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ESSENTIALITY AND ROLE OF NOVEL NUCLEOTIDASES INVOLVED IN *TRYPANOSOMA BRUCEI* PYRIMIDINE HOMEOSTASIS

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Nucleotide metabolism has been an area of great interest for the discovery of novel targets against many diseases since a balanced pool of deoxyribonucleotides is required for correct DNA replication and repair. Particularly relevant for cell survival is the maintenance of a balanced dUTP/dTTP ratio in the pyrimidine pool, as several DNA polymerases cannot distinguish between the two nucleotides and incorporate indiscriminately one or the other depending on their availability. We have previously shown that thymidine kinase (TbTK) has a major role in the maintenance of the dUTP/dTTP ratio and the response to genotoxic agents in bloodstream forms of *Trypanosoma brucei*. We reported that TbTK is essential for parasite viability, both *in vitro* and *in vivo* thus demonstrating that phosphorylation of deoxyuridine and/or thymidine is important for the maintenance of the dTTP pool even in the absence of a source of extracellular pyrimidines. These observations indicated a role of the enzyme in *de novo* synthesis and pointed towards the existence of an intracellular deoxynucleoside pool available for phosphorylation. In this work, we have aimed at characterizing nucleotidases that could be involved in the generation of intracellular metabolites important for thymidylate *de novo* biosynthesis. Interestingly, we have identified in *Trypanosoma brucei* an HD domain containing nucleotidase highly similar to human SAMHD1. The absence of the protein in knock-out mutants results in a loss of cell

viability and disturbances in cell cycle progression, which could be completely reverted by the supplementation of thymidine or deoxyuridine. In addition, the lack of the HD nucleotidase could also be rescued by the expression of the human dCMP deaminase, which catalyses the deamination of dCMP to dUMP. Metabolomic analysis by mass spectrometry demonstrated that the absence of the enzyme gives rise to severe perturbations in pyrimidine metabolism. Thus, altogether our results suggest that this HD domain containing nucleotidase is a vital contributor to dTTP biosynthesis and we propose this class of enzymes as relevant players in nucleotide homeostasis in trypanosomes.