing the electrons to reduce the G-S-S-G dimer.
Figure 7. The pentose phosphate pathway. The first three reactions generate the energy carrier NADPH in the process of converting glucose-6-phosphate to ribulose-5-phosphate. The Ru5P is important as a precursor to nucleotide synthesis, as well as for production of other sugars and important metabolic intermediates, such as fructose-6-phosphate and glyceraldehyde-3-phosphate. Transketolase then transfers the terminal two carbons of ribulose-5-P to xylulose-5-P, making sedoheptulose-7-phosphate and G3P. Transaldolase comes up next. It transfers a 3-carbon unit from sedoheptulose-7-P to the G3P, forming erythrose-4-phosphate and fructose-6-phosphate. Transketolase is used again at this point, transferring a 2-carbon unit from xylulose-5-phosphate to erythrose-4-phosphate and generating more G3P and fructose-6-P.