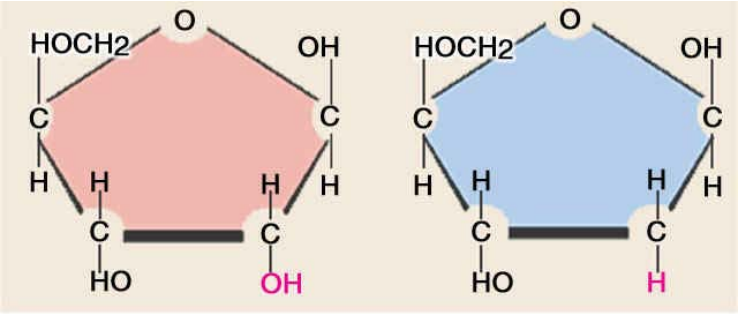
Pentose Phosphate Pathway



Ribose Deoxyribose

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Pentose Phosphate Pathway

- The predominant pathway for glucose catabolism is glycolysis which yield pyruvate followed by oxidation to CO_2 in the Krebs cycle
- Pentose phosphate pathway (PPP) is an anabolic rather than catabolic pathway. PPP is an alternative pathway for glucose metabolism which draws G6P from the glycolysis cycle
- PPP occurs in the cytosol of the cell. It has two main purposes:

1. To generate NADPH molecules (universal reductant) required for biosynthetic pathways and detoxification reactions

IN ANY ANABOLIC REACTION WE NEED REDUCTION AGENT

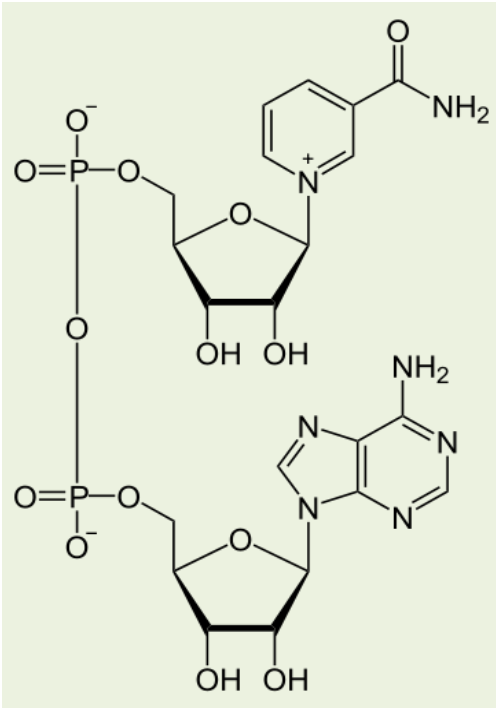
2. To generate the pentose sugar "ribose-5-phosphate" required for nucleotides and nucleic acids biosynthesis

Nicotinamide Adenine Dinucleotide

- Nicotinamide adenine dinucleotide, abbreviated as NAD^+, is a coenzyme found in all living cells
- It is composed of two nucleotides linked through their phosphate groups
- The coenzyme is found in two forms in cells:

1. The oxidized form "NAD^+" is an oxidizing agent which can accept electrons from other molecules and becomes reduced

2. The reduced form "NADH" which can be used as a reducing agent (electrons donor)

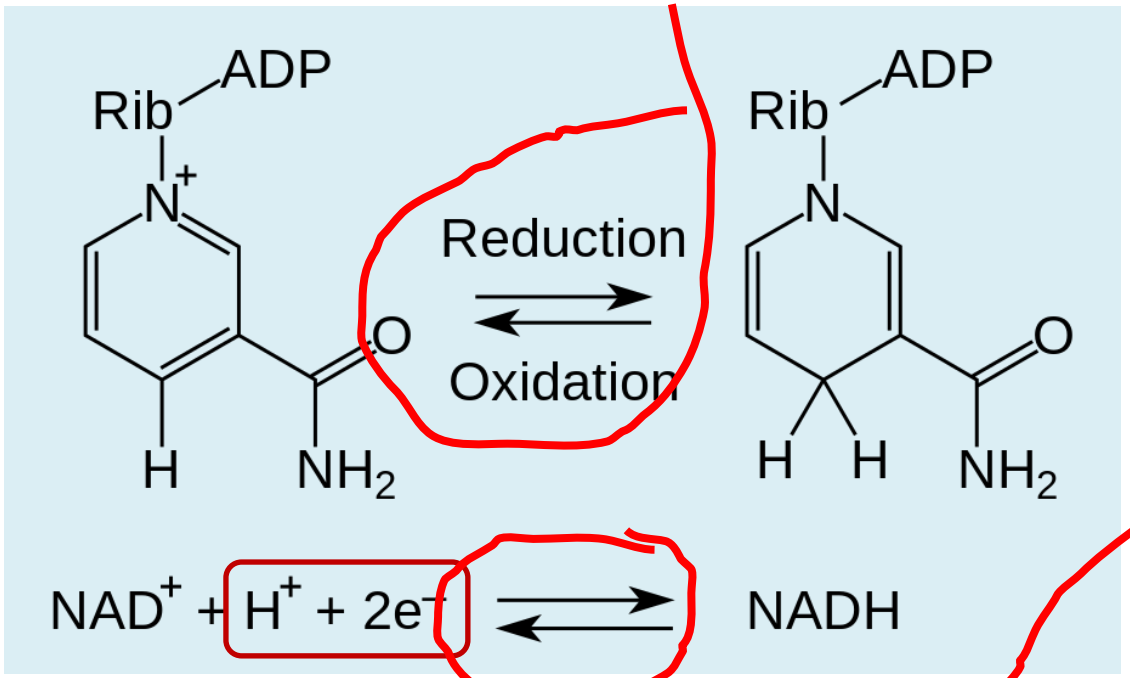


NAD^+

NAD+ 1- 2 NUCLEUTIDE →ONE HAVE ADENINE BASE OTHER HAVE NICOTINAMIDE LINKED TOGATHER BY PHOSPHATE GROUP \
HAVE + CAHRGE ON NICOTINAMIDE RING
2- CO ENZYME FOR REDUCTION REACTION EITHER ELECTRON DONOR OR ACCEPTOR

Nicotinamide Adenine Dinucleotide

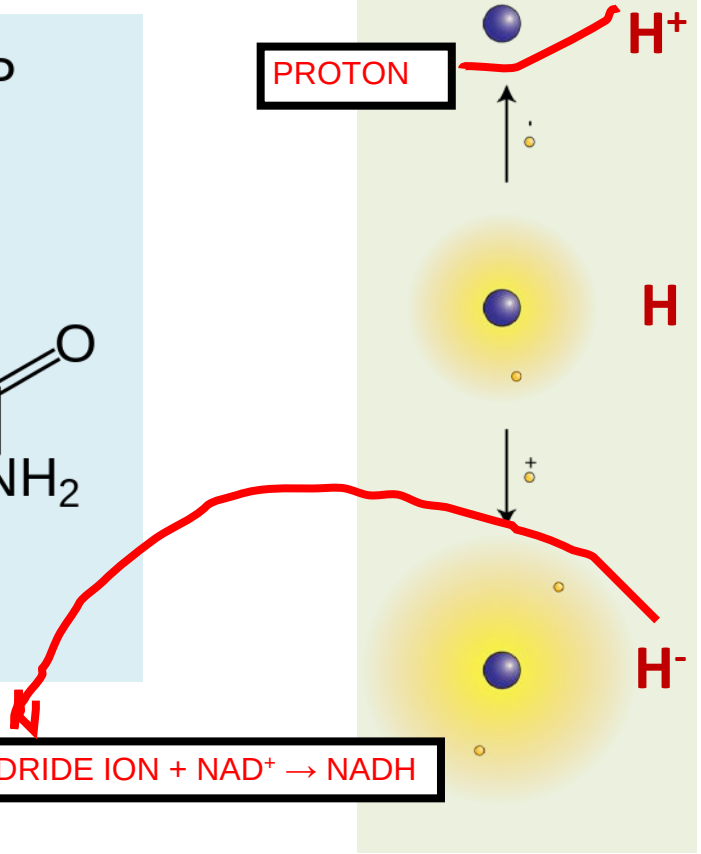
- Therefore, Nicotinamide adenine dinucleotide is used in redox reactions during metabolism carrying electrons from one reaction to another ($RH_2 + NAD^+ \rightarrow NADH + H^+ + R$)



