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Review

# The Pentose Phosphate Pathway in Parasitic Trypanosomatids

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**Parasitic trypanosomatids cause important diseases. Dissecting the biochemistry of these organisms offers a means of discovering targets against which inhibitors may be designed and developed as drugs. The pentose phosphate pathway is a key route of glucose metabolism in most organisms, providing NADPH for use as a cellular reductant and various carbohydrate intermediates used in cellular metabolism. The pathway and its enzymes have been studied in *Trypanosoma brucei*, *Trypanosoma cruzi*, and various *Leishmania* species. Its functions in these parasites are becoming clear. Some enzymes of the pathway are essential to the parasites and have structural features distinguishing them from their mammalian counterparts, and this has stimulated several programs of inhibitor discovery with a view to targeting the pathway with new drugs.**

## The Pentose Phosphate Pathway: A Key Pathway in Trypanosomatids

The pentose phosphate pathway (PPP, also called the hexose monophosphate shunt) is a key component of cellular metabolism, tightly connected to glycolysis as a major consumer of glucose. Its primary roles are to generate NADPH as a source of reducing power and other products that feed diverse parts of metabolism. These include ribose 5-phosphate (R5P) for nucleotide synthesis and erythrose 4-phosphate (E4P) for biosynthesis of aromatic amino acids and various vitamins [1–3]. Here we focus on the PPP of the major pathogens from the trypanosomatid family, *Trypanosoma brucei*, *Trypanosoma cruzi*, and *Leishmania* spp. All of these parasites are transmitted between mammalian hosts by insect vectors, and thus exist in distinct life cycle stages, each morphologically and biochemically adapted to specific conditions associated with their environment.

The PPP takes particular importance in these parasites since a first-line antimicrobial defence in mammalian hosts involves the production of reactive oxygen species, which are counteracted by NADPH-dependent reactions in the parasite, making the PPP a vital part of the defence mechanism of the parasite. However, as a result of differences between the separate species and life stages, the activity and essentiality of the pathway varies, and these differences are discussed later. In addition to the classical cytosolic localisation, the pathway is present in glycosomes, specific organelles of trypanosomatids. *In vitro* experiments indicated that flux through the PPP is increased in response to elevated oxidative stress [4,5], thus it is likely that similar regulation occurs during life cycle transformations and in response to changing environments.

Current drugs used against the diseases caused by these parasites are inadequate for a number of reasons and the development of new and improved therapeutic options is a priority. The PPP has long been considered to offer potential drug targets and the recently invigorated quest for inhibitors of enzymes of the pathway in cancer [6–8] means that new possibilities to seek

### Trends

The pentose phosphate pathway, or hexose monophosphate shunt, has re-emerged as a pathway of cellular metabolism considered of substantial interest due to its central role in viability and particularly in growth of cancer cells.

New tools allowing studies on the impact of individual enzymes of the pathway on trypanosomatid parasites have emerged and our understanding of the pathway in these organisms is growing.

Some enzymes of the pathway, such as glucose-6-phosphate dehydrogenase, 6-phosphogluconate dehydrogenase, and transketolase, have been considered as potential drug targets due to their essentiality and differences when considered alongside their mammalian counterparts.

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compounds that might inhibit the pathway in the parasites are emerging. Hence, we consider it pertinent to review the current knowledge of the PPP enzymes considered as potential drug targets, and emphasise differences between the respective trypanosomatid species and life cycle stages.

## Biochemical Roles of the PPP and Its Substrates

The pathway is conventionally divided into two branches (Figure 1), the first three reactions comprising the oxidative PPP while the following sugar interconversions make up the non-oxidative PPP. The oxidative branch uses glucose 6-phosphate (G6P) from glycolysis and converts it to 6-phospho-D-glucono-1,5-lactone using glucose-6-phosphate dehydrogenase (G6PDH) (EC 1.1.1.49) with NADP as a cofactor. The second enzyme, 6-phosphogluconolactonase (6PGL) (EC 3.1.1.17) produces 6-phosphogluconate (6 PG). Following this, 6-phosphogluconate dehydrogenase (6PGDH) (EC 1.1.1.44) produces a $CO_2$ molecule and ribulose 5-phosphate (Ru5P) while creating another molecule of NADPH.

