Carbohydrates
Metabolism

Hexose Monophosphate Shunt (HMP)
Pentose Phosphate Pathway (PPP)
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**Pentose Phosphate Pathway (PPP)**

An alternative pathway of glucose oxidation for producing:

- ribose 5- phosphate
  - RNA, DNA
  - ATP, GTP, NAD, NADP, FAD, FMN

- NADPH
  - Fatty acids & Steroid hormones synthesis
  - Synthesis of reduced glutathione

Enzymes of HMP are located in the cytosol
The HMP shunt does not generate ATP but has 2 major metabolic functions:

1. The generation of **NADPH** for reductive synthesis, e.g. fatty acids and steroid hormones biosynthesis.

2. The production of **pentose** for nucleic acids and nucleotides biosynthesis.
A) Irreversible Oxidative Reactions

- Oxidative portion consists of **three reactions** that for each molecule of glucose 6-P oxidized lead to formation of:

  - Ribulose 5-P
  - two NADPH
  - CO₂

- This part of the pathway is particularly important in the:
  - Liver, lactating mammary glands, & adipose, that are active in **NADPH-dependent** biosynthesis of **fatty acids**
  - Testes, ovaries, placenta & adrenal cortex that are active in **NADPH-dependent** biosynthesis of **steroid hormones**
  - Erythrocytes, which require **NADPH** to keep glutathione reduced.
HMP shunt can be divided into 2 phases

A) Oxidative phase of HMP: irreversible

Glucose 6-phosphate undergoes dehydrogenation and decarboxylation to give ribulose 5-phosphate, CO$_2$ and 2 NADPH,H$^+$

This is done through:

1. *Glucose 6-phosphate dehydrogenase (G6PD)* catalyzes irreversible oxidation of glucose 6-phosphate to 6-phosphogluconate, utilizing NADP$^+$ as coenzyme.

2. *6-phosphogluconate dehydrogenase (6PGD)* catalyzes the oxidative decarboxylation of 6-phosphogluconate to ribulose 5-phosphate and CO$_2$
Oxidative phase of HMP:

Glucose-6-phosphate Dehydrogenase

6-Phosphogluconolactone hydrolase

6-Phosphogluconate Dehydrogenase
Oxidative phase of HMP shunt

Glucose 6-phosphate

6-Phosphogluconolactone

6-Phosphogluconate

Ribulose 5-phosphate

Non-oxidative phase
B) **Non-oxidative phase:** reversible

1. The non-oxidative reactions catalyze the interconversion of 3-, 4-, 5-, and 7-carbon sugars.

2. These reactions permit **ribulose 5-phosphate** to be converted to:

   - Ribose 5-phosphate by isomerase enzyme.
   - Intermediate of glycolysis such as fructose 6-phosphate & glyceraldehyde 3-phosphate.

The enzymes needed are:

- epimerase
- transketolase
- transaldolase
Epimerase inter-converts the two epimers: ribulose-5-P and xylulose-5-P.

Isomerase converts ribulose-5-P (ketose) to ribose-5-P (aldose).
Note: Transketolase enzyme catalyzes the transfer of 2-C fragment & utilizes thiamine pyrophosphate (TPP) as coenzyme.
Transaldolase catalyzes the transfer of 3-C fragment.
Non-Oxidative phase of HMP shunt

Ribulose-5-phosphate
  /  \\
Xylulose-5-phosphate  Ribose-5-phosphate
    /  \\
  Transketolase  Glyceraldehyde-3-phosphate
    /  \\
Sedoheptulose-7-phosphate  Erythrose 4-phosphate
      /  \\
Glyceraldehyde 3-phosphate  Fructose 6-phosphate  Fructose 6-phosphate
      \\
Transketolase  Transaldolase
Regulation of HMP Shunt

- **Insulin** induces the synthesis of G6PD and 6-PGD.
- Therefore, HMP shunt is stimulated by CHO feeding, and inhibited by fasting.
- **NADPH** is an allosteric inhibitor for the previous 2 enzymes.
Relationship between glycolysis and PPP

1- Conversion of pentose-P to intermediates of glycolysis
Cells that carry out reductive biosynthetic reactions have a greater need for NADPH than for ribose 5-P.
In this case, transketolase and transaldolase convert the ribulose 5-P → GAP + fructose 6-P (glycolysis intermediates).