REVERSIBLE SO THEY ARE REGENRATED WITHOUT CONSUMED

REMAIN IN MEDIA

PROTON



HYDRIDE ION + $NAD^+ \rightarrow$ NADH

Nicotinamide Adenine Dinucleotide Phosphate

- Nicotinamide adenine dinucleotide phosphate (abbreviated as $NADP^+$) differs from NAD^+ in the presence of additional phosphate group on the C2' of the adenosine ribose ring

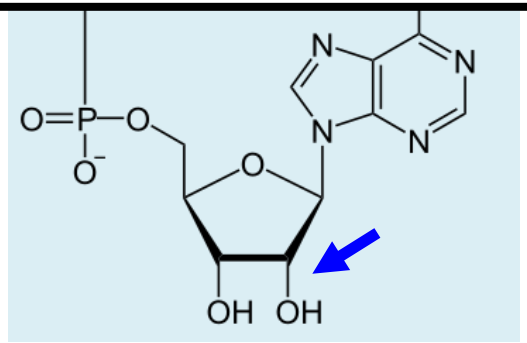
NADP+/ NADPH CAN BE CONVERTED INTO EACH OTHER BY OXIDATION-REDUCTION REACTION WHICH OCCURS LIKE THE NAD+/NADH

$NADP^+ + 2e^- + 2H^+ \rightarrow NADPH + H^+$

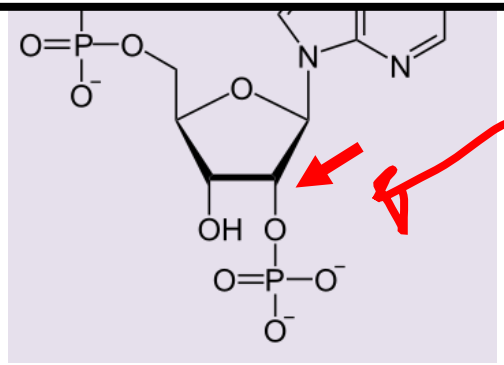
HYDRIDE ION + $NADP^+ \rightarrow$ NADPH

FUNCTION ARE DIFFERENT BETWEEN $NADP^+$ AND NAD^+

THE CELL LOOK TO NAD^+ AS A SOURCE OF ENERGY IN FORM OF ELECTRON



NAD^+



$NADP^+$

Nicotinamide Adenine Dinucleotide Phosphate

WE NEED MORE NADPH (REDUCING AGENT) AND
RIBOSE-5-PHOSPHATE FOR NUCLEIC ACID SYNTHESIS

- Nicotinamide adenine dinucleotide phosphate exists in two forms: $NADP^+$ the oxidized form and NADPH the reduced form
- This coenzyme is used in **anabolic** rather than catabolic reactions such as lipid and nucleic acid synthesis which require NADPH as **reducing agent**. Additionally, it has a role in **detoxification** reactions
- Pentose phosphate pathway is the major source of NADPH in animals (continuously regenerated from $NADP^+$)
- Tissues such as liver, adipose tissue, mammary gland and adrenal gland are rich in PPP enzymes because NADPH is used for fatty acids and steroids biosynthesis
- High level of PPP enzymes also seen in rapidly proliferating cells but PPP is nearly absent in other tissues like skeletal muscles

$NADP^+/NADPH$

OXIDAZED FORM IN ANABOLIC PATH WAY (NOT LIKE NAD+)
SO THE NADPH IS UNEVESIAL **REDUCING AGENT** IN ANABOLIC PATHWAY
IT IS USED IN DETOXCIFICATION REACTION

WE CAN REGENRATE THE NAD+ FROM THE NADH:
1- UNDER AEROBIC CONDITION WE USE ETC
2- UNDER ANEROBIC CONDITION WE USE LACTATE DEHYDEOGENASE ENZYME

Nico

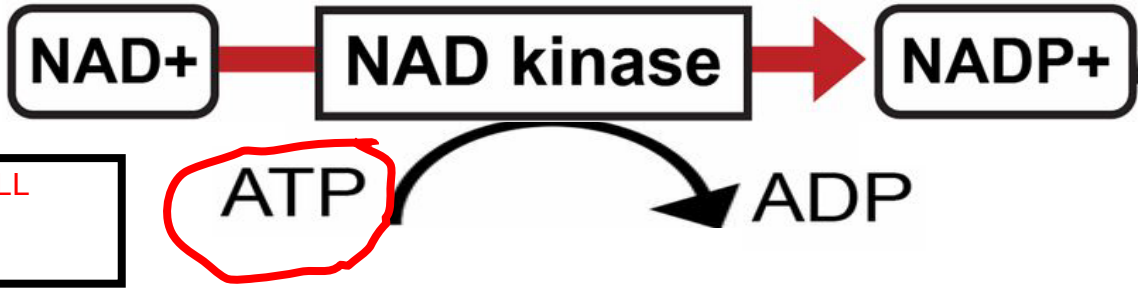
VIT B3(PRECURSOR OF BOTH NAD+ AND NADP+) WHEN ITS FOUND IN ACIDIC FORM AND ITS FUNCTIONAL GROUP IS COOH→NICOTINIC ACID **OR** AMIDE GROUP AS FUNCTIOAL GROUP →NH2-C=O→ NICTOINAMIDE

FORM SCRATCH FROM THE ZERO

- Nicotinamide adenine dinucleotide is synthesized by two different metabolic pathways:

1. A *de novo* pathway: most organisms synthesize NAD^+ from simple components like tryptophan in animals and aspartic acid in plants.

- Some NAD^+ is converted to $NADP^+$ via NAD^+ kinase which phosphorylate NAD^+ in an ATP-dependent step

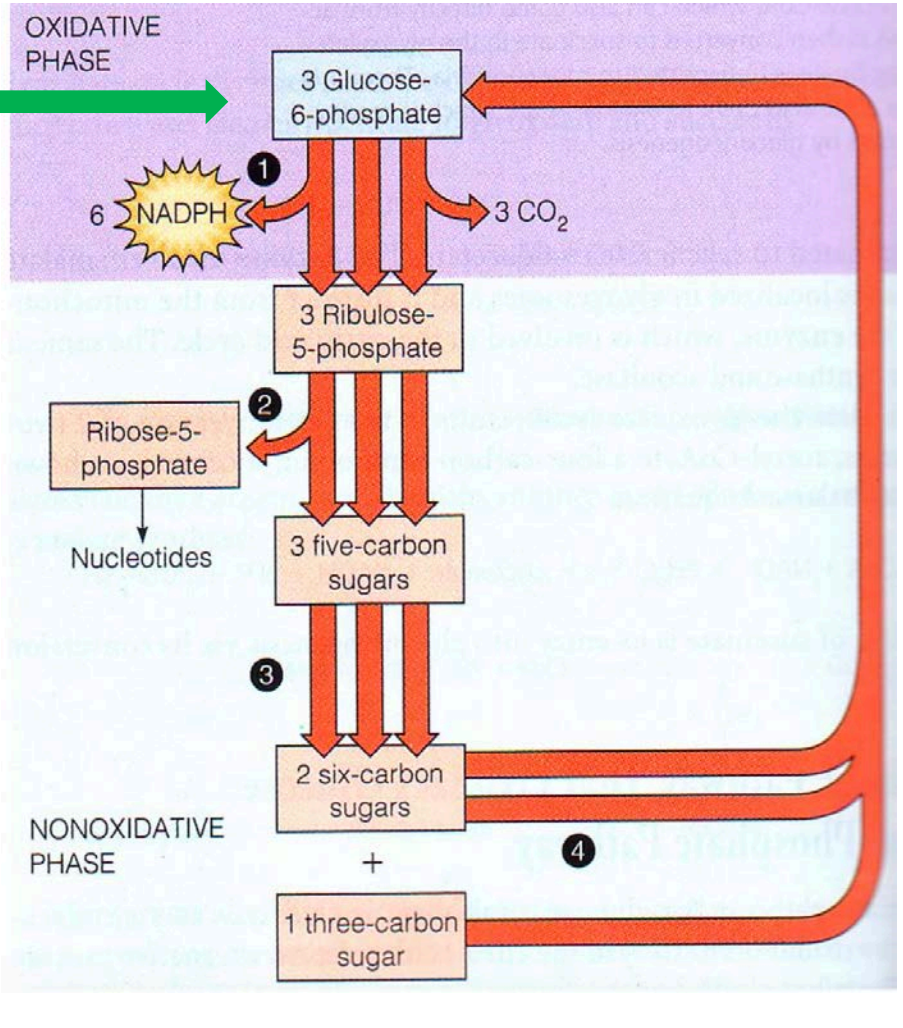


RECYCLING AND THE CELL HAVE PRECURSOR

2. A salvage pathways: by recycling preformed components back to NAD^+ such as nicotinic acid and nicotinamide obtained from food (i.e. niacin or vitamin B3)

