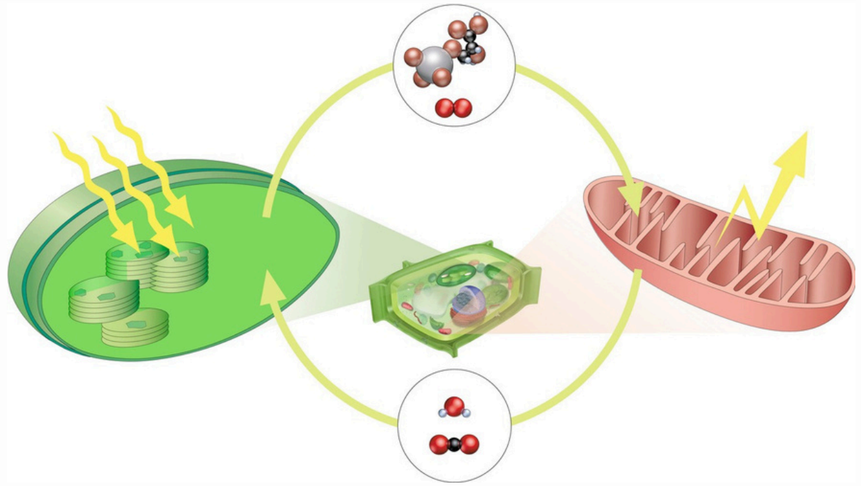
AL-FARABI KAZAKH NATIONAL UNIVERSITY
FACULTY OF BIOLOGY AND BIOTECHNOLOGY
DEPARTMENT OF BIOTECHNOLOGY



Lecture 4

The Pentose Phosphate Pathway

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Lecture Plan

1. What is the Pentose Phosphate Pathway?
2. Why is the pathway important?
3. Cellular location
4. Overall pathway and main products
5. Oxidative phase
6. Non-oxidative phase
7. Regulation of the pathway
8. Relationship between PPP and glycolysis
9. Physiological significance

CONTENTS

Learning objectives

Bytheend of the lecture, students should be ableto:

1. Define the Pentose Phosphate Pathway.
2. Explain the main functions of the pathway.
3. Identify the cellular location of the PPP.
4. Distinguish between the oxidative and non-oxidative phases.
5. Identify the major substrates, intermediates and products of each phase.
6. Explain the role of NADPH in cellular metabolism.
7. Explain the importance of ribose-5-phosphate for nucleotide synthesis.
8. Identify the key regulatory enzyme of the oxidative phase.
9. Explain the relationship between the PPP and glycolysis.
10. Describe the physiological importance of the pathway in different tissues.
11. Explain the role of the PPP in protection against oxidative stress.
12. Describe the biochemical basis of G6PD deficiency.

Definition of PPP

The Pentose Phosphate Pathway (PPP) is an alternative pathway for the metabolism of glucose-6-phosphate.

Unlike glycolysis, its primary purpose is not ATP production.

The pathway provides two important products:

NADPH

Used for:

- reductive biosynthesis;
- antioxidant defense;
- maintaining reduced glutathione.

