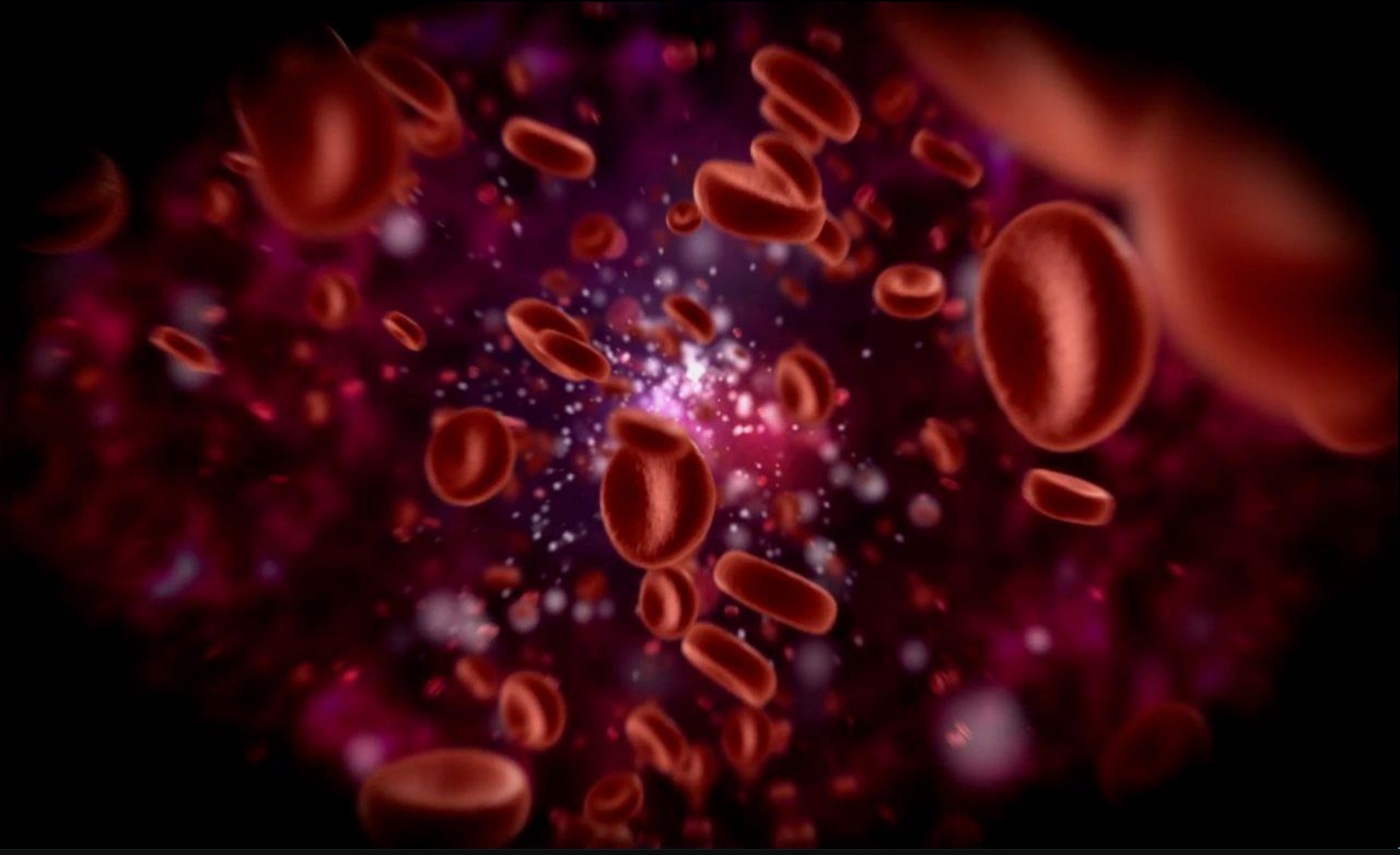


ATHAR BATCH

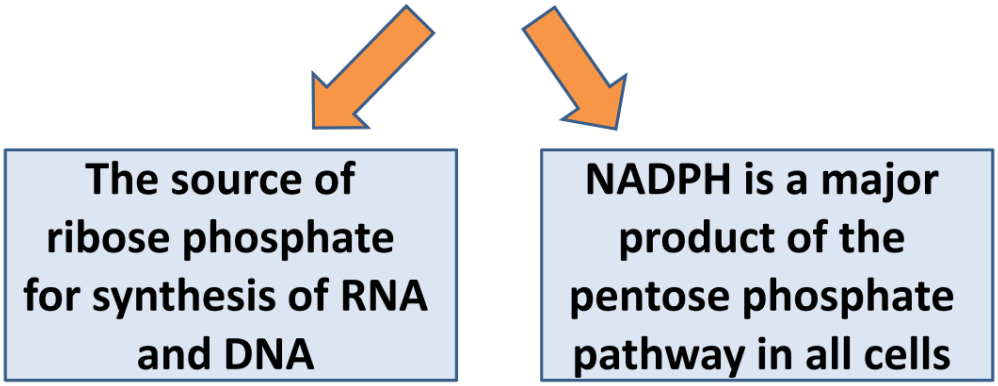
BIOCHEMISTRY

lecture : 2

Done by: Salsabeel Alhawatmeh

النادي الطبي

pentose phosphate pathway
(Hexose Monophosphate Shunt or HMP-shunt)

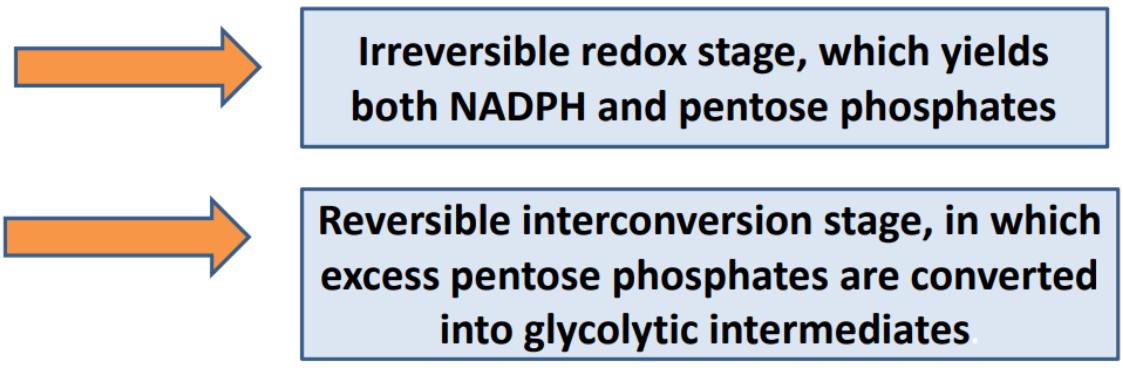


- **The pentose phosphate pathway is a cytosolic pathway present in all cells**
- **This pathway is active in the cytosol of many cells e.g. liver, adipose tissues, adrenal cortex, ovaries, testis, red cells and retina.**

✓ The main function of HMP-shunt is to produce two molecules (ribose phosphate and NADPH) which are very important for all cells but mainly RBCs. (We will explain why later)

✓ HMP shunt can occur in all types of cells but is very active in certain types of cells (mentioned above in the slide).