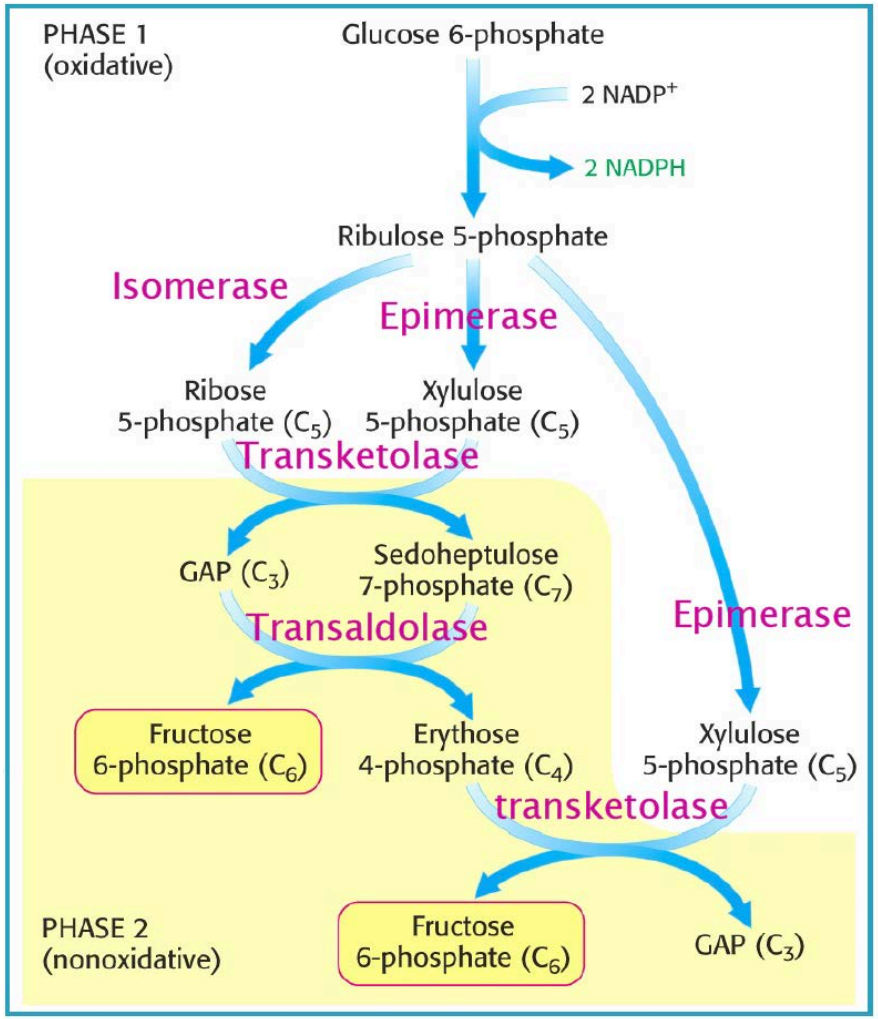
From Glycolysis to PPP

ate



Pentose Phosphate Pathway

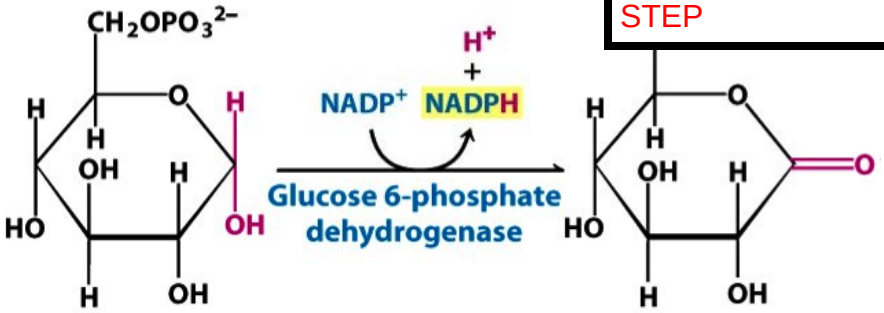
- The PPP pathway consists of two phases: the oxidative phase (irreversible reactions) during which NADPH molecules are generated and the non-oxidative phase (reversible reactions) during which different sugars phosphates are synthesized according to cellular need



The Oxidative Pathway

- **Step 1:** Glucose-6-phosphate (G6P) is oxidized by G6P dehydrogenase generating 6-phosphogluconolactone. One $NADP^+$ is reduced to NADPH

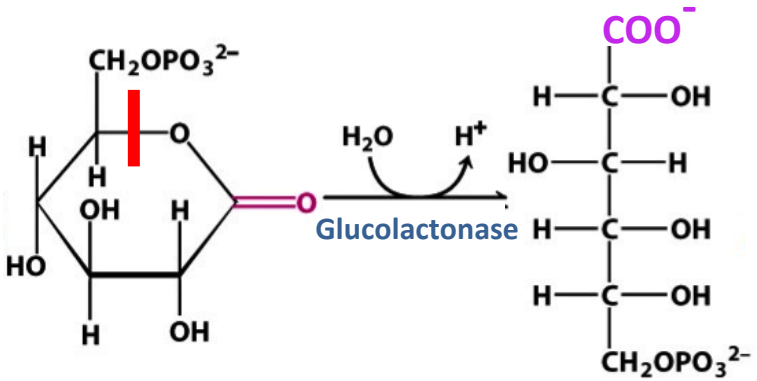
1-GENERATION OF FIRST NADPH
2- THESE STEP ARE REGULATORY STEP



Glucose-6-P **6-Phosphogluconolactone**

- **Step 2:** 6-phosphogluconolactone is hydrolyzed in presence of H_2O by glucolactonase to 6-phosphogluconate

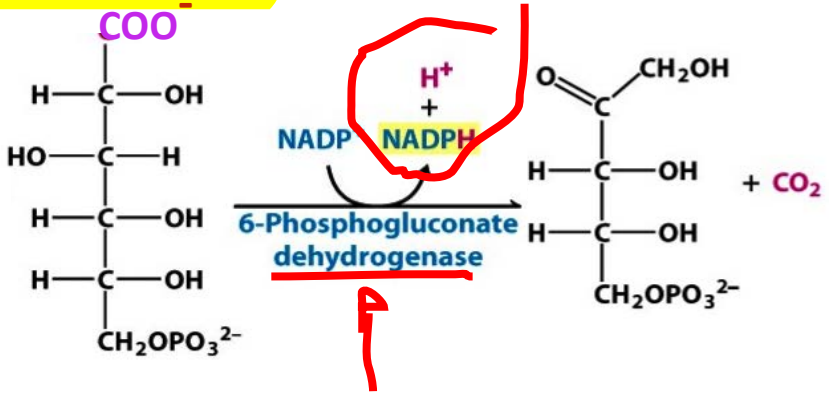
The Oxidative Pathway



6-Phosphogluconolactone **6-Phosphogluconate**

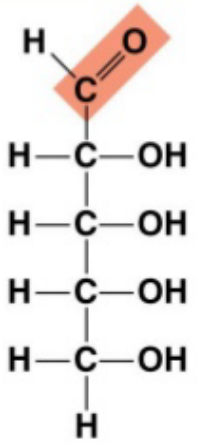
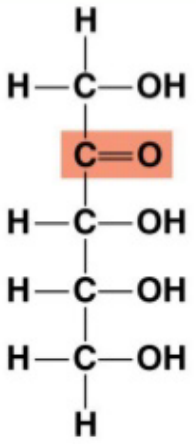
GENERATION OF SECOND NADPH MOLECULE

