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Evolution, dynamics and specialized functions of glycosomes in metabolism and development of trypanosomatids

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Kinetoplastea such as trypanosomatid parasites contain specialized peroxisomes that uniquely contain enzymes of the glycolytic pathway and other parts of intermediary metabolism and hence are called glycosomes. Their specific enzyme content can vary strongly, quantitatively and qualitatively, between different species and during the parasites' life cycle. The correct sequestering of enzymes has great importance for the regulation of the trypanosomatids' metabolism and can, dependent on environmental conditions, even be essential. Glycosomes also play a pivotal role in life-cycle regulation of *Trypanosoma brucei*, as the translocation of a protein phosphatase from the cytosol forms part of a crucial developmental control switch. Many glycosomal proteins are differentially phosphorylated in different life-cycle stages, possibly indicative for unique forms of activity regulation, whereas many kinetic activity regulation mechanisms common for glycolytic enzymes are absent in these organisms. Glycosome turnover occurs by autophagic degradation of redundant organelles and assembly of new ones. This may provide the trypanosomatids with a manner to rapidly and efficiently adapt their metabolism to the sudden, major nutritional changes often encountered during the life cycle. This could also have helped facilitating successful adaptation of kinetoplastids, at multiple occasions during evolution, to their parasitic life style.

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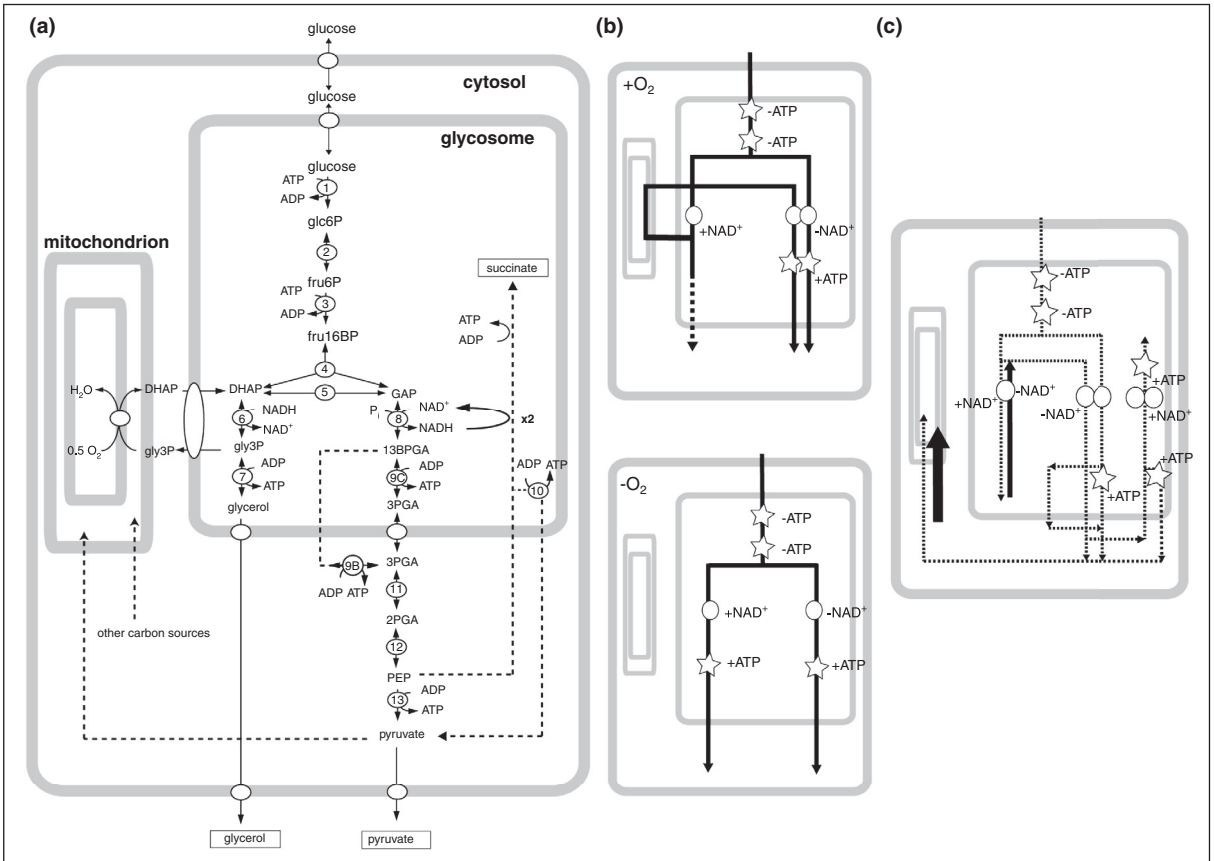
Introduction

