Key proteins in the polyamine-trypanothione pathway as drug targets against Trypanosoma cruzi

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In trypanosomatids, redox homeostasis is centered on trypanothione (N 1,N8-bis(glutathionyl)spermidine, T(SH)2), a low molecular weight thiol that is distinctive for this taxonomic family and not present in the mammalian host. Thus, the study of the metabolism of T(SH)2 is interesting as a potential therapeutic target. In this review, we summarize the existing evidence about the metabolism of thiols in Trypanosoma cruzi, focused on those proteins that can be considered the best candidates for selective therapy. Herein, we examine the biosynthetic pathway of T(SH) 2, identifying three key points that are susceptible to attack pharmacologically: the activity of the trypanothione reductase (TR), the function of glutamate-cysteine ligase (GCL) and polyamine transport in T. cruzi. TR has been widely studied and is a good example for the development of the medicinal chemistry of antichagasic compounds. Conversely, GCL and the polyamine uptake system are high flow points in the reductive meta