- **Step 3:** 6-phosphogluconate undergoes oxidative decarboxylation to yield ribulose-5-phosphate, CO_2 and another NADPH. Initially, OH at C3 is oxidized to carbonyl group and subsequently carboxyl group at C1 is eliminated as CO_2



6-Phosphogluconate **Ribulose-5-phosphate**

The Oxidative Pathway

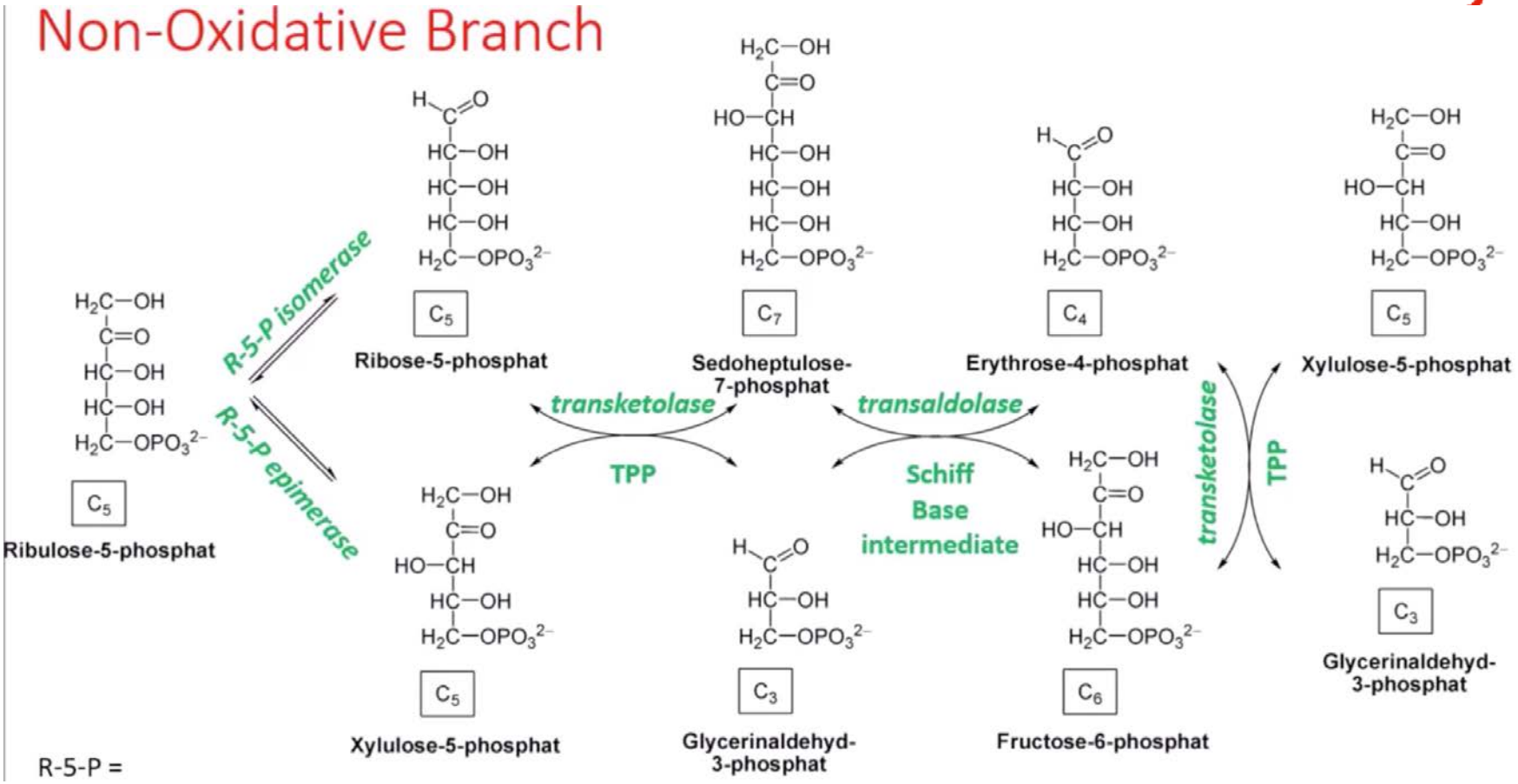
Aldose (Aldehyde Sugar)	Ketose (Ketone Sugar)
Pentoses: 5-carbon sugars ($C_5H_{10}O_5$)	
 Ribose	 Ribulose

1-GENERATION OF 2 NADPH
2- REMOVE OF ONE CARBON ATOM

- **The net result of this process is:**

G6P + 2NADP$^+$ + H_2O → ribulose-5-phosphate + 2NADPH + 2H^+ + CO_2

The Non-oxidative Pathway



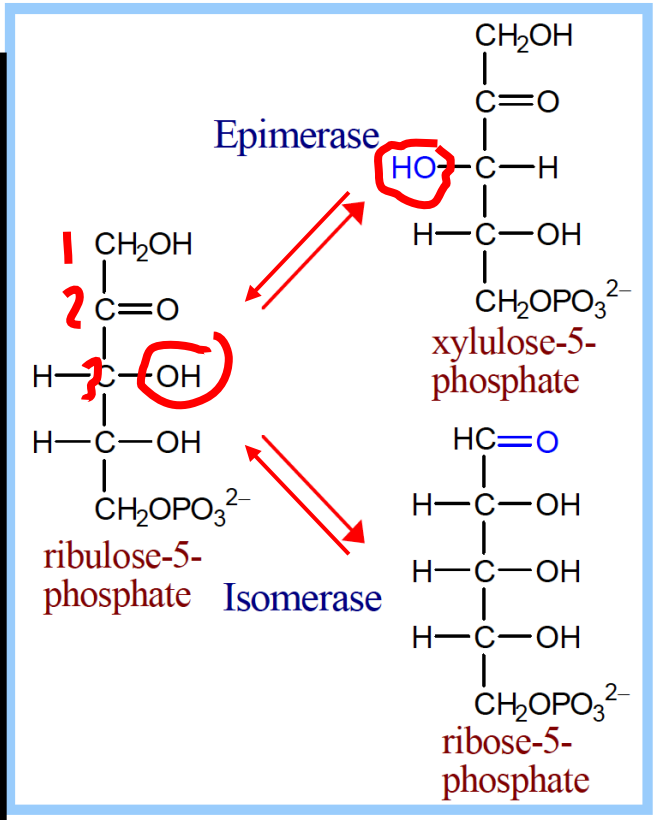
The non-oxidative pathway is the alternative fates of pentose phosphates

The Non-oxidative Pathway

- **Step 1**: is the beginning of the non-oxidative phase. Some of the ribulose molecules are converted to ribose-5-phosphate by phosphopentose isomerase and some are converted to xylulose-5-phosphate by phosphopentose 3-epimerase

3OH R→L

the primary aim of the PPP has been done when cells reach ribose-5-phosphate and generation of NADPH
why the cell complete the reaction if the goal is done ???
1- in rapidly proliferating cells the cell will stop here (it is need ribose-5-phosphate and NADPH for nucleic acid synthesis
2- in other tissue (like adipose tissue) →we need only the NADPH(for fatty acid synthesis) and cell does not need the ribose-5-phosphate in such large amount →so it will accumulate in these cell each time the cell enter the PPP because cell do not need them →the cell have to follow reversible pathway in non-oxidative reaction → to reach intermediate(SUCH AS fructose-6-phosphate) can enter the glycolysis →so the cell make conncetion between PPP AND glycolysis TO GIT RID FROM ribose-5-phosphate

