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Trypanosoma brucei polyamine biosynthesis enzyme structures provide information about novel metabolism and regulation

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Trypanosoma brucei is a neglected tropical disease endemic to Africa. We structurally characterize enzymes in biosynthetic pathways of trypanosomatids to potentially exploit them as targets for development of anti-proliferative agents. The polyamine spermidine is essential for post-translational hypusine modification of eukaryotic initiation factor 5A (eIF5A), which is catalyzed by deoxyhypusine synthase (TbDHS). In trypanosomatids, deoxyhypusine synthase (DHS) activity is dependent on heterotetramer formation between two paralogs, DHSc and DHSp, both with minimal activity on their own due to missing catalytic residues. We determined the X-ray structure of TbDHS showing a single functional shared active site is formed at the DHSc/DHSp heterodimer interface, with deficiencies in one subunit complemented by the other. Each heterodimer contains two NAD+ binding sites, one housed in the functional catalytic site and the second bound in a remnant dead site that lacks key catalytic residues. Differences between trypanosomatid and human DHS that could be exploited for drug discovery were identified.

Catalytically inactive enzyme paralogs occur in many genomes, including the trypanosomatids. Some regulate their active counterparts, but the structural principles of this regulation remain largely unknown. We report X-ray structures of Trypanosoma brucei S-adenosylmethionine decarboxylase alone and in functional complex with its catalytically dead paralogous partner, prozyme. We show monomeric TbAdoMetDC is inactive because of autoinhibition by its N-terminal sequence. Heterodimerization with prozyme displaces this sequence from the active site through a complex mechanism involving a cis-to-trans proline isomerization, reorganization of a beta-sheet, and insertion of the N-terminal alpha-helix into the heterodimer interface, leading to enzyme activation. These studies elucidate an allosteric mechanism in an enzyme and a plausible scheme by which such complex cooperativity evolved.

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