Structural characterization of dihydroorotate dehydrogenase: a promising target against tropical diseases

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Dihydroorotate dehydrogenase (DHODH) catalyses the fourth sequential step in the de novo pyrimidine nucleotide synthesis pathway with the oxidation of (S)-dihydroorotate to orotate, and the aid of a flavin cofactor and an electron receptor. Pyrimidines are essential metabolites in all cells. They are required not only for DNA and RNA biosynthesis, but also for biosynthesis of phospholipids and glycoproteins. The de novo pyrimidine biosynthetic pathway is intact in most organisms, including parasites responsible for different tropical diseases such as Trypanosoma cruzi, Leishmania major and Plasmodium falciparum. At present, there is a great interest in inhibitors of DHODH as therapeutic agents for the treatment of cancer, rheumatoid arthritis and parasitic diseases.

Here we present the structural characterization of DHODH from both Trypanosoma cruzi (TCDHODH) and Leishmania major (LMDHODH) based on a multidisciplinary approach that combines biochemical, biophysical and crystallographic methods. Our results are being used for the search of selective inhibitors as a tool against tropical diseases.