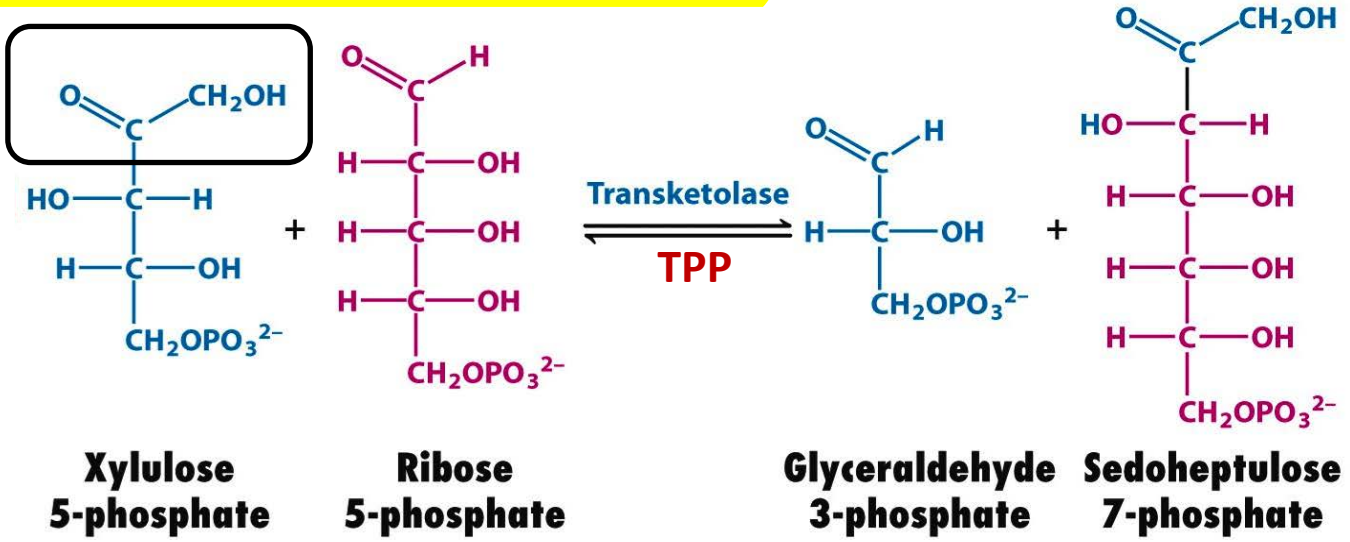


The Non-oxidative Pathway

- **Step 2:** the produced two pentoses: ribose-5-phosphate and xylulose-5-phosphate can react together in a reaction catalyzed by transketolase which transfers a two carbon fragment from xylulose-5-phosphate to ribose-5-phosphate to generate sedoheptulose-7-phosphate (7C) and glyceraldehyde-3-phosphate (3C)

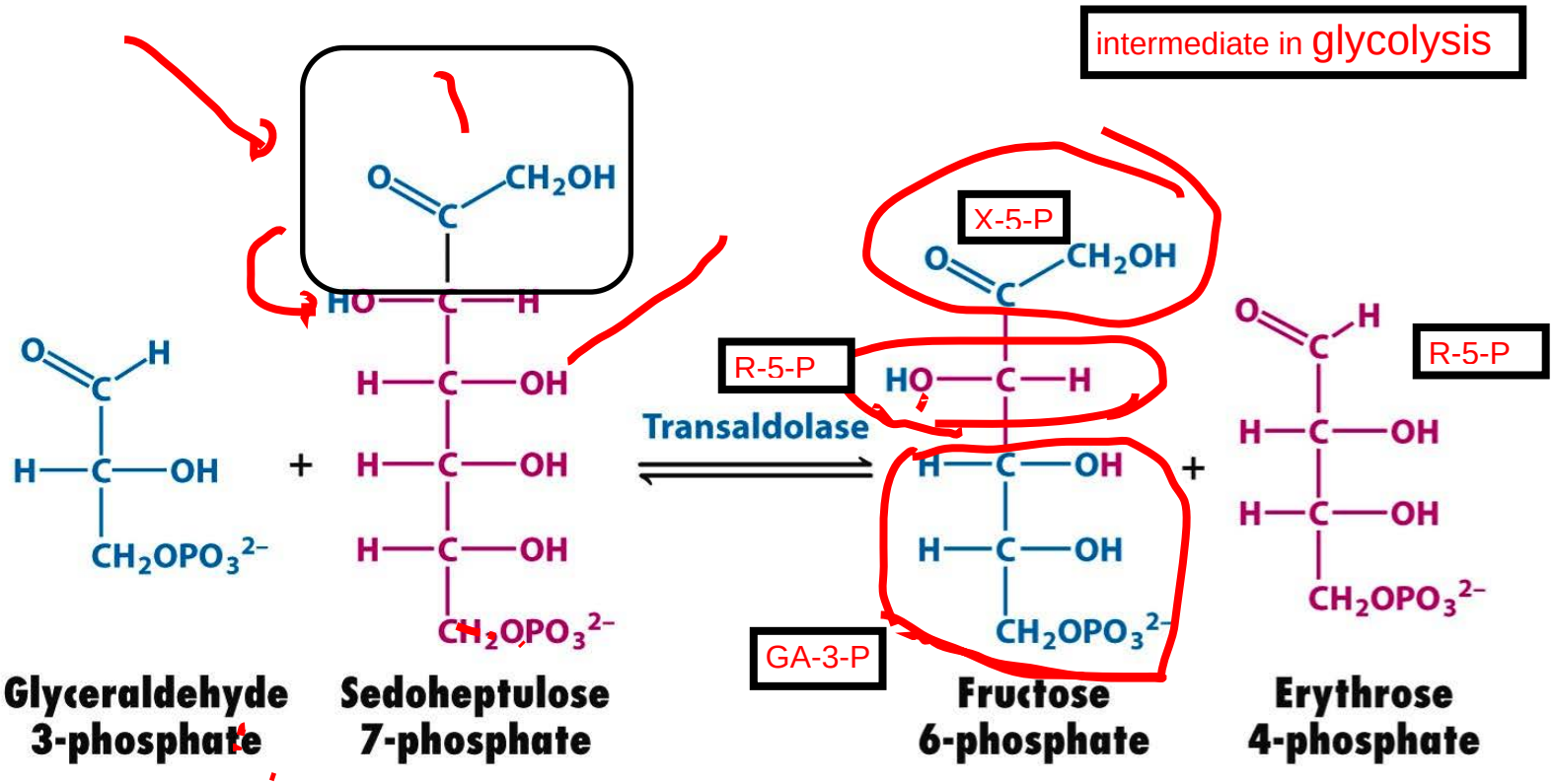
intermediate in glycolysis

- An activated glycolaldehyde fragment is transferred using thiamine pyrophosphate (TPP) as coenzyme



The Non-oxidative Pathway

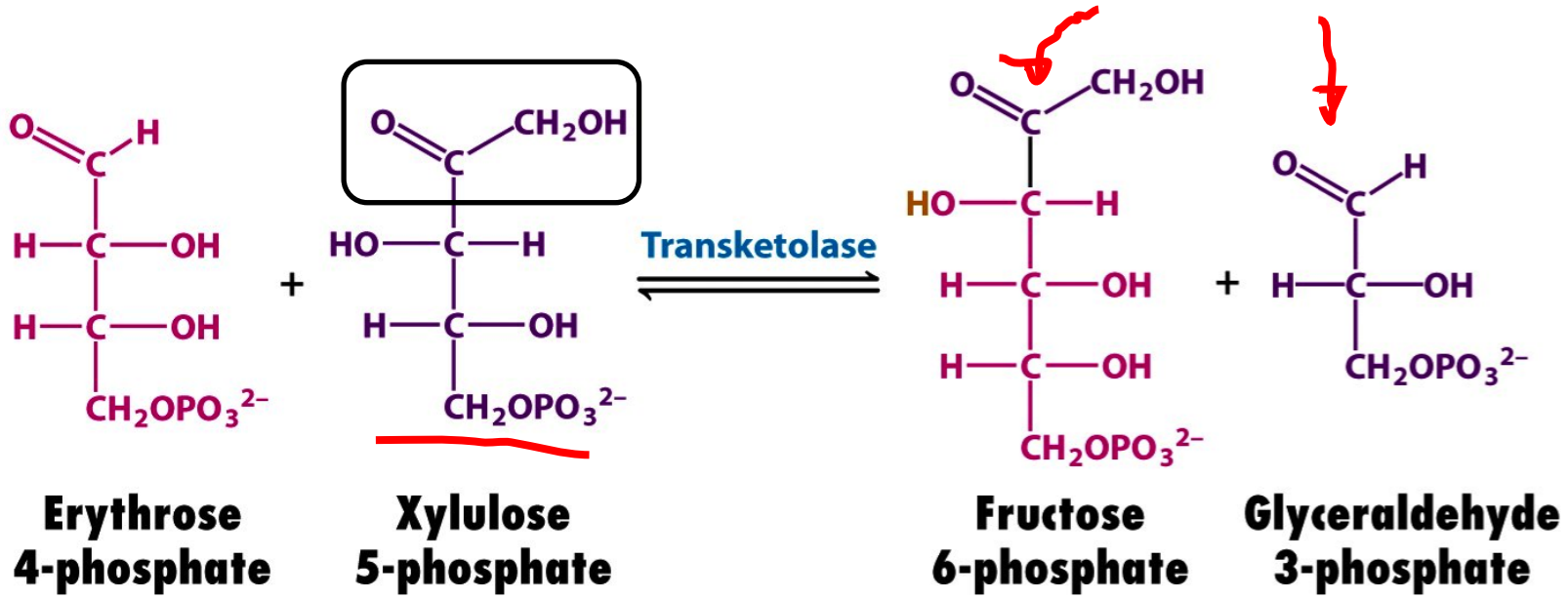
- **Step 3:** transaldolase acts on the transketolase two products with the transfer of dihydroxyacetone fragment (3C) from 7C substrate to 3C substrate. This reaction generates erythrose-4-phospahte and fructose-6-phoshate



