Allostery in Motion: *Trypanosoma brucei* enzyme brought to life by a dead paralog

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Pseudoenzymes are known to functionally regulate their active counterparts. We present a case study of such a regulation in *Trypanosoma brucei S*-adenosylmeyhionine decarboxylase (*Tb*AdoMetDC), which is 1000-fold activated by heterodimerization with its catalytically dead paralog, prozyme.

To gain insight into the activation mechanism, we solved crystal structures of both the low-activity monomeric *Tb*AdoMetDC and fully active heterodimeric *Tb*AdoMetDC/prozyme. The structures reveal that *Tb*AdoMetDC monomer activity is low due to autoinhibition, and that prozyme allosterically activates the complex by inducing intricate conformational changes that result in a relief of autoinhibition.

We were able to identify key segments of movement that facilitate long-range control of the *Tb*AdoMetDC active site from the dimerization interface: (1) flipping and slipping of beta-strands, (2) disordered-to-ordered transitioning of a loop, and (3) prolyl peptide bond cis-to-trans isomerization. These concerted changes lead to a stable active confirmation.

Our study reveals how pseudoenzymes can allosterically regulate cognate enzymes through a complex set of structural changes.