Ribose-5-phosphate

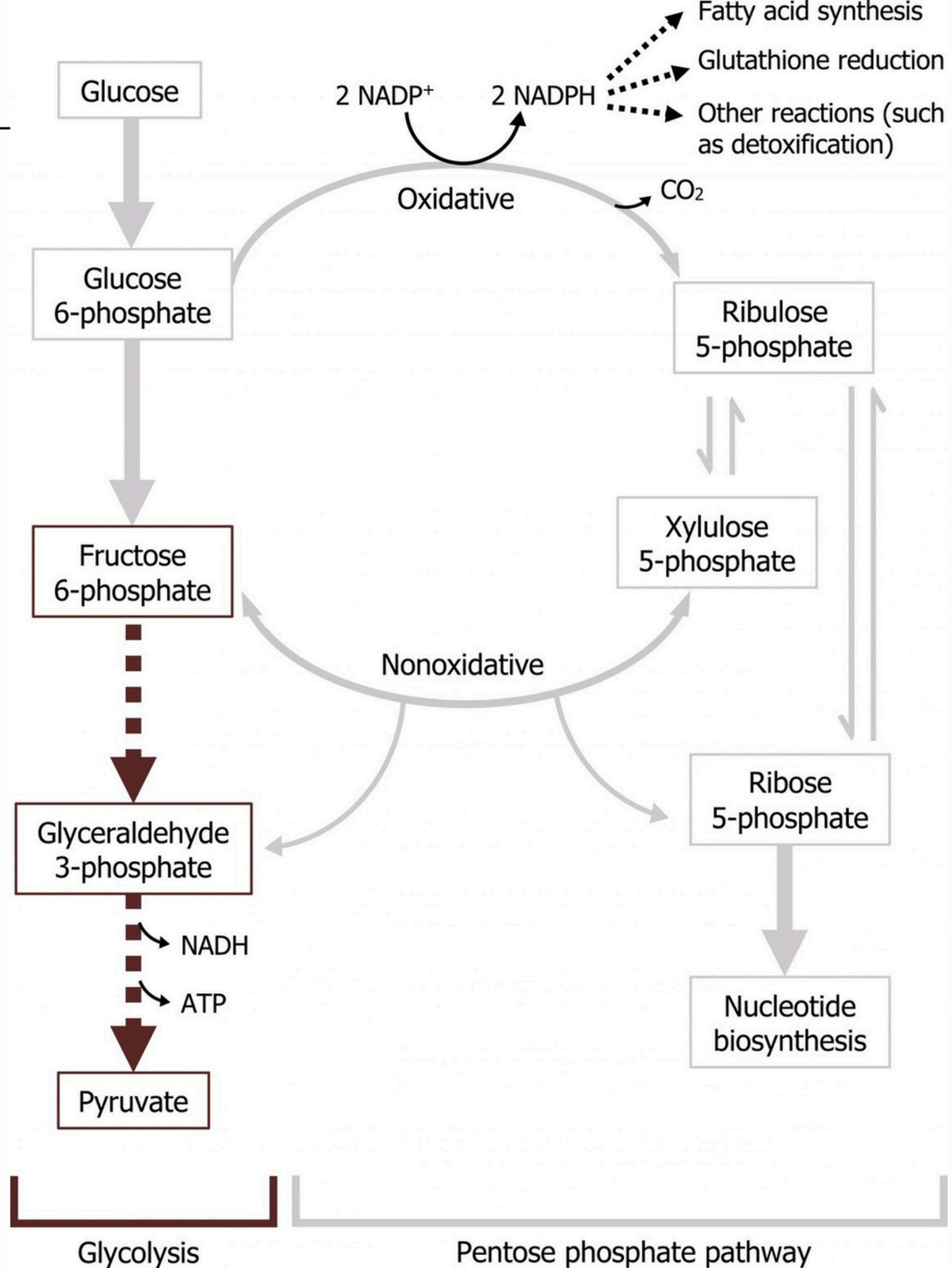
Required for:

- nucleotide synthesis;
- DNA synthesis;
- RNA synthesis.

The Pentose Phosphate Pathway occurs in the:
Cytosol
It is particularly active in tissues that require large amounts of NADPH or ribose-5-phosphate.
Examples include:

- Liver
- Adipose tissue
- Adrenal cortex
- Gonads
- Lactating mammary glands
- Red blood cells

The pathway begins with:
Glucose-6-phosphate
and has two major phases:
Glucose-6-phosphate
↓
Oxidative Phase
↓
NADPH + Ribulose-5-phosphate + CO_2
↓
Non-oxidative Phase
↓
Ribose-5-phosphate / Glycolytic intermediates
The two major functions are:
NADPH production
and
Pentose sugar production



The pathway is important because cells need NADPH and pentose sugars for different metabolic processes.

NADPH is required for:

- fatty acid synthesis;
- cholesterol synthesis;
- steroid hormone synthesis;
- maintenance of reduced glutathione;
- protection against reactive oxygen species.

Ribose-5-phosphate is required for:

- nucleotide synthesis;
- DNA synthesis;
- RNA synthesis.