- **The pentose phosphate pathway is divided into:**



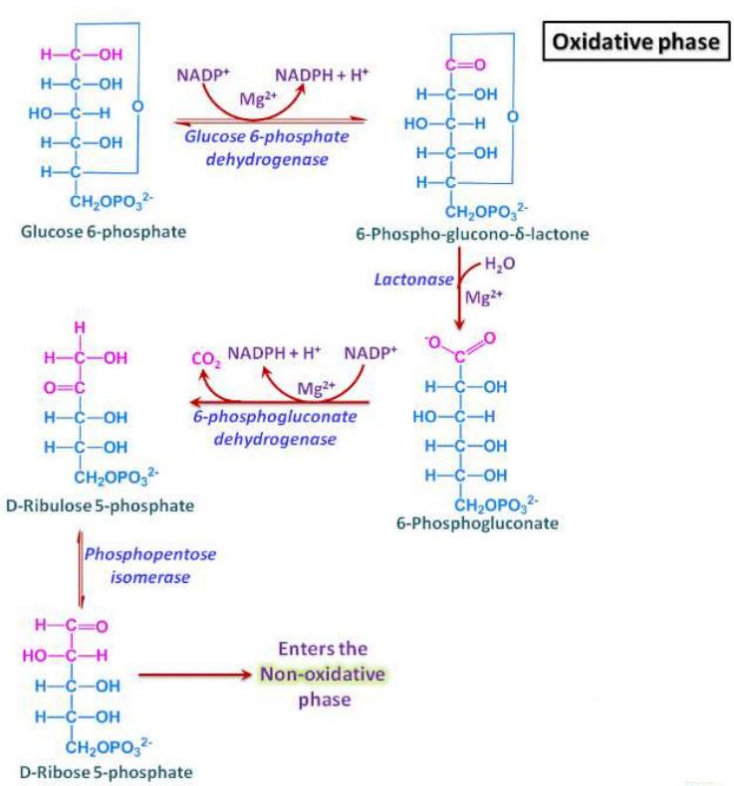
✓ Redox: oxidation-reduction reaction

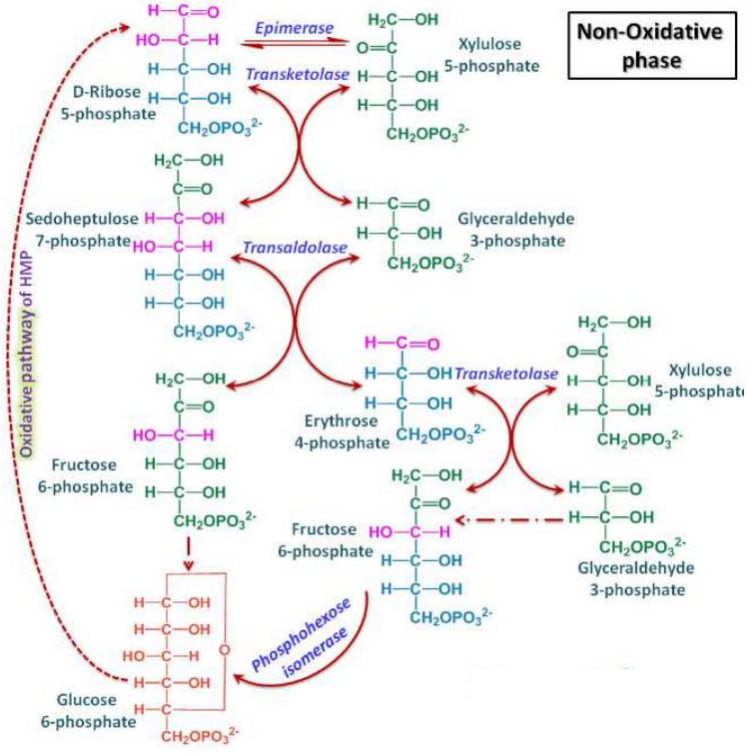
Both stages are important in the RBC, since it needs NADPH for reduction of glutathione, but has limited need for de novo synthesis of nucleotides.

✓ Importance of stage 1 for RBCs: production of NADPH.

