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Characterization of cystathionine γ-lyase from *T. gondii*: A target for drug development?

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Toxoplasma gondii is a protozoan parasite of medical and veterinary relevance responsible for toxoplasmosis in humans. As there is currently no vaccine available for human, the identification of good target candidates for future drug development is urgently required. A recent proteomic analysis of partially sporulated oocysts of *T. gondii* showed that oocyctes have a greater capability of *de novo* amino acid biosynthesis, shedding light on a stage-specific subset of proteins whose functional profile is consistent with the oocyst need to resist various environmental stresses. Among these putative oocyst/sporozoite-specific proteins, three enzymes involved in cysteine metabolism, i.e., cystathionine β-synthase, cystathionine γ-lyase (CGL) and cysteine synthase, were found. However, despite the central metabolic roles of these enzymes, the functionality of none of them has so far been investigated. Herein, CGL from *T. gondii* (TgCGL) has been cloned, expressed and physiochemically and enzymatically characterized. The purified TgCGL is a functional enzyme which splits L-cystathionine almost exclusively at the CγS bond to yield L-cysteine. This finding likely implies that the reverse transsulfuration pathway is operative in the parasite. The enzyme displays only marginal reactivity toward L-cysteine, which is also a mixed-type inhibitor of TgCGL activity, therefore indicating a tight regulation of cysteine intracellular levels in the parasite. Structure-guided homology modelling revealed two striking amino acid differences between human and parasite CGL active sites (Glu59 and Ser340 in human to Ser77 and Asn360 in toxoplasma). Mutation of these two residues to the corresponding residues in human revealed their importance in modulating both substrate and reaction specificity of the parasitic enzyme. Our findings might have far-reaching implications for the use of TgCGL as anti-toxoplasmosis drug target.

Recent Publications

1. Astegno A, Maresi E, Bertoldi M, La Verde V, Paiardini A, et al. (2017) Unique substrate specificity of ornithine aminotransferase from *Toxoplasma gondii*. Biochem J. 474(6):939-955.
2. Astegno A, Bonza M C, Vallone R, La Verde V, D'Onofrio M, et al. (2017) Arabidopsis calmodulin-like protein CML36 is a calcium Ca2+ sensor that interacts with the plasma membrane Ca2+-ATPase isoform ACA8 and stimulates its activity. J Biol Chem. 292(36):15049-15061.
3. La Verde V, Trande M, D'Onofrio M, Dominici P and Astegno A (2018) Binding of calcium and target peptide to calmodulin-like protein CML19, the centrin 2 of *Arabidopsis thaliana*. Int J Biol Macromol. 108:1289-1299.
4. Rossignoli G, Phillips R S, Astegno A, Menegazzi M, Voltattorni CB, et al. (2018) Phosphorylation of pyridoxal 5'-phosphate enzymes: an intriguing and neglected topic. Amino Acids. 50(2):205-215.
5. Allegrini A, Astegno A, La Verde V and Dominici P (2017) Characterization of C-S lyase from *Lactobacillus delbrueckii subsp. bulgaricus* ATCC BAA-365 and its potential role in food flavour applications. J Biochem. 161(4):349-360.

Biography

Alessandra Astegno is interested in different aspects of Protein Chemistry and Enzymology, including folding, evolution and structure-function relationship of proteins and macromolecular assemblies. She is currently an Assistant Professor in Biochemistry at the Department of Biotechnology of the University of Verona. She has a solid background in recombinant protein expression and purification, functional and structural characterization of pyridoxal phosphate-dependent enzymes as well as metallo-proteins.

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