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Galactose metabolism in *Trypanosoma brucei*

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Summary

The study of galactose metabolism in *Trypanosoma brucei* reveals possible new drug targets

Significance and context

African sleeping sickness, or human African trypanosomiasis, is caused by the parasite *Trypanosoma brucei*, and more than 66 million people suffer from this debilitating disease. The parasite is transferred by a bite of the tsetse fly, which feeds on the blood of animals and humans. The vector's habitat is the vegetation along watercourses and lakes, forest edges, and areas of scrub savanna in Africa. Once inoculated into the human host by an infected tsetse fly, *T. brucei* proliferates and invades all organs. The host mounts an adaptive immune response which kills most of the invading parasites. But the trypanosome has the capacity to vary the composition of its surface coat protein antigens and thus a small number evade the immune system and multiply exponentially. The trypanosome can express thousands of variant proteins. The immune system eventually becomes exhausted by these repeated challenges, and the parasite develops in lymph and blood, causing a variety of debilitating conditions. The parasite can also invade the nervous system, leading to the characteristic 'sleeping sickness' in which patients fall into a coma and die.

The blood-stream form of the parasite is characterized by the presence of many galactose-containing glycoproteins, including the variant surface glycoprotein (VSG) that forms a dense coat around the *T. brucei* cell and is recognized by the host immune system. Although the blood-stream form can import glucose (Glc) from the host, this transport system cannot be used for galactose (Gal), suggesting that galactose may be formed through the epimerization of UDP-Glc into UDP-Gal by a UDP-Glc-4'-epimerase. Roper *et al*. isolated a UDP-Glc-4'-epimerase-encoding gene, *galE*, from *T. brucei* and characterized its function and importance for pathogenesis.

Key results

The sequence of a human UDP-Glc-4'-epimerase was used to screen the databases and a *T. brucei* clone was identified. This 1,764 base-pair genomic clone contained a 1,188-bp open reading frame, named *galE*. The encoded protein shows significant similarity with UDP-Glc-4'-epimerase sequences of *Escherichia coli*, *Saccharomyces cerevisiae*, *Caenorhabditis elegans*, *Drosophila melanogaster*, and

human. It was shown by quantitative PCR that the gene was transcribed in the blood-stream form as well as in the procyclic form. The *galE* gene was overexpressed in *E. coli* and the corresponding recombinant protein was purified. Both the specific activity and the K_m value of the recombinant protein were similar to those of commercially available *Streptococcus thermophilus* epimerase and reported values of UDP-Glc-4'-epimerases. To investigate the importance of *galE* gene expression for pathogenesis, a conditional null mutant was constructed using a *T. brucei* cell line. These experiments showed that most cells died after 3-4 days growth when expression of *galE* was inhibited; but when *galE* expression was allowed again after 10 days, surviving cells started to divide normally. Northern blot analyses further showed that *galE* mRNA was absent from the mutant cell lines as soon as 8 hours after *galE* expression was blocked. Thus, Roper *et al*. have shown the importance of galactose metabolism for parasite viability in culture or *in vivo*.

Links

Advances in sequencing the genome of *T. brucei* are reported at the TIGR%20*Trypanosoma%20brucei*%20genome%20project, the TIGR%20*Trypanosoma%20brucei*%20gene%20index, The%20Sanger%20Institute:%20*Trypanosoma%20brucei* website, and the *Trypanosoma%20brucei*%20genome%20network.

Reporter's comments

Roper *et al*. isolated and characterized a *T. brucei* gene encoding UDP-Glc-4'-epimerase involved in the synthesis of galactose and essential for parasite viability in culture and during pathogenesis. This protein and/or putative galactosyl transferases are candidate targets for anti-parasite drugs. Because *T. brucei* undergoes antigenic variation and genomic rearrangement, it might be useful to identify a set of drugs, each of which affects a particular step in galactose metabolism (such as the glucose transport system, the UDP-Glc-4'-epimerase, putative galactosyl transferases). These drugs should be specific for *T. brucei* enzymes, so that human host processes are affected as little as possible. Comparisons between the *T. brucei* enzymes and their human and/or mouse counterparts may reveal the required *T. brucei*-specific protein features.

Table of links

Proceedings%20of%20the%20National%20Academy%20of%20Sciences

TIGR%20*Trypanosoma%20brucei*%20genome%20project

TIGR%20*Trypanosoma%20brucei*%20gene%20index

The%20Sanger%20Institute:%20*Trypanosoma%20brucei*

Trypanosoma%20brucei%20genome%20network

References

1. Roper JR, Güther MLS, Milne KG, Ferguson MAJ: Galactose metabolism is essential for the African sleeping parasite *Trypanosoma brucei*. Proc Natl Acad Sci USA. 2002, 99: 5884-5889.