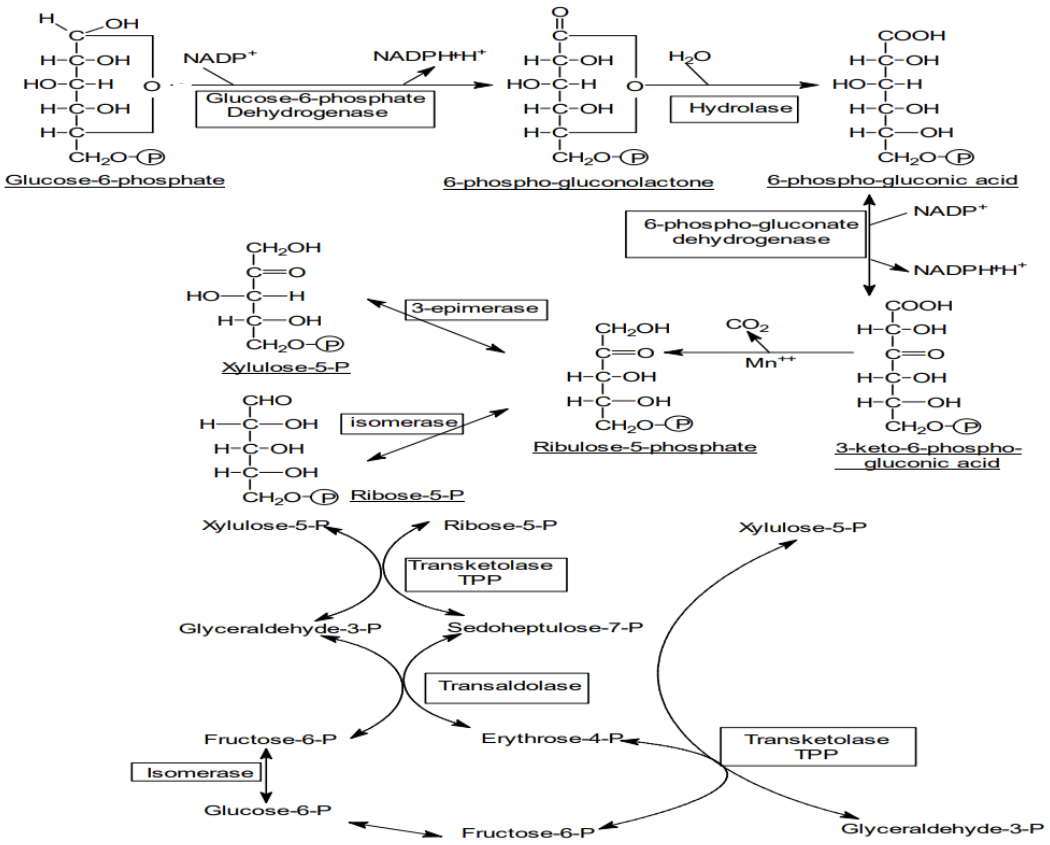
✓ Importance of stage 2 for RBCs: excess pentose phosphate produced in stage 1, which is not needed for RBCs, is converted in this stage to intermediate products that can contribute to glycolysis process. Therefor, this stage is important for cells that do not need to produce nucleotides.

✓ REMEMBER: pentose phosphate is needed for synthesis of nucleotides. Nucleotides are the structural units in DNA & RNA.





✓ الدكتورة ما شرحتهم



✓ Do not memorize the structures, they are not required for the exam. You must know the sequence of the pathway and the enzymes.

1) Glucose-6-phosphate (in ring structure) losses 2 hydrogens from C1 to form 6-phosphogluconolactone.
   - This step is irreversible and mediated by glucose-6-phosphatedehydrogenase.
   - NADP is required in this step. NADP take the 2 hydrogens (reduced), thus we get NADPH $+H^+$.
2) 6-phosphogluconolactone is hydrolyzed into 6-phosphogluconic acid.
   - This step is mediated by lactonase (hydrolase) enzyme with utilization of H_2O.

3) 6-phosphogluconic acid is dehydrogenated into 3-keto-6-gluconic acid which is then decarboxylated to ribulose-5-phosphate.
    - This step is mediated by 6-phosphoglutonate dehydrogenase enzyme which requires NADP. NADP is reduced to NADPH + H^+
    - dehydrogenation is coupled with decarboxylation by the same enzyme.
4) Rearrangement of ribulose-5-phosphate by isomerase enzyme (to get ribose-5-phosphate) or by epimerase enzyme (to get xylulose-5-phosphate)
    - Remember: the functional group of ribulose is (acetone), whereas the functional group of ribose is (aldehyde).

هون بتخلص phase 1

5) Ribose-5-phosphate and xylulose-5-phosphate are converted to glyceraldehyde-3-phosphate (3 carbons) and sedoheptulose-7-phosphate (7 carbons) ...how???
Xylulose-5-p losses 2 carbon units to form glyceraldehyde-3-phosphate. The 2 carbon units from xylulose are added to ribulose-5-phophate to from sedoheptulose-7-p.
    - This step is mediated by transketolase enzyme.
    - TPP: thymine pyrophosphate, derived from vitamin B1. A coenzyme of transketolase enzyme.
6) Glyceraldehyde-3-phophate and sedoheptulose-7-p are converted into fructose-6-p (6C) and erythrose-4-p (4C) ... how???
Sedoheptulose-7-p losses 3 carbon units and Glyceraldehyde-3-p gains these 3 carbon units.
    - This step is mediated by transaldolase enzyme.