2- Conversion of glycolysis intermediates to pentose-P
Cells that carry out nucleotides biosynthesis have a greater need for ribose than for NADPH. In this case, the non-oxidative reactions convert GAP & fructose 6-P → ribose 5-P in the absence of the oxidative steps.
# Differences between HMP & Glycolysis

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<thead>
<tr>
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<th>HMP</th>
<th>Glycolysis</th>
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<tbody>
<tr>
<td><strong>Coenzymes</strong></td>
<td>NADP⁺, TPP</td>
<td>NAD⁺, ATP</td>
</tr>
<tr>
<td><strong>CO₂</strong></td>
<td>Produced</td>
<td>Not produced</td>
</tr>
<tr>
<td><strong>H₂O</strong></td>
<td>Used</td>
<td>Produced</td>
</tr>
<tr>
<td><strong>ATP</strong></td>
<td>Not generated</td>
<td>Generated</td>
</tr>
<tr>
<td><strong>Pentose 5-P</strong></td>
<td>Produced</td>
<td>Not produced</td>
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Metabolic Uses of NADPH

Reductive biosynthesis

Reduction of hydrogen peroxide (H$_2$O$_2$)

Cytochrome P450 monooxygenase system

Synthesis of nitric oxide (NO)
A. **Reductive biosynthesis**

- Like NADH, **NADPH** can be considered as a high-energy molecule.
- However, the electrons of NADPH are used in reductive biosynthesis, rather than for transfer to oxygen as is the case with NADH.
- Thus, in the PPP, part of the energy of **glucose 6-P** is conserved in **NADPH** that can be used as a source of electrons for the biosynthesis of **fatty acids**, **cholesterol** and **steroidal hormones**.
B- Reduction (detoxification) of H₂O₂

- H₂O₂ is one of a family of reactive oxygen species (ROS) formed from the partial reduction of molecular O₂.

- ROS can cause serious damage to DNA, proteins, and unsaturated lipids, and can lead to cell death.

- Reduced glutathione, a tripeptide-thiol (γ-glutamyl cysteinyl glycine), can detoxify H₂O₂ in a reaction, catalyzed by glutathione peroxidase, forming oxidized glutathione, which no longer has protective properties.

- Cells regenerate reduced glutathione in a reaction catalyzed by glutathione reductase, using NADPH as a source of reducing equivalents.
Detoxification of $\text{H}_2\text{O}_2$

NADPH indirectly provides electrons for reducing $\text{H}_2\text{O}_2$. 
C. Cytochrome P450 monooxygenase system

- Monooxygenases (mixed function oxidases) incorporate one atom from molecular O$_2$ into a substrate creating OH, with the other atom being reduced to H$_2$O.
- The cytochrome P450 monooxygenase system uses NADPH to provide the required reducing equivalents.
- The overall reaction catalyzed by a cytochrome P450 enzyme is:

  $$R-H + O_2 + NADPH + H^+ \rightarrow R-OH + H_2O + NADP^+$$

where R may be a steroid, drug, or other chemical.
D. Synthesis of nitric oxide (NO)

• NO is a mediator in many biologic systems. It causes vasodilation by relaxing vascular smooth muscle, acts as a neurotransmitter & prevents platelet aggregation.
Glucose 6-P Dehydrogenase Deficiency

- G6PD deficiency is an X-linked inherited disease characterized by hemolytic anemia due to inability to detoxify oxidizing agents.

Role of G6PD in red blood cells

- Diminished G6PD activity → ↓ NADPH → ↓ detoxification of free radicals and peroxides formed within the cell.

- Glutathione also helps maintain the reduced states of sulfhydryl (SH) groups in proteins, including hemoglobin.

- Oxidation of those SH → formation of denatured proteins that form insoluble masses (called Heinz bodies) that attach to the red cell membranes.
Role of G6PD in red blood cells

• Although **G6PD** deficiency occurs in all cells, RBC are most sensitive, where **PPP** provides the **only source for NADPH**.

• Erythrocyte has **no nucleus or ribosomes** and **cannot renew** its supply of the enzyme. Thus, red blood cells are particularly vulnerable to enzyme variants with diminished stability.
B. Precipitating factors in G6PD deficiency

- Some patients with **G6PD deficiency** develop **hemolytic anemia** if they are:
  - Treated with an oxidant drug
  - Ingest fava beans
  - Contract a severe infection

**Oxidant drugs**: Remembered as **AAA**

- **Antibiotics**
  - sulfamethoxazole
  - chloramphenicol
- **Antimalarials**
  - primaquine
  - **not** quinine
- **Antipyretics**
  - acetanilide
  - **not** acetaminophen
**Favism:** is seen in patients with Mediterranean variant of G6PD deficiency.

- These patients are particularly susceptible to hemolytic effect of the **fava (broad) bean**, **dietary staple** in Mediterranean region.

- The hemolytic effect of ingesting fava beans, is not observed in all individuals with G6PD deficiency, but all patients with favism have G6PD deficiency.

**Infection:**

- It is most common cause of hemolysis in G6PD deficiency.
- The inflammatory response to infection → generation of **free radicals** in **macrophages**, which can **diffuse** into RBC & cause oxidative damage.