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Structural studies on ornithine decarboxylase from Leishmania infantum, a key enzyme in the polyamine and trypanothione metabolisms

Ornithine decarboxylase (ODC) is a homodimeric, PLP-dependent enzyme that plays a key role in the polyamine biosynthesis, catalysing the rate-limiting decarboxylation of ornithine to putrescine. Polyamines are essential promoters of the proliferation of cells and are fundamental in cellular processes such as replication of DNA and apoptosis. Moreover, in trypanosomatids the synthesis of polyamines is strongly connected to the redox metabolism. Indeed, the polyamine spermidine is needed for the synthesis of trypanothione, a dithiol analog to glutathione used by trypanosomatids to neutralize the reactive oxygen species produced by macrophages to fight the infection. For this reason, ODC is an appealing target to develop drugs against the diseases caused by tryanosomatids (leishmaniases and trypanosomiases). As a matter of fact, eflornitine also known as DFMO (DiFluoro Methyl Ornithine) is the first line drug for the treatment of the neurological stage of sleeping sickness caused by Trypanosoma brucei gambiense. Sequence analysis shows that, besides the canonical domain, ODC from Leishmania spp. is characterized by an additional N-terminal extension of around 250 aminoacids with unknown structure and function. We crystallized ODC from Leishmania infantum (LiODC) and collected a diffraction dataset at 3.6 Å resolution, allowing us to build a model that comprises about the 60 % of the protein sequence; in addition to the canonical C-terminal domain, a portion of the N-terminal domain is visible in the structure (segments: 122-180 and 211-224) resulting to be folded into three alpha helices. The first 120 N-terminal residues as well as four long insertions in the C-terminal domain are not visible in the structure. SAXS and preliminary Cryo-EM experiments reveal the presence of multiple conformations for the LiODC dimers supporting a strong flexibility of the first 120 residues and of the C-terminal domain loops.

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