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 falcipurum*. At present, there is a great interest in inhibitors of DHODH as therapeutic agents for the treatment of cancer, rheumatoid arthrits and parasitic diaseases.

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.