Many secrets of L-asparaginase, the oldest protein-based cancer drug

L-asparaginase (a hydrolase converting L-asparagine to L-aspartic acid) was the first enzyme to be used in clinical practice as an anticancer agent after its approval in 1978 as a component of a treatment protocol for childhood acute lymphoblastic leukemia (ALL). Structural and biochemical properties of L-asparaginases have been extensively investigated during the last half century, providing an accurate structural description of the enzyme isolated from a variety of sources, as well as clarifying the mechanism of its activity. The lecture will focus on critical assessment of the current state of knowledge of primarily structural, but also selected biochemical properties of “bacterial-type” L-asparaginases from different organisms. The most extensively studied members of this enzyme family are L-asparaginases highly homologous to one of the two enzymes from *Escherichia coli* (usually referred to as EcAI and EcAII). Members of this enzyme family, although often called bacterial-type L-asparaginases, have been also identified in such divergent organisms as archaea or eukarya. Over 100 structural models of L-asparaginases have been deposited in the Protein Data Bank during the last 30 years. One of the prime achievements of structure-centered approaches was the elucidation of the details of the mechanism of enzymatic action of this unique hydrolase that utilizes a side chain of threonine as the primary nucleophile. The molecular basis of other important properties of these enzymes, such as their substrate specificity, are still being evaluated. Results of structural and mechanistic studies of L-asparaginases are being utilized in efforts to improve the clinical properties of this important anticancer drug.