Ru5P is further converted through the nonoxidative PPP, either by ribose-5-phosphate isomerase (RPI) (EC 5.3.1.6) into R5P, a critical cellular metabolite used in nucleotide synthesis, or to

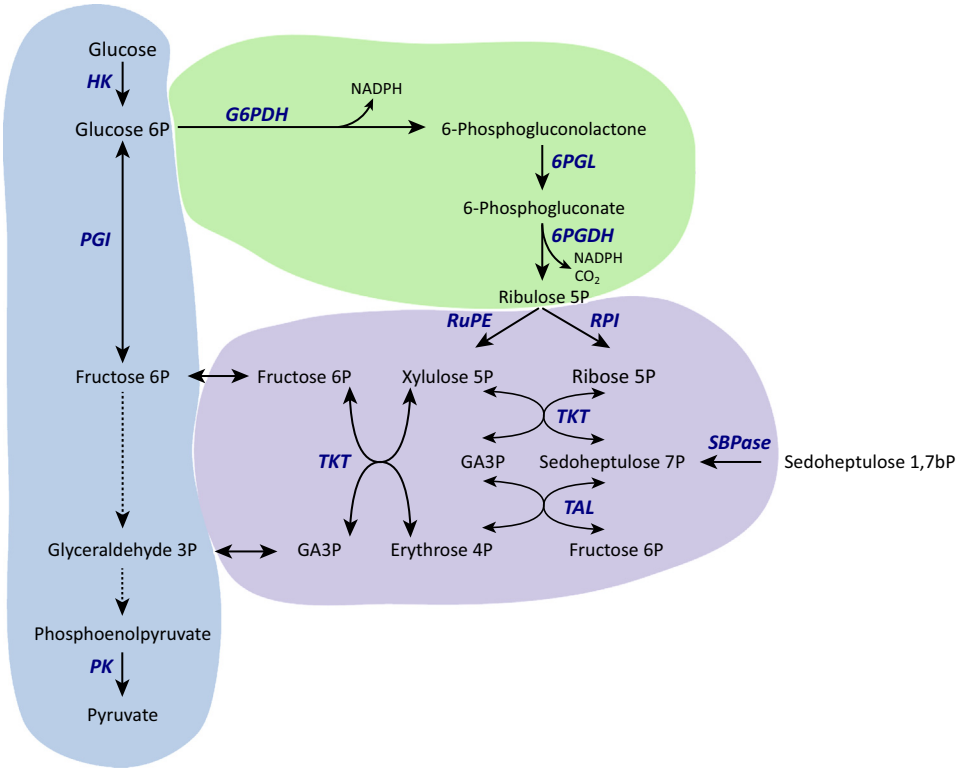


Figure 1. Classical Depiction of the Pentose Phosphate Pathway. Glucose can be metabolised via glycolysis or through the pentose phosphate pathway, branching at glucose 6-phosphate. The glycolytic pathway is shaded in blue and enzymes hexokinase (HK), phosphoglucose isomerase (PGI), and pyruvate kinase (PK) are marked. Other reactions between fructose 6-phosphate and glyceraldehyde 3-phosphate (GA3P) are summarised through the presence of dotted lines. The oxidative branch of the pentose phosphate pathway, shaded in green, comprises the enzymes glucose-6-phosphate dehydrogenase (G6PDH), 6-phosphogluconolactonase (6-PGL), and 6-phosphogluconate dehydrogenase (6PGDH). The nonoxidative branch, shaded in lilac, comprises the enzymes ribulose-5-phosphate epimerase (RuPE), ribose-5-phosphate isomerase (RPI), transketolase (TKT), and transaldolase (TAL). Sedoheptulose-1,7-bisphosphatase (SBPase), which can introduce sedoheptulose 1,7-bisphosphate to the pathway, is also depicted.

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