3. Pentose phosphate (PP) pathway

The pentose phosphate (PP) pathway, also called the hexose monophosphate shunt. Compared to energy production pathways such as glycolysis and citric acid,The pentose-phosphate cycle is not used as a source of ATP, but mainly as a means to obtain reducing power (NADPH) and intermediate metabolites such as ribose 5 phosphate (nucleotides) and erythrose 4 phosphate (amino acids).One glucose molecule catalyzes the net production of two NADPH molecules. NADPH is used in the synthesis of reducing agents (fatty acids, cholesterol, steroid hormones)..NADPH can also be used to maintain redox status and combat oxidative stress via the regeneration of reduced glutathione (GSH) by the action of glutathione reductase (red blood cells and neurons).

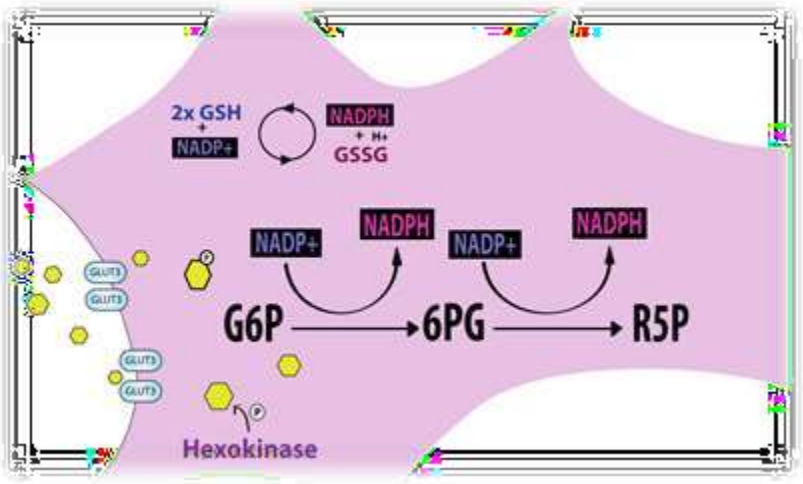

Figure 10: Simplified diagram of glucose metabolism via the pentose phosphate pathway. GLUT3: carrier 3, G6Pglucose-6-phosphate, 6PG: 6-phosphogluconate, R5P: ribose-phosphate, GSH reduced glutathione, GSSG: oxidized glutathione.

3.1. Steps

The PP (phosphorus) reaction is a network of seven enzymes that interconvert sugars to phosphates (Figure 11), occurring in two steps: (i) an oxidative phase and (ii) a non-oxidative phase (regeneration of 5 molecules of Glucose-6-P (G6P) from 6 molecules of ribulose-5-P). Two key enzymes control this step: glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase (steps 1 and 3).

- ***Oxidative pathway***

The oxidative pathway is a part consisting of reactions catalyzed by glucose-enzymes.

6-phosphate dehydrogenase (G6PDH), 6-phosphogluconolactonase (6PGL) and 6-phosphogluconate dehydrogenase (6PGDH). These enzymes oxidize glucose-6-phosphate to 6-phosphogluconolactone, hydrolyze lactone to 6-phosphogluconate and oxidize 6-phosphogluconate to ribulose-6-phosphate, respectively. The overall reaction catalyzed by the oxidative pathway of PP is the oxidation of glucose-6-phosphate to ribulose-5-phosphate and $CO_2$2During oxidation, G6P also degrades NADPH (Figure 10).

- ***Non-oxidative pathway***

The non-oxidative portion of PPP consists of reactions catalyzed by the enzymes ribulose-5-phosphate isomerase (R5PI), ribulose-5-phosphate-3-epimerase (R5PE), transaldolase (TA), and transketolase (TC). R5PI and R5PE convert ribulose-5-phosphate to ribose-5-phosphate and xylulose-5-phosphate, respectively. The reactions catalyzed by transaldolase (TA) and transketolase (TC) interconvert a range of phosphorylated aldoses (ribose-5-phosphate, erythrose-4-phosphate, glyceraldehyde-3-phosphate) and ketoses (xylulose-5-phosphate, fructose-6-phosphate, sedoheptulose-7-phosphate). This network of phosphorylated sugars is linked to glycolysis through their common intermediates glyceraldehyde-3-phosphate and fructose-6-phosphate.