Therefore, the PPP supports both:

Biosynthesis and Cellular antioxidant defense

Two PhasesofthePentosePhosphatePathway

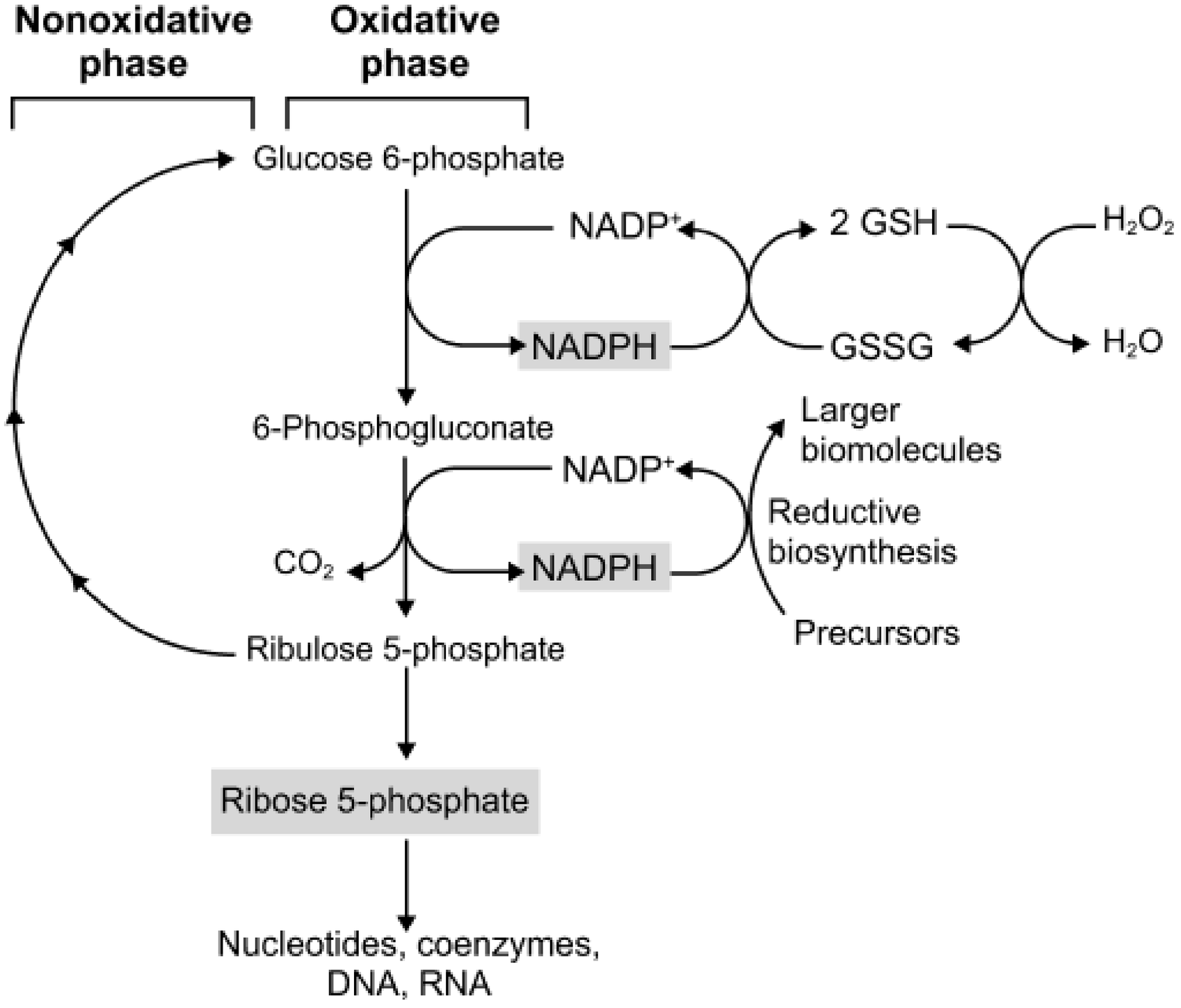
The PPP consists of two interconnected phases:

1. Oxidative Phase

- Irreversible
- Produces NADPH
- Releases CO_2
- Produces ribulose-5-phosphate

2. Non-oxidative Phase

- Reversible
- Rearranges pentose phosphates
- Produces ribose-5-phosphate
- Can produce glycolytic intermediates