7) *Fructose-6-phosphate is converted to glucose-6-phosphate (for glycolysis) by isomerase enzyme.*

8) *A xylulose-5-p molecule (produced by another HMP shunt) gives 2 carbon units to erythrose-4-p to become fructose-6-p, and forms glyceraldehyde-3-p. fructose is then converted to glucose-6-p. glyceraldehyde-3-p is involved in glycolysis.*

- *This step is mediated by transketolase enzyme.*

✓ *So, we got intermediate products for glycolysis pathway…*

- Transketolase transfers two-carbon unit (carbons 1 & 2) of a ketose onto the aldehyde carbon of an aldose sugar (TPP is needed).

- Transaldolase transfers three-carbon dihydroxyacetone moiety (carbons 1–3) of a ketose onto the aldehyde carbon of an aldose sugar (No TPP is needed).

- This pathway branches from glycolysis at the level of Glc-6-P: thus, its alternative designation, the hexose monophosphate shunt.

- The pentose phosphate pathway is sometimes described as a shunt, rather than a pathway, because **when pentoses are not needed for biosynthetic reactions, the pentose phosphate intermediates are recycled back into the mainstream of glycolysis by conversion into Fru-6-P and glyceraldehyde-3-phosphate.**

- This rerouting is especially important in the RBC and in nondividing or quiescent cells, where there is limited need for synthesis of DNA and RNA.

- In tissues with active lipid biosynthesis, e.g. liver, adrenal cortex or lactating mammary glands, the NADPH is used in redox reactions required for biosynthesis of cholesterol, bile salts, steroid hormones and triglycerides.

- The liver also uses NADPH for hydroxylation reactions involved in the detoxification and excretion of drugs.

- The RBC has little biosynthetic activity, but still shunts about 10% of glucose through the pentose phosphate pathway, in this case almost exclusively for the production of NADPH.

- The NADPH is used primarily for the reduction of a cysteine-containing tripeptide, glutathione (GSH), an essential cofactor for antioxidant protection.

✓ *Liver is the main organ for detoxification.*

Importance of HMP in red cells:

- Red cells are liable for oxidative damage by H_2O_2 due to their role in oxygen transport.
- H2O2 is a powerful oxidant that produces damage of cellular DNA, proteins and phospholipids.
- H_2O_2 in red cells oxidizes the iron of Hb to form methemoglobin. In addition H_2O_2 produces lipid peroxidation, which increases the cell membrane fragility.
- **Glutathione reductase and glutathione peroxidase** are important for removal of H2O2.

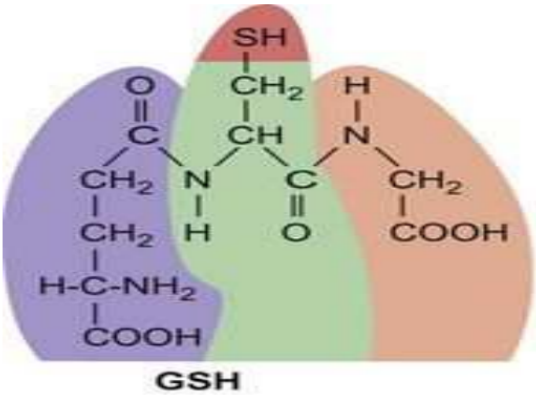
✓ *Since the main function of RBCs is to transport O2, there is a possibility for oxidative damage by H2O2.*

✓ *RBCs protect themselves by glutathione reductase and glutathione peroxidase.*

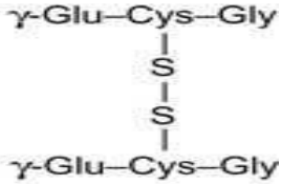
- The major role of HMP in red cells, is the production of NADPH, which protect these cells from oxidative damage by providing **reduced glutathione** for removal of H_2O_2 .

So what is glutathion? And what is its function?