3.1. Regulation

The flow through the PP is specifically modulated in each tissue according to the Physiological parameters. Tissues with biosynthetic functions, such as the liver or adipose tissue, have a high capacity to accelerate PP flux, while other cells, such as muscle cells, lack this capacity. Flux is modulated by the activity of G6PD, the main regulator of PP. This enzyme controls the entry of glucose-6-phosphate into PPP. G6PDis inhibited by a high concentration of NADPH and by intermediates of fatty acid biosynthesis.

The regulation of the pentose phosphate pathway depends on cellular needs. The main modes of pentose phosphate pathways are illustrated in Figure 12.

- **Mode 1:** This mode dominates when the demand for R5P is greater than that for NADPH, for example in cases of cell proliferation. In this situation, the glycolytic metabolites 3GP and F6P can be converted to R5P via reversible PP through a non-

oxidative pathway.

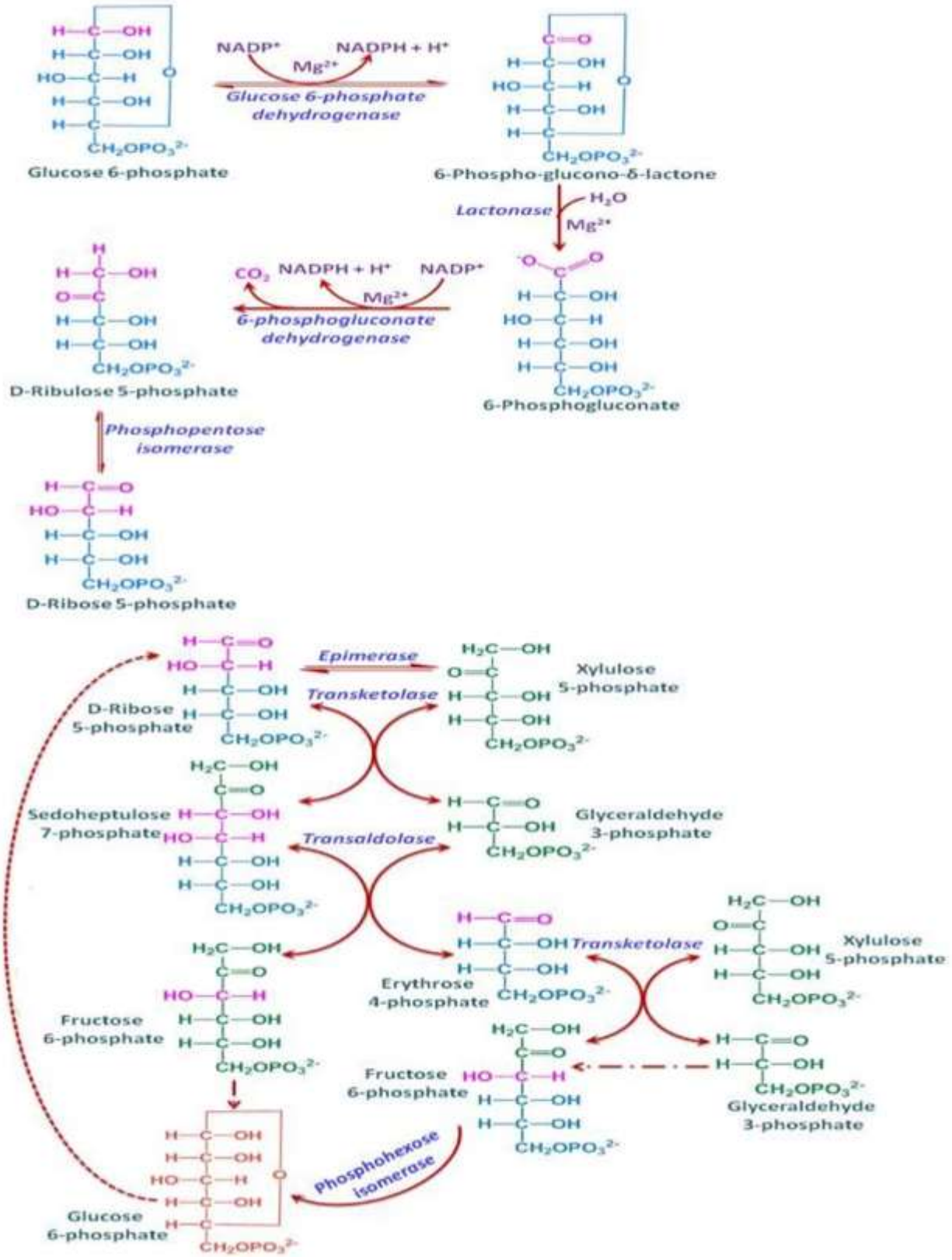

Figure 11: Pentose-phosphate pathway.

- **Mode 2**: This mode occurs when the requirements for NADPH and R5P are balanced.

  Then, from one molecule of G6P, two molecules of NADPH and one molecule of R5P can be obtained without the generation of glycolytic metabolites.
- **Mode 3**: This pathway is adopted when the cellular need for NADPH exceeds that

  of R5P and ATP, for example, during fatty acid synthesis in adipocytes. The non- oxidative phase of the pathway leads to the conversion of ribulose 5-phosphate to fructose 6-phosphate (F6P) and glyceraldehyde 3-phosphate (G3P). Subsequently, these glycolytic metabolites, through gluconeogenesis, form G6P, which can re- enter PPP to produce more NADPH.
- **Mode 4**: The cellular requirement for NADPH and ATP is greater than that for R5P. As