Nonoxidative phase
Oxidative phase
Glucose 6-phosphate
NADP+
NADPH
2 GSH
GSSG
H2O2
H2O
6-Phosphogluconate
NADP+
NADPH
CO2
Larger biomolecules
Reductive biosynthesis
Precursors
Ribulose 5-phosphate
Ribose 5-phosphate
Nucleotides, coenzymes, DNA, RNA

Oxidative phase

The oxidative phase is the first part of the Pentose Phosphate Pathway. It converts glucose-6-phosphate into a five-carbon sugar and, most importantly, generates NADPH.

Unlike glycolysis, this phase does not produce ATP.
The main outcomes are:

- NADPH – provides reducing power for biosynthetic and antioxidant reactions.
- Ribulose-5-phosphate – a five-carbon sugar that can be used in the next phase.
- CO_2 – released during oxidative decarboxylation.

The most important product of the oxidative phase is NADPH.
NADPH is different from NADH, even though both molecules carry high-energy electrons.
NADH
Mainly supports ATP production through the electron transport chain.
NADPH
Mainly provides reducing power for:

- fatty acid synthesis;
- cholesterol synthesis;
- steroid hormone synthesis;
- maintenance of antioxidant systems;
- protection against oxidative stress.

Simple way to remember:

NADH → energy production
NADPH → biosynthesis + protection

Reaction 1: Glucose-6-Phosphate Dehydrogenase

Glucose-6-phosphate→ 6-Phosphoglucono-δ-lactone
Enzyme: Glucose-6-phosphate dehydrogenase (G6PD)
This is the first reaction of the PPP and the main regulatory point of the pathway.
During the reaction:
$NADP^+$ → NADPH
The activity of G6PD reflects how much NADPH the cell needs.
When NADPH is being consumed rapidly, $NADP^+$ increases and stimulates the pathway.
When NADPH is already abundant, the pathway slows down.

G6PD is the rate-limiting enzyme of the oxidative phase

Reaction 2: Formation of 6-Phosphogluconate

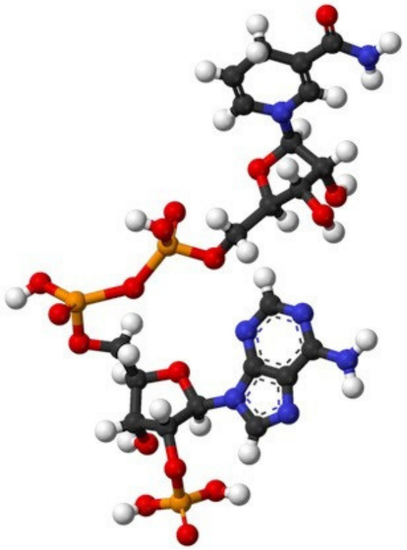
6-Phosphoglucono-δ-lactone → 6-Phosphogluconate
Enzyme: 6-Phosphogluconolactonase
This reaction prepares the molecule for the next oxidative step.
Water is added to the lactone structure, producing 6-phosphogluconate.
This reaction does not generate NADPH directly. It prepares the intermediate for the reaction that follows.

Reaction 3: Oxidative Decarboxylation

6-Phosphogluconate→ Ribulose-5-phosphate
Enzyme: 6-Phosphogluconate dehydrogenase
This is another important oxidative reaction.
Three things happen:

- the molecule is oxidized;
- $NADP^+$ is reduced to NADPH;
- one carbon is removed as CO_2.

Final products:
Ribulose-5-phosphate + NADPH + CO_2



The oxidative phase produces the two main products of the Pentose Phosphate Pathway: **NADPH and ribulose-5-phosphate.**

NADPH provides reducing power for fatty acid, cholesterol and steroid synthesis and helps protect cells from oxidative stress.

Ribulose-5-phosphate enters the non-oxidative phase and can be converted into other pentose phosphates.

During the pathway, CO_2 is also released.

Main products: 2 NADPH + ribulose-5-phosphate + CO_2

The non-oxidative phase is the second part of the Pentose Phosphate Pathway. Unlike the oxidative phase, it does not produce NADPH and does not involve the release of carbon dioxide. Instead, its main function is to rearrange five-carbon sugar phosphates according to the metabolic needs of the cell.

