Pentose phosphate pathway

The **pentose phosphate pathway** (also called the **phosphogluconate pathway** and the **hexose monophosphate shunt**) is a metabolic pathway parallel to glycolysis. It generates NADPH and pentoses (5-carbon sugars) as well as ribose 5-phosphate, a precursor for the synthesis of Nucleotides. While the pentose phosphate pathway does involve oxidation of glucose, its primary role is anabolic rather than catabolic. The pathway is especially important in red blood cells (erythrocytes).

There are two distinct phases in the pathway. The first is the oxidative phase, in which NADPH is generated, and the second is the non-oxidative synthesis of 5-carbon sugars. For most organisms, the pentose phosphate pathway takes place in the cytosol; in plants, most steps take place in plastids.[1]

Similar to glycolysis, the pentose phosphate pathway appears to have a very ancient evolutionary origin. The reactions of this pathway are mostly enzyme-catalyzed in modern cells, however, they also occur non-enzymatically under conditions that replicate those of the Archean ocean, and are catalyzed by metal ions, particularly ferrous ions (Fe(II)).[2] This suggests that the origins of the pathway could date back to the prebiotic world.

The primary results of the pathway are:

- The generation of reducing equivalents, in the form of NADPH, used in reductive biosynthesis reactions within cells (e.g. fatty acid synthesis).
- Production of ribose 5-phosphate (R5P), used in the synthesis of nucleotides and nucleic acids.
- Production of erythrose 4-phosphate (E4P) used in the synthesis of aromatic amino acids.

Aromatic amino acids, in turn, are precursors for many biosynthetic pathways, including the lignin in wood.[

Dietary pentose sugars derived from the digestion of nucleic acids may be metabolized through the pentose phosphate pathway, and the carbon skeletons of dietary carbohydrates may be converted into glycolytic/gluconeogenic intermediates.

In mammals, the PPP occurs exclusively in the cytoplasm. In humans, it is found to be most active in the liver, mammary glands, and adrenal cortex.[The PPP is one of the three main ways the body creates molecules with reducing power, accounting for approximately 60% of NADPH production in humans.[

One of the uses of NADPH in the cell is to prevent oxidative stress. It reduces glutathione via glutathione reductase, which converts reactive H_2O_2 into H_2O by glutathione peroxidase. If absent, the H_2O_2 would be converted to hydroxyl free radicals by Fenton chemistry, which can attack the cell. Erythrocytes, for example, generate a large amount of NADPH through the pentose phosphate pathway to use in the reduction of glutathione.

Phases

Oxidative phase

In this phase, two molecules of $NADP^+$ are reduced to NADPH, utilizing the energy from the conversion of glucose-6-phosphate into ribulose 5-phosphate.

Oxidative phase of pentose phosphate pathway.

Glucose-6-phosphate (**1**), 6-phosphoglucono-δ-lactone (**2**), 6-phosphogluconate (**3**), ribulose 5-phosphate (**4**)

The entire set of reactions can be summarized as follows:

Reactants	Products	Enzyme	Description
Glucose 6-phosphate + NADP+	→ 6-phosphoglucono-δ-lactone + **NADPH**	glucose 6-phosphate dehydrogenase	Dehydrogenation. The hydroxyl on carbon 1 of glucose 6-phosphate turns into a carbonyl, generating a lactone, and, in the process, NADPH is generated.
6-phosphoglucono-δ-lactone + H_2O	→ 6-phosphogluconate + H^+	6-phosphogluconolactonase	Hydrolysis
6-phosphogluconate + $NADP^+$	→ ribulose 5-phosphate + **NADPH** + CO_2	6-phosphogluconate dehydrogenase	Oxidative decarboxylation. $NADP^+$ is the electron acceptor, generating another molecule of NADPH, a CO_2, and ribulose 5-phosphate.

The overall reaction for this process is:

Glucose 6-phosphate + 2 $NADP^+$ + H_2O → ribulose 5-phosphate + 2 NADPH + 2 H^+ + CO_2

The pentose phosphate pathway's nonoxidative phase

Reactants	Products	Enzymes
ribulose 5-phosphate	→ ribose 5-phosphate	Ribose-5-phosphate isomerase
ribulose 5-phosphate	→ xylulose 5-phosphate	Ribulose 5-Phosphate 3-Epimerase
xylulose 5-phosphate + ribose 5-phosphate	→ glyceraldehyde 3-phosphate + sedoheptulose 7-phosphate	transketolase
sedoheptulose 7-phosphate + glyceraldehyde 3-phosphate	→ erythrose 4-phosphate + fructose 6-phosphate	transaldolase
xylulose 5-phosphate + erythrose 4-phosphate	→ glyceraldehyde 3-phosphate + fructose 6-phosphate	transketolase

Net reaction: 3 ribulose-5-phosphate → 1 ribose-5-phosphate + 2 xylulose-5-phosphate → 2 fructose-6-phosphate + glyceraldehyde-3-phosphate

Pentose phosphate pathway

Every living organism has a set of blueprints in each of their cells called DNA and RNA. These blueprints are essential for life because they are the information on how to build the protein structures that make up each and everyone of us. Given the structural and functional importance of DNA and RNA for all living things, there are many layers of quality control to help avoid and correct mistakes when DNA and RNA are initially made.