Glutathione (GSH) is a tripeptide γ-glutamyl-cysteinyl-glycine. It is present in cells, 99% in the reduced (thiol) form, and is an essential coenzyme for protection of the cell against a range of oxidative and chemical insults. **Most of the NADPH formed in the red cell is used by glutathione reductase which is a flavoprotein enzyme (contains FAD) to maintain GSH in the reduced state.**



GSH

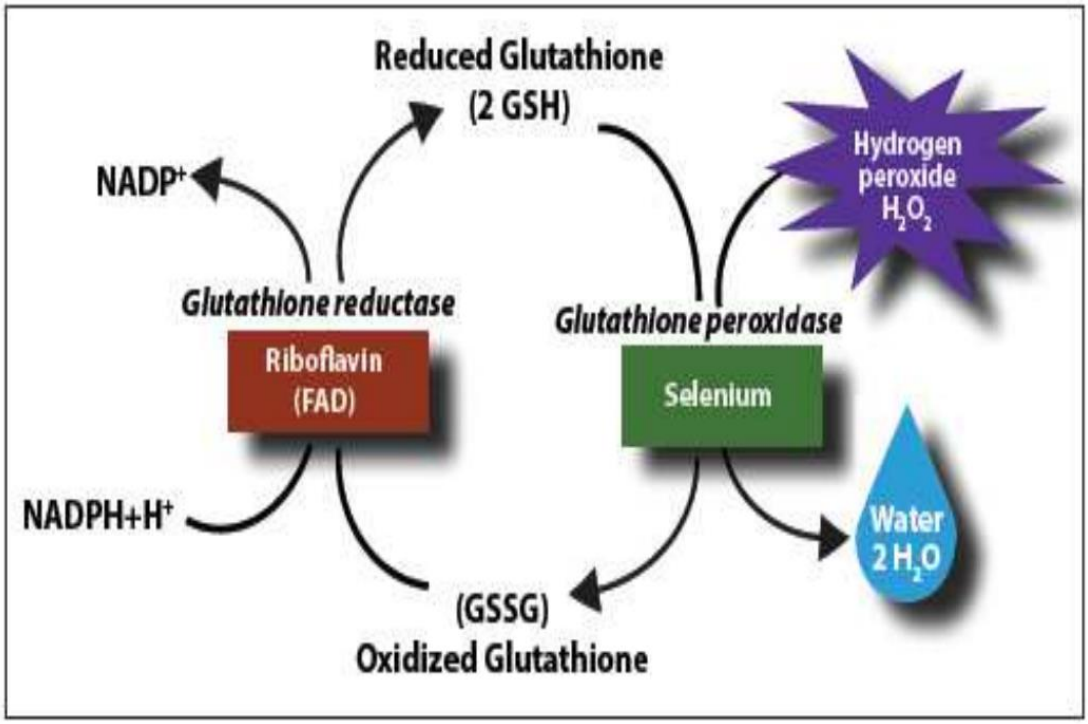


GSSG

- ✓ *Glutathione is not a protein.*
- ✓ *Reduced form of glutathione is characterized by the presence of (SH) group in cysteine amino acid.*

- Reduced glutathione (G-SH) is a coenzyme for the enzyme **glutathione peroxidase** (contains selenium) that reduces hydrogen peroxide to water, protecting cells from its toxic effects.

- During its function as a coenzyme for antioxidant activities, GSH is oxidized to the disulfide form, GSSG, which is then regenerated by the action of **glutathione reductase .**



- ✓ *Glutathione peroxidase removes 2 H from 2 SH groups in 2 glutathione molecules and add it to hydrogen peroxide → formation of $2H_2O$.*
- ✓ *Glutathione is thus become oxidized. It is reduced again by glutathione reductase which depends on NADPH (that is why NADPH is very important for RBCs)*

FAVISM

- It is a genetic deficiency of glucose-6-phosphate dehydrogenase (G6PD).
- The red cell capacity to protect itself from oxidative damage is markedly decreased (due to decreased concentration of NADPH).
- Administration of certain drugs (premaquine, asprin or sulfonamides), which stimulate the production of H_2O_2 or eating fava beans (contain oxidizing agents as divicine and isouramil) produce lysis of the fragile red cells.
- **Treatment :** Avoid fava beans & oxidizing drugs. Blood transfusion is done after crisis.
- Although G6PD deficiency occurs in all cells of the affected individual, it is **most sever in erythrocytes** where **HMP pathway provides the only means of generating NADPH** – other tissues have alternative sources of NADPH production. The RBCs has no nucleus or ribosomes and cannot renew its supply of the enzyme.
- Deficiency of G6PD in the red blood cells is the most common enzymopathy (diseases caused by abnormalities of enzymes)
- G6PD gene is located on X-chromosome so the abnormal genes in affected males are of maternal origin (It is an X-linked recessive disorder)

✓ *Favism is the most common enzyme deficiency related disease.*

✓ *More common in males*