7.1: Pentose phosphate pathway

The pentose phosphate pathway (PPP — also known as the hexose monophosphate shunt) is a cytosolic pathway that interfaces with glycolysis. In this pathway, no ATP is directly produced from the oxidation of glucose 6-phosphate; instead the oxidative portion of the PPP is coupled to the production of NADPH. In addition to generating NADPH, which is essential for detoxification reactions and fatty acid synthesis, it also produces five-carbon sugars required for nucleotide synthesis.

Oxidative and nonoxidative functions

There are two parts of the pathway that are distinct and can be regulated independently. The first phase, or oxidative phase, consists of two irreversible oxidations that produce NADPH. As noted above, NADPH is required for reductive detoxification and fatty acid synthesis. (NADPH is not oxidized in the ETC.) In the red blood cell, this is extremely important as the PPP pathway provides the only source of NADPH. NADPH is essential to maintain sufficient levels of reduced glutathione in the red blood cell. Glutathione is a tripeptide commonly used in tissues to detoxify free radicals and reduce cellular oxidation.

The nonoxidative phase of the pathway allows for the conversion of ribulose 5-phosphate into ribose 5-phosphate, which is needed for nucleotide synthesis (figure 7.1). All of these interconversions in the nonoxidative pathway are reversible and use the enzymes transketolase or transaldolase to move two-carbon or three-carbon units on to other sugar moieties to generate a variety of sugar intermediates. Transketolase requires thiamine pyrophosphate (TPP) as a cofactor. This is of clinical relevance as TPP levels can be measured by addressing the activity of transketolase in a blood sample. A reduction in transketolase activity is an indicator of a thiamine deficiency.
Figure 7.1: Overview of the pentose phosphate pathway and its interface with glycolysis.

Any compounds unused by the nonoxidative pathway will eventually be converted to fructose 6-phosphate or glyceraldehyde 3-phosphate, both of which will re-enter the glycolytic pathway (figures 7.1 and 7.2).

Figure 7.2: Pentose phosphate pathway and its connection to glycolysis and glutathione synthesis.
Regulation of the pentose phosphate pathway

The key regulatory enzyme for the pentose phosphate pathway is within the oxidative portion. Glucose 6-phosphate dehydrogenase oxidizes glucose 6-phosphate to 6-phosphogluconolactone, and is regulated by negative feedback. In this two-step reaction NADPH is also produced, and high levels of NADPH will inhibit the activity of glucose 6-phosphate dehydrogenase. This ensures NADPH is only generated as needed by the cell; this is the primary regulatory mechanism within the pathway.

The nonoxidative phase is not regulated; however, in conditions where there is a high demand for nucleotide production (such as in the case for highly proliferative cells), the nonoxidative part of the pathway can function independently of the oxidative phase to produce ribose 5-phosphate from the glycolytic intermediates fructose 6-phosphate and glyceraldehyde 3-phosphate (figure 7.2).

Requirement of the pentose phosphate pathway in RBCs

The two essential products of this pathway are NADPH and ribose 5-phosphate. NADPH is a high-energy compound often used for reductive biosynthesis as it cannot be oxidized in the ETC. It is also used by many tissues to scavenge (and detoxify) reactive oxygen species (ROS) before causing cellular damage. This is especially important in red blood cells; RBCs lack malic enzyme, making this the only pathway that can generate NADPH. A lack of NADPH in RBCs (such as due to a glucose 6-phosphate dehydrogenase deficiency) can cause excessive hemolysis, leading to the clinical presentation of jaundice (figure 7.3).

Glutathione (GSH) is a tripeptide compound consisting of glutamate, cysteine, and glycine. It plays a key role in scavenging reactive oxygen species (ROS), which cause both DNA and cellular/protein damage. Reduction of GSH in the red blood cell is done exclusively through a series of oxidation reduction reactions using NADPH. The loss of NADPH in RBCs therefore increases ROS and can lead to hemolysis (figure 7.3).

Summary of pathway regulation

<table>
<thead>
<tr>
<th>Metabolic pathway</th>
<th>Major regulatory enzyme</th>
<th>Allosteric effectors</th>
<th>Hormonal effects</th>
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<td>Pentose phosphate pathway</td>
<td>Glucose 6-phosphate dehydrogenase</td>
<td>NADPH (-)</td>
<td>None</td>
</tr>
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</table>

Table 7.1: Summary of pathway regulation.
References and resources

Text


Figures

Grey, Kindred, Figure 7.2 Pentose pathway and its connection to glycolysis and glutathione synthesis. 2021. [https://archive.org/details/7.2_20210926, CC BY 4.0](https://archive.org/details/7.2_20210926).

Lieberman M, Peet A. Figure 7.1 Overview of the pentose phosphate pathway and its interface with glycolysis. Adapted under Fair Use from Marks’ Basic Medical Biochemistry. 5th Ed. pp 543. Figure 27.1 Overview of the pentose phosphate pathway. 2017.

Lieberman M, Peet A. Figure 7.3 NADPH in the red blood cell as a means of reducing glutathione. Adapted under Fair Use from Marks' Basic Medical Biochemistry. 5th Ed. pp 549. Figure 27.7 Hemolysis caused by reactive oxygen species (ROS). 2017.