During this phase, ribulose-5-phosphate is converted into other pentose phosphates, including ribose-5-phosphate and xylulose-5-phosphate.

These molecules can then undergo a series of reversible reactions that change the number of carbon atoms in the sugar phosphates.

An important feature of the non-oxidative phase is its reversibility. This allows the cell to produce ribose-5-phosphate when it needs nucleotides or to convert excess pentose phosphates into intermediates that can enter glycolysis.

The non-oxidative phase makes the Pentose Phosphate Pathway metabolically flexible. The cell does not always need the same amount of NADPH, ribose-5-phosphate, and other carbohydrate intermediates. Therefore, the products of the pathway can be redirected depending on the current requirements of the cell.

When a cell is actively dividing, it requires large amounts of ribose-5-phosphate for the synthesis of nucleotides, which are necessary for DNA and RNA production. In this situation, the pathway can favor the formation of pentose sugars.

On the other hand, when the cell mainly requires NADPH and does not need large amounts of ribose-5-phosphate, the carbon skeletons of pentose phosphates can be rearranged into fructose-6-phosphate and glyceraldehyde-3-phosphate. These compounds are also intermediates of glycolysis.

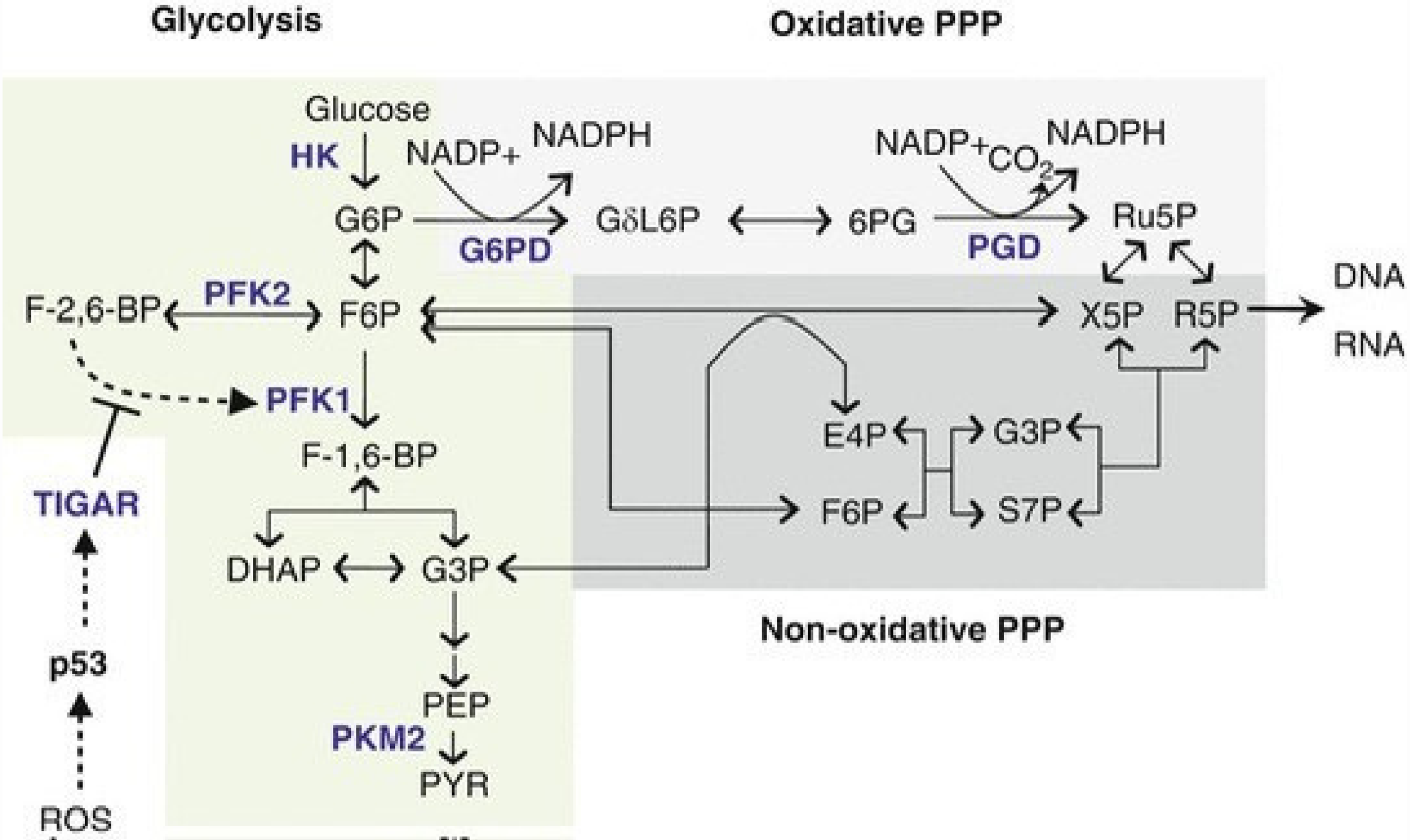
Therefore, the non-oxidative phase allows carbon from the Pentose Phosphate Pathway to be returned to central carbohydrate metabolism.