While the products of glycolysis are sent through the rest of cellular respiration to produce energy, there is also an alternative branch off glycolysis to produce the sugars that make up DNA and RNA. This pathway, called the Pentose Phosphate Pathway, is special because no energy in the form of ATP, or adenosine triphosphate, is produced or used up in this pathway.

How does it happen?

Similarly to some of the processes in cellular respiration, the molecules that go through the pentose phosphate pathway are mostly made of carbon. The easiest way to understand this pathway is to follow the carbon.

The breakdown of the simple sugar, glucose, in glycolysis provides the first 6-carbon molecule required for the pentose phosphate pathway. During the first step of glycolysis, glucose is transformed by the addition of a phosphate group, generating glucose-6-phosphate, another 6-carbon molecule. The pentose phosphate pathway can use any available molecules of glucose-6-phosphate, whether they are produced by glycolysis or other methods.

Now, we are ready to enter the first of two phases of the pentose phosphate pathway: 1) The oxidative phase and 2) The non-oxidative phase.

The oxidative phase:

The "oxidative" word of this phase comes from the process of oxidation. Oxidation is the breakdown of a molecule as it loses at least one of its electrons.This phase is made up of 2 irreversible steps:

Step 1:

Glucose-6-phosphate is oxidized to form lactone. NADPH is produced as a byproduct of this reaction as NADP^++start superscript, plus, end superscript is reduced as glucose-6-phosphate is oxidized. Following the oxidation of glucose-6-phosphate, another reaction, catalyzed by a different enzyme, uses water to form 6-phosphogluconate, the linear product.

NADPH is similar in structure and function as the high energy electron shuttle, NADH, mentioned in the cellular respiration articles. NADPH has an added phosphate group and is used in the cell to donate its electrons, just like NADH. Once NADPH has donated its electrons it is said to be oxidized (oxidation = loss of electrons) and is now symbolized as, NADP^++start superscript, plus, end superscript. NADPH is often used in reactions that build molecules and occurs in a high concentration in the cell, so that it is readily available for these types of reactions.

Step 1: Oxidative phase

Step 2:

Next, a carbon is removed (cleaved) and CO_22start subscript, 2, end subscript is released. Once again, the electrons released from this cleavage is used to reduce NADP^++start superscript, plus, end superscript to NADPH. This new 5-carbon molecule is called ribulose-5-phosphate.

Step 2: Oxidative phase

The non-oxidative phase:

The non-oxidative phase is really handy because these reactions are *reversible*. This allows different molecules to enter the pentose phosphate pathway in different areas of the non oxidative phase and be transformed up until the first molecule of the non-oxidative phase (ribulose-5-phosphate). Ribulose-5-phosphate is the precursor to the sugar that makes up DNA and RNA, and is also a product of the oxidative stage.

Step 3:

Ribulose-5-phosphate can be converted into two different 5-carbon molecules. One is the sugar used to make up DNA and RNA called, *ribose*-5-phosphate and this is the molecule we will focus on. *Ribulose*-5-phosphate isn't being divided because the carbon count is the same in the next step.

Step 3: Non-oxidative phase

Step 4:

The rest of the cycle is now made up of different options that depend on the cell's needs. The ribose-5-phosphate from step 3 is combined with another molecule of ribose-5-phosphate to make one, 10-carbon molecule. Excess ribose-5-phosphate, which may not be needed for nucleotide biosynthesis, is converted into other sugars that can be used by the cell for metabolism.

The 10-carbon molecule is interconverted to create a 3-carbon molecule and a 7-carbon molecule. The 3-carbon product can be shipped over to glycolysis if it needs. That being said, recall that we can also work our way back up to another molecule in this phase. So that 3-carbon molecule could also be shipped over from glycolysis and transformed into ribose-5-phosphate for DNA and RNA production.

Step 5:

The 3-carbon molecule and the 7-carbon molecule, from the interconversion above in step 4, interconvert again to make a new 4-carbon molecule and 6-carbon molecule. The 4-carbon molecule is a precursor for amino acids, while the 6-carbon molecule can be used in glycolysis. The same reversal of steps in option 4 can happen here as well.

Overview of pentose phosphate pathway

The pentose phosphate pathway takes place in the cytosol of the cell, the same location as glycolysis. The two most important products from this process are the ribose-5-phosphate sugar used to make DNA and RNA, and the NADPH molecules which help with building other molecules.

- **Consider the following**

  NADPH is readily available to donate its electrons in the cell because it occurs in such high concentration. Aside from helping build molecules, what kind of benefit is this really for the cell? NADPH is able to donate its electrons to compounds that fight dangerous oxygen molecules. These compounds are called antioxidants and you've probably heard about them being in some foods. Antioxidants donate electrons to neutralize dangerous oxygen radicals (super reactive oxygen molecules). Once they have given away their electrons, antioxidants need to quickly reload in case there are more oxygen radicals. NADPH is able to give antioxidants their constant flow of electrons to fight oxygen crime.

Reactions of the Pentose Phosphate Pathway