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Review

Extracellular functions of glycolytic enzymes of parasites: Unpredicted use of ancient proteins

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ABSTRACT

In addition of their usual intracellular localization where they are involved in catalyzing reactions of carbohydrate and energy metabolism by glycolysis, multiple studies have shown that glycolytic enzymes of many organisms, but notably pathogens, can also be present extracellularly. In the case of parasitic protists and helminths, they can be found either secreted or attached to the surface of the parasites. At these extracellular localizations, these enzymes have been shown to perform additional, very different so-called "moonlighting" functions, such as acting as ligands for a variety of components of the host. Due to this recognition, different extracellular glycolytic enzymes participate in various important parasite–host interactions such as adherence and invasion of parasites, modulation of the host's immune and haemostatic systems, promotion of angiogenesis, and acquisition of specific nutrients by the parasites. Accordingly, extracellular glycolytic enzymes are important for the invasion of the parasites and their establishment in the host, and in determining their virulence.

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Contents

Abbreviations: ALD, aldolase; ENO, enolase; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; HK, hexokinase; PFK, phosphofructokinase; PGAM, phosphoglycerate mutase; PGI, glucose-6-phosphate isomerase; PYK, pyruvate kinase; TIM, triosephosphate isomerase.

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1. Introduction

Glycolysis, which is a metabolic pathway involved in ATP and NADH production, also plays a central role in metabolism by providing its intermediates to several other pathways. Glycolysis is found in almost all organisms and for this reason can be considered as an ancient process. Its most common form is the Embden–Meyerhof pathway, but other variants can be found in many organisms. It comprises 10 enzyme-catalyzed steps that convert glucose into pyruvate (Fig. 1). Although glycolysis has been extensively studied from kinetic, structural and functional points of view in both prokaryotic and eukaryotic organisms, this pathway and its enzymes continue revealing new features that help to deepen our understanding of the multiple functions of the process and its enzymes as exerted in different cells. Glycolysis occurs normally in the cytosol and although considered as being freely soluble, glycolytic enzymes often interact with each other in multi-enzyme complexes and with cellular structures such as the cytoskeleton or membranes, and such interactions can modulate their functional properties [1]. Moreover, in some organisms, as is the case for parasites belonging to the trypanosomatid group, glycolysis can also be organized within organelles related to peroxisomes named glycosomes [2].

Although the metabolism in parasites can vary as part of strategies to adapt their life style to the niches occupied in their hosts, the majority of parasitic protists and helminths appear to perform glycolysis. Dependent on the nutrients found in their environment and the stage of their life cycle, many parasitic organisms rely preferentially on glucose catabolism to generate ATP. Moreover, in several parasites this catabolism involves solely glycolysis, without further metabolism of its end product pyruvate or lactate, as for example, in the bloodstream form of the sleeping sickness-causing kinetoplastid *Trypanosoma brucei* [3] and in the intra-erythrocytic stage of the malaria parasite *Plasmodium falciparum* [4].