Transketolase and Transaldolase

Themain enzymes responsible for therearrangementofsugarphosphatesinthe non-oxidative phaseare transketolase and transaldolase.

Transketolase transfers a two-carbon unit from one sugar phosphate to another, while transaldolase transfers a three-carbon unit. Through the combined activity of these enzymes, several five-carbon sugars can be converted into three- and six-carbon carbohydrate intermediates. The final products of these reactions include fructose-6-phosphate and glyceraldehyde-3-phosphate, which can enter glycolysis.

An important biochemical fact is that transketolase requires the thiamine pyrophosphate (TPP) as a cofactor. TPP is derived from vitamin B1 (thiamine). Therefore, the normal functioning of the non-oxidative phase also depends on an adequate supply of vitamin B1.


Glycolysis
Oxidative PPP
Glucose
HK
NADP+
NADPH
G6P
G6PD
GδL6P
6PG
NADP+
CO2
NADPH
PGD
Ru5P
DNA
RNA
PFK2
F-2,6-BP
F6P
X5P
R5P
PFK1
F-1,6-BP
E4P
G3P
TIGAR
F6P
S7P
DHAP
G3P
Non-oxidative PPP
p53
PEP
PKM2
PYR
ROS

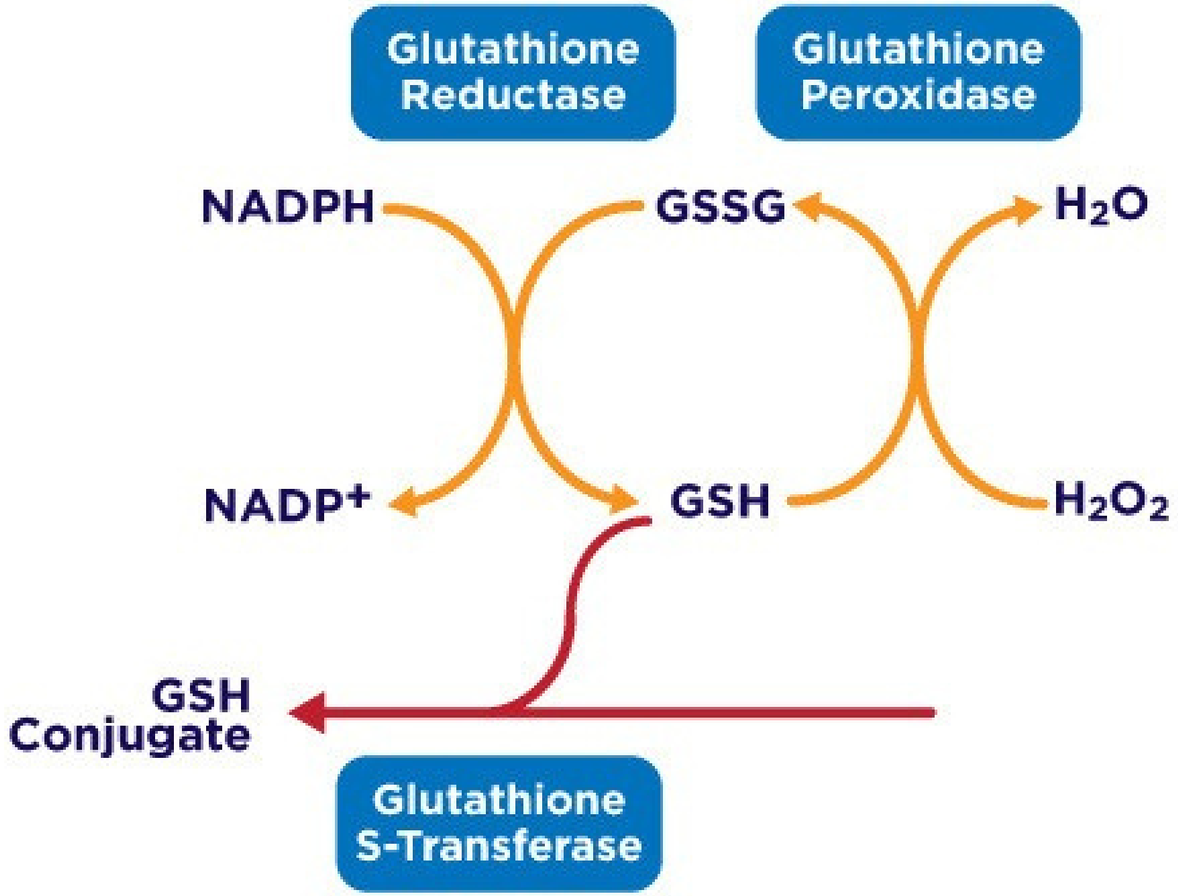
The Pentose Phosphate Pathway and glycolysis are interconnected through **glucose-6-phosphate** and several common intermediates.