The Non-oxidative Pathway

- **Step 4:** transketolase acts on another molecule of xylulose-5-phosphate by transferring glycolaldehyde fragment (2C) to erythrose-4-phospahte (4C). This produces glyceraldehyde-3-phosphate and fructose-6-phosphate

intermediate in glycolysis



Pentose Phosphate Pathway

- **Oxidative phase:**

3 G6P + 6 $NADP^+$ + 3 H_2O → 3 pentose-5-phosphate +

6 H^+ + 6 NADPH + 3 CO_2

- **Non-oxidative phase:**

2 xylulose-5-phosphate + 1 ribose-5-phosphate →

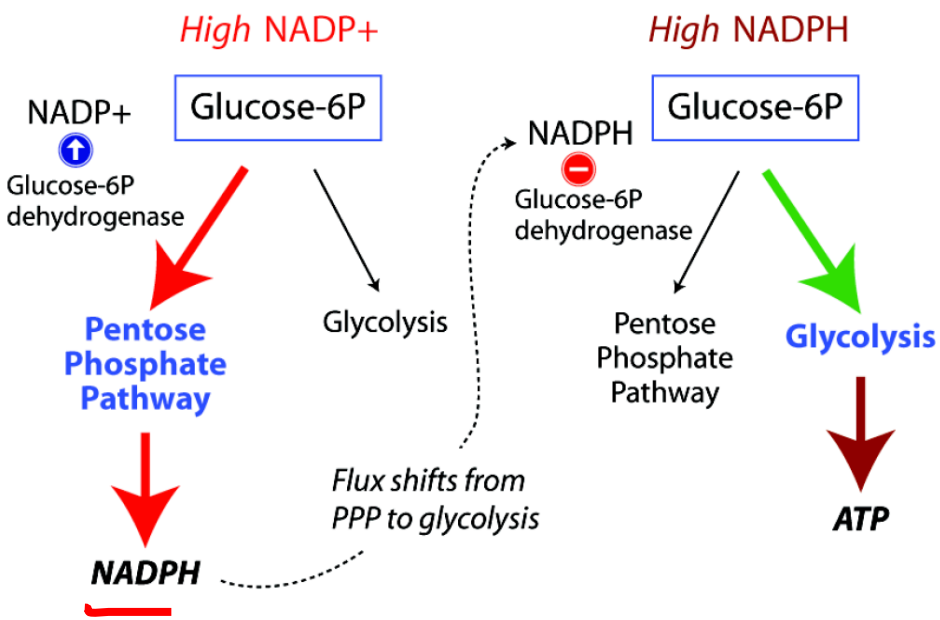
2 fructose-6-phosphate + 1 glyceraldehyde-3-phosphate

FOR EACH G-6-P IT WILL GIVE
1-2NADPH
2- 1 RIBOSE-5-PHOSPAHTE
CO2

Pentose Phosphate Pathway Regulation

- The activity of glucose-6-phosphate dehydrogenase (catalyzing the rate limiting reaction) is controlled by the ratio of NADPH/$NADP^+$
- It is allosterically stimulated by $NADP^+$ and strongly inhibited by NADPH

THE CELL NEED DETERMINE THE FATE OF G-6-P



Regulation of the G6PD activity controls flux through the glycolytic pathway and pentose phosphate pathways

ALLOSTRIC ENZYME IT HAS TOW BINDING SITE
1- CATALYTIC SITE FOR ITS FUNCTION
2- ALLISTRIC SITE >REGULATORY SITE FOR ACTIVATOR OR INHIBITOR
G-6-P DEHYDROGENASE ACTIVATED BY $NADP^+$ AND INHIBITED BY NADPH

Metabolic Needs of the Cell Direct the Fates of PPP products

IT IS MAINLY ANABOLIC BUT CAN BE CATOBOLIC IN CERTAIN CONDITION AND ITS DETERMINE BY THE NEED OF THE CELL

- Although PPP is not primarily an energy-generating pathway but in certain modes it can operate to oxidize glucose completely to CO_2 and H_2O
- The actual fates of PPP sugar phosphates depend on the metabolic needs of the cell in which the pathway is functioning
- Therefore, PPP can operate in various modes/scenarios to maximize the level of its different products (i.e. NADPH, ribose-5-phosphate and ATP)
- Because of the multiple metabolic needs of a particular cell, more than one model operates in that cell in temporal fashion (time based)

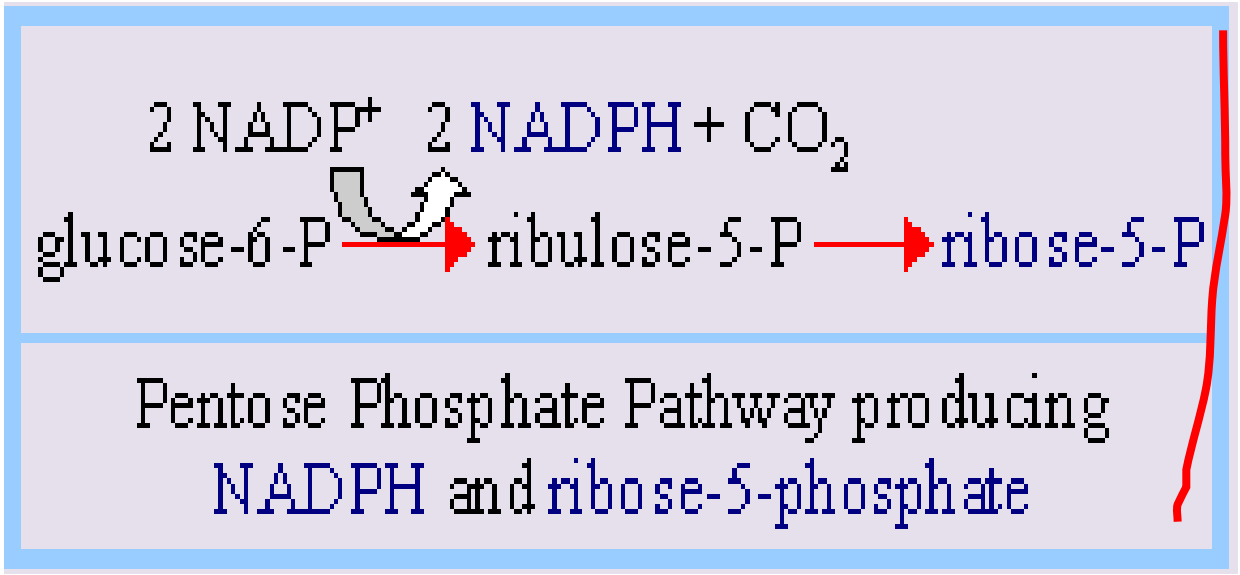
TEPORAL MODE IN CELL SO ITS CAN BE CHNNGED EASILY IN THE SAME CELL

Metabolic Needs of the Cell Direct the Fates of PPP products

RAPIDLY PROLIFERATING CELL

1. First Metabolic Mode **"nucleic acids biosynthesis"**

- If the primary need is for nucleotide and nucleic acid synthesis (as in rapidly proliferating cells), the major product is ribose-5-phosphate and most of the non-oxidative phase does not take place. Some NADPH are also produced