Trypanosomatids are organisms that belong to the Kinetoplastea, a large group of flagellated free-living and parasitic protists, which are characterized by a number of unique features. Most notable is the possession of a kinetoplast, a special part of these organisms' single mitochondrion containing a complex DNA structure, called kDNA. Another characteristic is the presence of glycosomes, unusual peroxisomes that harbor the major part of the glycolytic pathway, hence their name. All known trypanosomatid species are parasitic, infecting a large variety of organisms such as mammals—including human—reptiles, insects and even plants. The human-infective parasites, which are transmitted by insects, are responsible for potentially deadly diseases.

These parasites have a complicated life cycle; they are transmitted between humans and other mammals by insects. *Trypanosoma brucei*, that causes sleeping sickness in people living in sub-Saharan Africa, is introduced in the human bloodstream by the bite of an infected tsetse fly when taking a bloodmeal. The trypanosomes multiply as so-called long-slender bloodstream forms (BSF) in the circulatory system of the host where they subsequently differentiate into non-replicating short-stumpy forms that are pre-adapted to life in a new fly. In the fly's midgut, the stumpy forms develop into proliferating procyclic forms (PCF) that, while undergoing several consecutive morphological changes, migrate to the salivary glands. *Trypanosoma cruzi*, responsible for Chagas disease in Latin-America, is transmitted between humans and animals by a blood-sucking reduviid bug, which deposits its infective feces on the skin. After entry through skin wounds and mucous

Figure 1



compartment		enzyme	Aman and Wang, 1986[a]		Hart et al 1984[b]	Albert et al, 2005, Haanstra, 2009[c]	DDUV[d]	other
			protein	activity	activity	activity	activity	protein
glycosome	1	hexokinase	-82%	-96%	-93%	-89%	-98%	
	2	phosphoglucoisomerase	-55%	-81%	-82%	-59%	-90%	
	3	phosphofructokinase	-53%	-92%	-80%	-70%	-73%	
	4	aldolase	-90%	-79%	-64%[e]	-99%	-95%	
	5	triosephosphate isomerase	-3%	-40%	+38%	+12%	+3%	
	6	glycerol-3-phosphate dehydrogenase	+12%	-28%	+3%	+38%	-53%	
	7	glycerol kinase	n.d.	-93%	+28%	+70%	-66%	
	8	glyceraldehyde-3-phosphate dehydrogenase	-43%	-44%	-91%		-67%	
	9B/C	phosphoglycerate kinase B (cytosolic) or C (glycosomal)[f]					-97%	
	10	**pyruvate phosphate dikinase**						+[g]
cytosol	11	**phosphoglycerate mutase**					+500%	
	12	**enolase**					-6%	
	13	**pyruvate kinase**				-98%	-94%	

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(a) Overview of glucose metabolism in Trypanosomatidae. Solid lines represent the major glycolytic routes that are expressed in BSF *T. brucei* and in most developmental stages of all trypanosomatid parasites, dashed lines are extensions that can be present dependent on environmental conditions in PCF *T. brucei* (and possibly in other trypanosomatids) and under specific environmental conditions also in BSF cells [47]. Glycosomal β-oxidation and alanine production in glycosomes of *T. cruzi* (and possibly PCF *T. brucei*) are not depicted. The numbered enzymes are also in panel d. **(b)** Schematic depiction of the glycolytic branches that are used in BSF *T. brucei* in the presence or absence of oxygen. **(c)** Schematic depiction of the glycolytic branches that are used in PCF *T. brucei* (and other trypanosomatid parasites). Solid lines represent dominant branches, dashed lines represent pathways that are downregulated, but can be used with glucose as a carbon source. **(d)** An overview of the quantitative differences in