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Poster

A family portrait of L-asparaginases taken by crystallography

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The simple hydrolysis of the amide group at the side chain of L-asparagine, leading to L-aspartate and ammonia, has at least three enzymatic solutions in the living organisms, catalyzed by enzymes classified in three structural Classes and five types. Class 1 L-asparaginases, formerly known as bacterial-type (a misnomer, as representatives are found in all domains of life), have been thoroughly studied, as some type II enzymes of Class 1 are potent antileukemic drugs. Their catalytic center, originally postulated to be a T-K-D version of the serine protease triad, has been recently re-interpreted as a system of two T residues with a proton relay involving an activated Y residue and a chain of water molecules, that works according to a double-displacement mechanism. The origin of the Y residue in these homotetrameric enzymes differentiates types I and II enzymes. Class 2 L-asparaginases are Ntn-hydrolases, i.e. are expressed as single-chain precursors that undergo autoproteolytic activation, liberating a nucleophilic T residue at the N terminus of subunit beta. The enzymatic activity (which can also hydrolyze L-Asn modifications, e.g. beta-peptides or glycopeptides) is based on a pair of T residues that also work in a ping-pong mode. Some Class 2 L-asparaginases are activated by K+ cations bound in an activation loop. The prototypes IV and V of Class 3 L-asparaginases (so far found in bacteria and fungi) are from the symbiotic bacterium Rhizobium etli. By structural homology to such enzymes as serine beta-lactamases or glutaminases, the active site in this Class was identified as consisting of two S K tandems and an odd Zn2+ binding site that plays a role in substrate docking, but not in catalysis. One of the S-K tandem S residues is the primary nucleophile but its activation is a mystery. It is also a mystery why, and by what mechanism, some of these proteins have the S nucleophile phosphorylated.

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