Glucose-6-phosphate can enter glycolysis when the cell mainly needs ATP, or the PPP when it requires NADPH or ribose-5-phosphate.

The non-oxidative phase can return carbon to glycolysis as fructose-6-phosphate and glyceraldehyde-3-phosphate.

NADPH and Oxidative Stress

NADPH is essential for maintaining the cell's antioxidant defense.
It supports the regeneration of reduced glutathione (GSH), which helps neutralize reactive oxygen species (ROS).
This protects cellular components such as proteins, lipids and DNA from oxidative damage.



PPP in Red Blood Cells

The Pentose Phosphate Pathway is especially important in red blood cells because mature erythrocytes lack mitochondria.
They depend on the PPP for NADPH production, which is required to maintain reduced glutathione and protect the cell from oxidative damage.
Therefore, impaired PPP activity can make erythrocytes particularly vulnerable to oxidative stress.

Features	Why it matters
No mitochondria	Erythrocytes cannot use oxidative phosphor ylation
High oxygen exposure PPP activity	They are continuously exposed to oxygen and ROS
NADPH	Provides NADPH
GSH	Maintains reduced glutathione (GSH) Protects the cell from oxidative damage
G6PD deficiency	Increased risk of oxidative damage and hemolysis

Task for students

1. What is the Pentose Phosphate Pathway and where does it occur?
2. What are the two major functions of the PPP?
3. What are the two phases of the pathway?
4. Which phase produces NADPH?
5. Why is NADPH important for the cell?
6. What is the role of ribose-5-phosphate?
7. Which enzyme catalyzes the first reaction of the PPP?
8. What is the role of transketolase and transaldolase?
9. How is the PPP connected to glycolysis?
10. Why is the PPP particularly important in red blood cells?

Conclusion

The pentosephosphate pathway occurs in the cytosol and supplies NADPH and pentose sugars without directly producing ATP.

The irreversible oxidative phase produces two NADPH, one ribulose-5-phosphate and one CO_2 per glucose-6-phosphate.

The reversible non-oxidative phase supplies ribose-5-phosphate for nucleotide synthesis and connects the pathway to glycolysis.

G6PD controls the oxidative phase according to cellular NADPH demand. NADPH supports reductive biosynthesis and glutathione regeneration.

The pathway protects cells against oxidative stress. Reduced G6PD activity makes red blood cells vulnerable to oxidative damage and hemolysis.

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