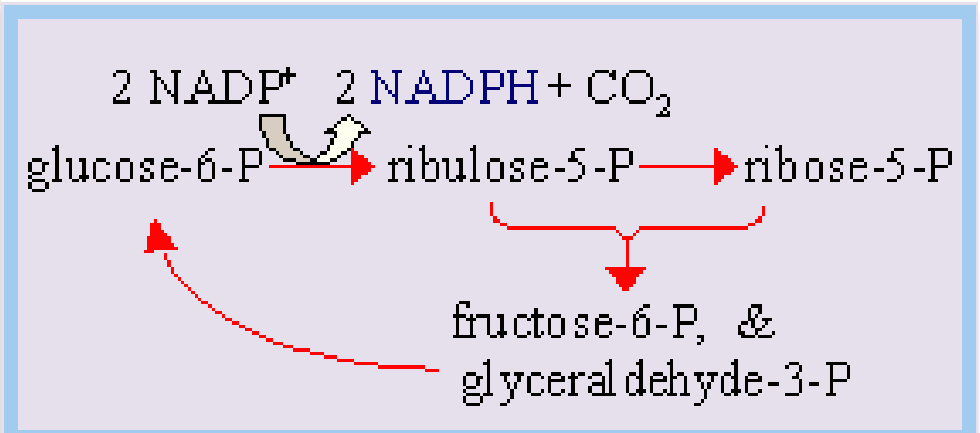
stop

Metabolic Needs of the Cell Direct the Fates of PPP products

2. Second Metabolic Mode **"NADPH Synthesis"**

- If the primary need is for NADPH (i.e. for fatty acids or steroids synthesis), the non-oxidative phase generates compounds that can be easily reconverted to G6P for subsequent passage through the oxidative phase maximizing the NADPH production

LIVER / ADIPOSE TISSUE
1-THE CELL NEED THE maximum AMOUNT OF NADPH
2-TI WILL REACH THE LAST STEP IN THE OXIDATIVE PHASE (HERE CELL GET NADPH AND RIBOSE-P)
A- THE FATE OF NADPH →USED IN FATTY ACID SYNTHESIS
2- THE FATE OF RIBOSE-5-P >IT WILL COMPLETE THE NON-OXIDATIVE REACTION AND GIVE F-6-P WITH GLYCERAL DEHYDE-3-P (THEY ARE INTERMEDIATE IN GLYCOLYSIS) BUT IT WILL BE USED FOR RESYNTHESIS OF G-6-P WHICH WILL BE USED AGAIN(REENTER IN PPP) FOR SYSTHESIS OF NADPH(MAXIMIZED AMOUNT OF NADPH)



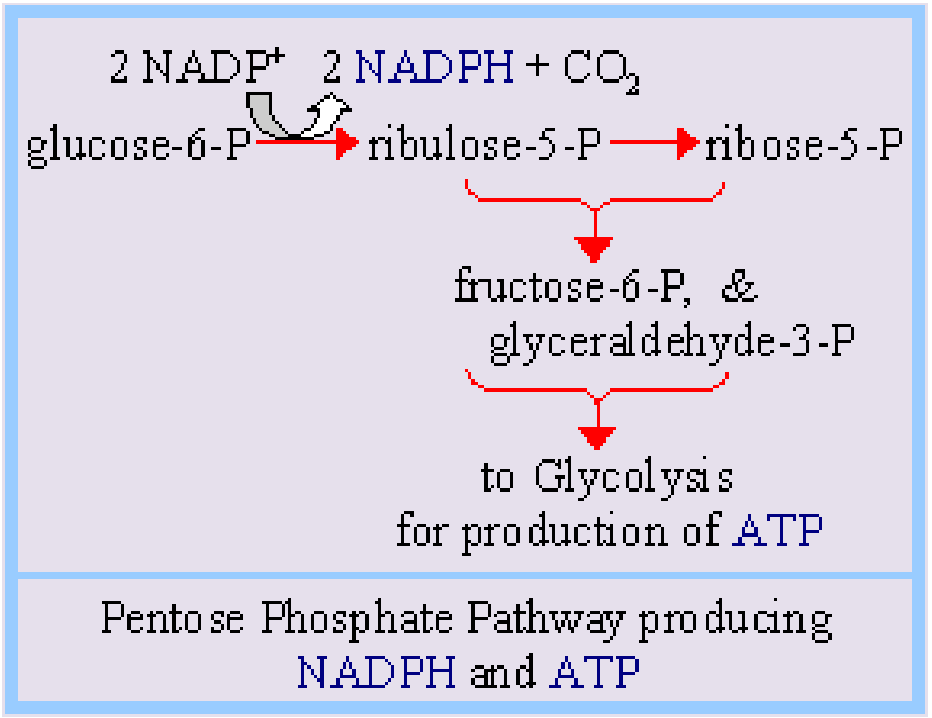
Pentose Phosphate Pathway producing maximum NADPH

Metabolic Needs of the Cell Direct the Fates of PPP products

3. Third Metabolic Mode **"Energy Generation"**

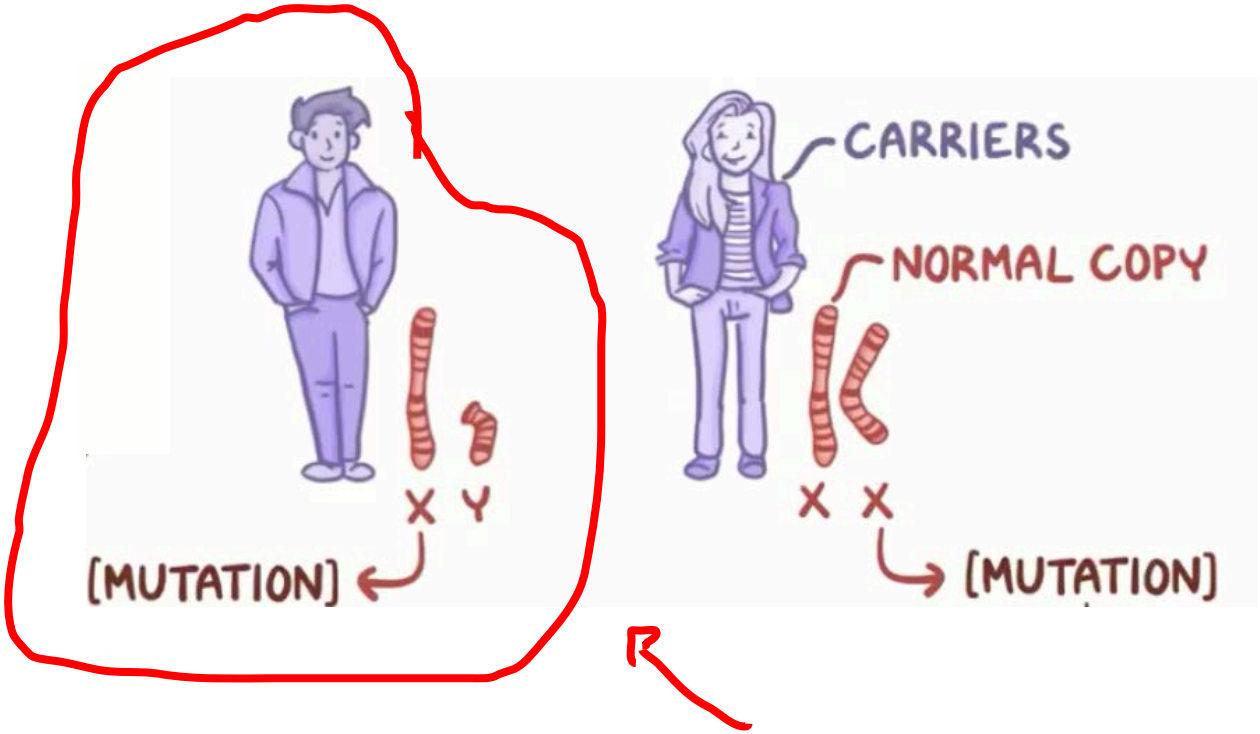
- If the cell in moderate need for both NADPH and ribose-5-phosphate, the end products of non-oxidative phase F6P and G3P can be further catabolized by glycolysis and TCA cycle to produce ATP.
  This pathway also produce some NADPH