  described in mode 3, ribulose 5-P is transformed into G3P and F5P via the non-oxidative process; however, in mode 4, these molecules are metabolized into pyruvate via glycolysis, which is associated with ATP formation.

4. Citric acid cycle

The Krebs cycle, or tricarboxylic acid cycle, takes place in the mitochondrial matrix.
But before reaching the matrix, pyruvate is oxidized and decarboxylated by pyruvate dehydrogenase to form NADH and acetyl-CoA. Acetyl-CoA then enters the cycle via citrate synthase, which transfers the acetyl group to oxaloacetic acid to synthesize citric acid. This is followed by a series of reactions leading to the regeneration of oxaloacetic acid while releasing energy in the form of a phosphorylated compound (GTP) and reducing power (NADH).2and FADH2) (Figure 13).

4.1. Regulation

The regulation of the TCA cycle, like that of glycolysis, occurs both at the level of substrate entry into the cycle and at key reactions of the cycle.

- ***ATP Availability and Cellular Need***

  When the cell's energy charge is low, the cycle operates at a rate faster.

- ***Pyruvate dehydrogenase***

  The generation of acetyl-CoA from carbohydrates is a major checkpoint in the cycle.

This is the reaction catalyzed by the pyruvate dehydrogenase complex. The pyruvate dehydrogenase complex is inhibited by acetyl-CoA and NADH and activated by coenzyme A (CoA-SH) and NAD^+.

- ***Citrate and citrate synthase***

The formation of citrate from oxaloacetate and acetyl CoA constitutes an element Important for control. ATP acts as an allosteric inhibitor of citrate synthase. Citrate inhibits PFK (a key enzyme in glycolysis).

- ***Isocitrate dehydrogenase***

ADP acts as a positive modifier, enhancing substrate binding. NADH is an inhibitor.