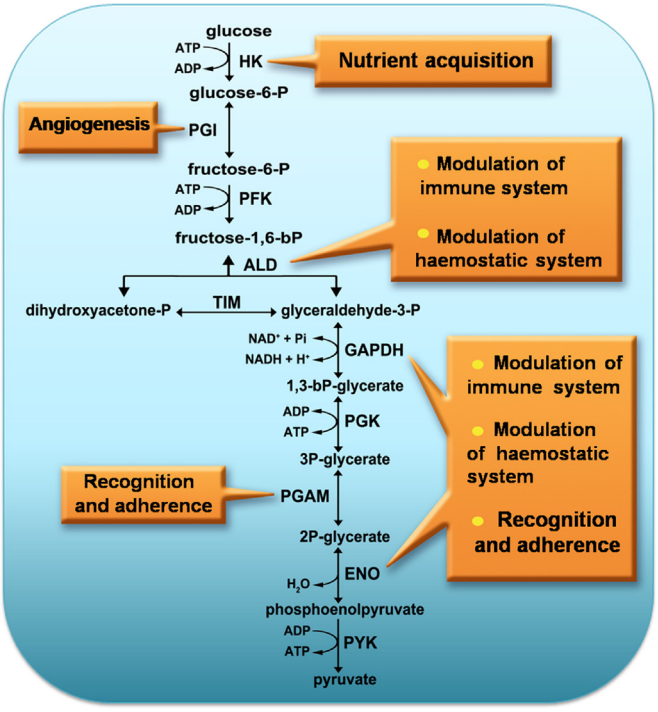

Fig. 1. The enzymatic pathway for glycolysis with indication of moonlighting functions observed for glycolytic enzymes of pathogenic protists and helminths when present outside the parasites. HK, hexokinase; PGI, glucose-6-phosphate isomerase; PFK, fructose-6-phosphate-1-kinase; ALD, fructose-bisphosphate aldolase; TIM, triose phosphate isomerase; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; PGK, phosphoglycerate kinase; PGAM, phosphoglycerate mutase; ENO, enolase; PYK, pyruvate kinase.

2. Glycolytic enzymes may have multiple functions

Besides their role in glycolysis, glycolytic enzymes may function in a variety of other cellular processes occurring at different locations within the cell such as in the nucleus and mitochondria [5,6]. In addition, these enzymes may also exert multiple functions in the extracellular milieu, either while attached to the cell surface or as secreted molecules. Due to this multifunctionality, glycolytic enzymes belong to the group of so-called “moonlighting proteins”. This term has been coined to describe proteins having one or more biological activities in addition to, and independent of, their original well-known function [7]. Ancient proteins such as glycolytic enzymes have acquired multiple moonlighting functions. One of the glycolytic enzymes that is particularly known for having a large number of different moonlighting functions, in both eukaryotic and prokaryotic organisms, is glyceraldehyde-3-phosphate dehydrogenase (GAPDH). These functions are unrelated to its catalytic activity in glycolysis. For example, in the pathogenic bacterium *Streptococcus pyogenes*, a surface-located GAPDH interacts with mammalian fibronectin and lysozyme [8]. GAPDH from *Streptococcus* spp. is also able to bind plasminogen, a protein of the fibrinolytic system of vertebrates and this interaction has been implicated in the virulence of the bacteria [9]. GAPDH of other bacteria has also been suggested to exert moonlighting functions involved in virulence [10]. In mammalian cells, GAPDH is additionally involved in many functions such as DNA repair and intracellular trafficking [11]; some of these other functions are determined by posttranslational modifications of the enzyme [5,11]. Another glycolytic enzyme with an array of moonlighting functions in both eukaryotes and prokaryotes is enolase (ENO) [10,12–14]. Although these two glycolytic enzymes are the ones most often reported with regard to multifunctionality, the other eight enzymes of the glycolytic pathway have each also at least one described moonlighting function [10]. Several functions unrelated to glycolysis have been attributed to these enzymes located at the surface of many cells or in the extracellular milieu. Most of these functions are involved in modulation of the immune system, or in recognition of components of the extracellular matrix or other extracellular proteins.

Parasites are not an exception to the finding that organisms can use their glycolytic enzymes for moonlighting functions. Since, as mentioned above, such extracellular functions can be related to virulence, these particular properties of glycolytic enzymes may even be very important in these infectious agents. Various moonlighting functions of glycolytic enzymes in parasitic protists have been reported [15]. In this review we will discuss the functions, either established as moonlighting or not, of extracellular glycolytic enzymes of pathogenic protists and helminths.

3. Extracellular localization of glycolytic enzymes

The mechanism by which glycolytic proteins reach the outside of cells is clearly unconventional, since these enzymes do not have a recognizable export signal sequence. Several glycolytic enzymes have been found associated with secreted vesicles such as exosomes, that are intracellularly derived from multivesicular bodies and released when they fuse with the plasma membrane. Alternatively, they have been found with shedding vesicles, another type of vesicles produced directly by budding of the plasma membrane [16,17]. Such vesicles are thus formed by one of the different mechanisms known for unconventional protein secretion by eukaryotes. Exosomes and other types of secreted vesicles have also been reported for protist parasites, such as trypanosomatids and

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