THE CELLS IN MODERATE NEEED FOR BOTH NADPH AND RIBOSE-5-P
THE F-6-P AND GLYCERALDEHYDE WILL RUN DOWNSTREAM IN GLYCOLYSIS



G6P Dehydrogenase Deficiency

- One of well known disorder is the deficiency in G6P dehydrogenase also known as "favism" consequently, reduced intracellular NADPH level. It is an X-linked recessive genetic condition



Favism

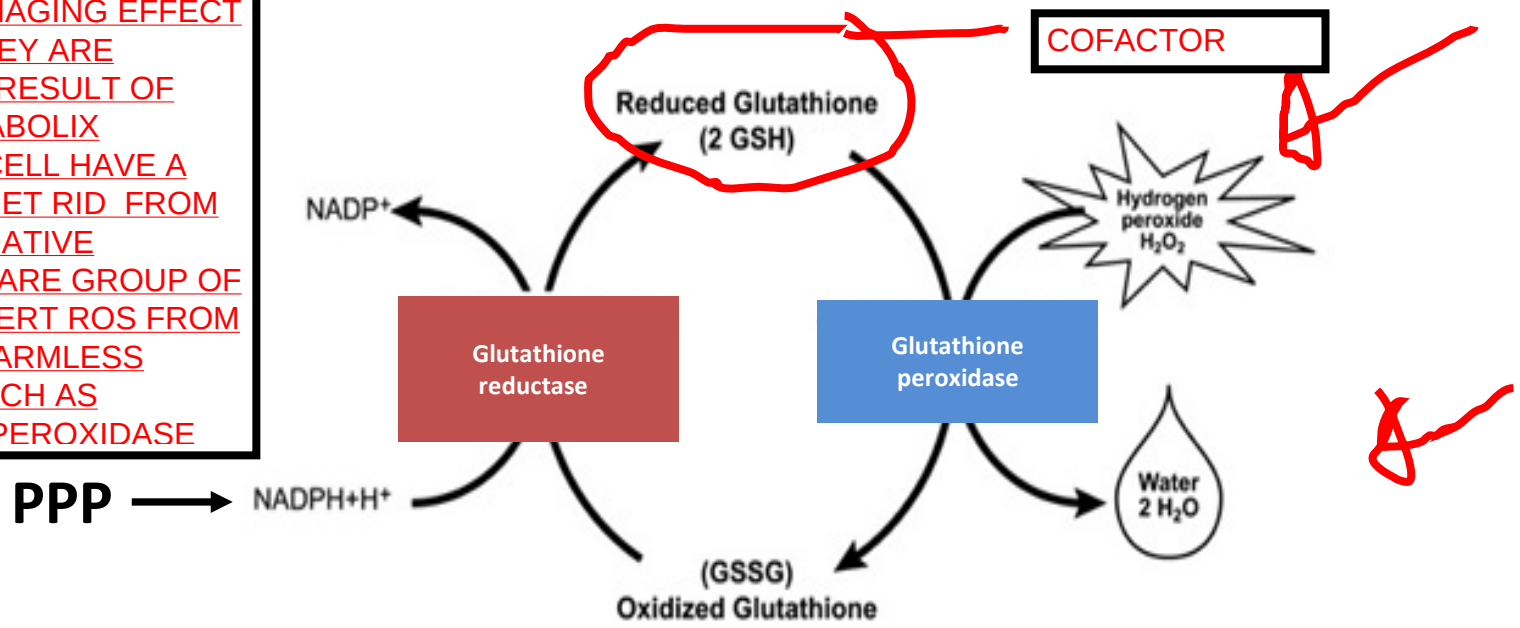
NADPH HAVE ANOTHER IMPORATANT ROLE BESIDE HELPING IN BIOSYSTHESIS
IT HAVE ROLE IN DETOXICIFCATION AND REMOVE ROS

G6P Dehydrogenase Deficiency

- Defects in PPP results in reduced intracellular NADPH level which participates in the glutathione cycle to protect cells against hydrogen peroxide
- G6PD enzyme prevents oxidative damage
- G6PD deficiency is characterized by hemolytic anemia

RBCS MOST AFFECTED

ROS HAVE DAMAGING EFFECT IN THE CELL THEY ARE PRODUCED AS RESULT OF MULTIPLE MATABOLIX PATHWWAY →CELL HAVE A SYSTEM FOR GET RID FROM ROS (ANTI-OXIDATIVE SYSTEM) THEY ARE GROUP OF ENZYME CONVERT ROS FROM HARMFUL TO HARMLESS SUBSTANCE SUCH AS GLUTATHIONE PEROXIDASE

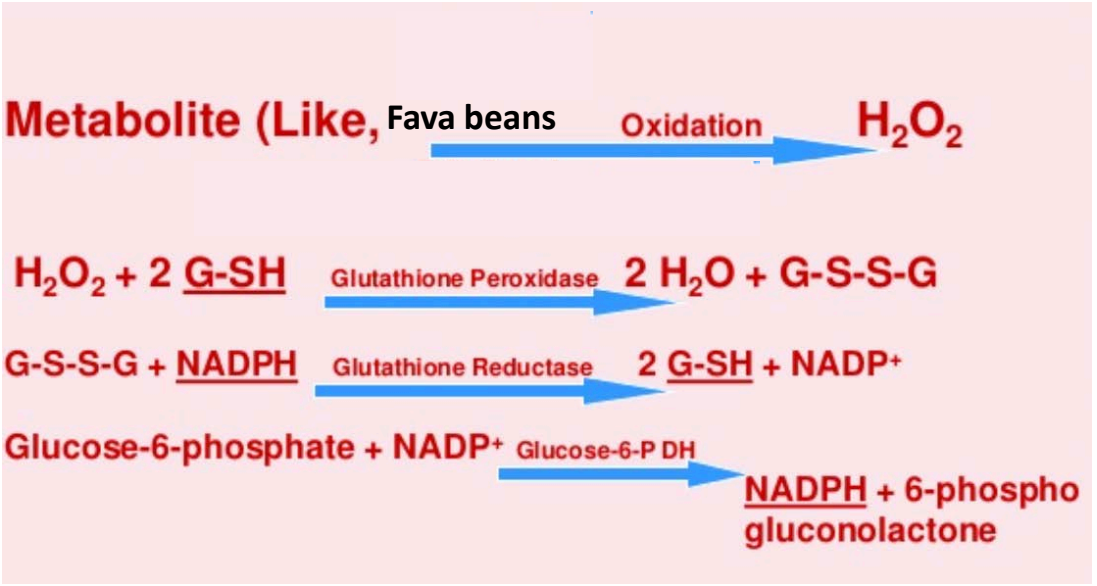


1-FOVA NEANS CONTAIN TOXIC ALKALOID→ ACT AS REDUCING AGENT CONVERT $O_2 \rightarrow OH^-$
THEY HELP IN FORMATION OF ROS →↑ OXIDATIVE STRESS ON CELL
2-VIRAL + BACTERIAL INFECTION → IMMUNE SYSTEM SYNTHESIS ROS FOR USE IT IN KILLING THESE INFECTIOUS AGENT SO →↑ OXIDATIVE STRESS ON CELL
3- SOME MEDICATION LIKE ASPIRIN/CHLOROQUINE /SULFAMETHOXAZOLE →↑ GENERATION OF **ROS**

- PPP is active pathway in RBCs for generation of reducing power. Actually, NADPH in RBCs is important to keep a high ratio of the reduced glutathione which is vital to protect cells from damaging effect of ROS (detoxification process)
- People with this deficiency are asymptomatic until stressed
- People with G6PD deficiency are at risk of hemolytic anemia (destruction of RBCs) in state of oxidative stress such as exposure to infection, some medications and certain foods (e.g. broad or fava beans)
- Oxidative stress is due to imbalance between the generation of ROS or free radicals (e.g. H_2O_2, ·OH,…) and the removal by specific cellular enzymes (antioxidants) like glutathione peroxidase (enzyme abundant in cells)

G6P Dehydrogenase Deficiency

- Oxidative stress depletes the reduced form of glutathione (GSH) and G6P dehydrogenase deficiency disorder can not supply enough NADPH to regenerate GSH from the oxidized one (GSSG)



- Damaged RBCs are recycled to the spleen. The hemoglobin is metabolized to bilirubin causing jaundice in high concentration