- ***Alpha ketoglutarate dehydrogenase***

It is inhibited by succinyl-CoA and NADH.

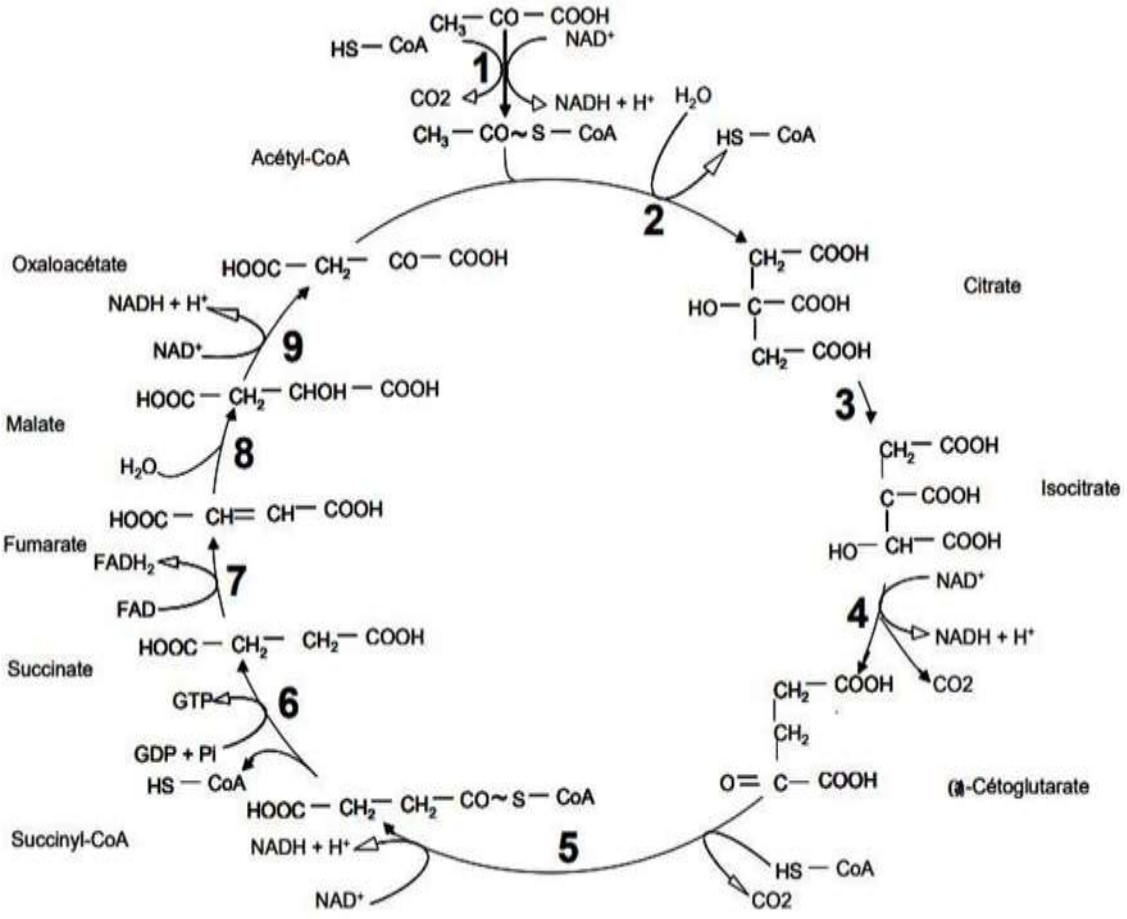

Figure 13: Krebs cycle.

1pyruvate dehydrogenase (enzyme complex);2citrate synthase;3, aconitase;4, isocitrate dehydrogenase;5, α-ketoglutarate dehydrogenase (enzyme complex);6 succinyl-CoA synthetase;7succinate dehydrogenase;8fumarase;9, malate dehydrogenase.