The Structure of a Mitochondrial Peptidasome

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The pitrilysin endometalloproteases perform an essential molecular scavenger function in the cell by removing potentially harmful peptides. Especially the insulin-degrading enzyme (IDE) has obtained much attention, in part due to IDE's ability to degrade the degenerative amyloid-ß peptide associated with Alzheimer's disease. Presequence protease (PreP) is an organellar homologue to IDE and was recently identified as a protease responsible for the degradation of targeting peptides in both mitochondria and chloroplasts. The ability of PreP to degrade small, unfolded peptides in mitochondria is of particular interest in light of recent findings, which link amyloid-ß to the mitochondrial toxicity associated with Alzheimer's disease.

The 2.1Å resolution crystal structure of PreP from *Arabidopsis thaliana* represents the first structure from the pitrilysin protease family. The 995-residue polypeptide forms an enclosed chamber of more than 10,000Å^3 that shields the proteolytic site. The fact that proteolysis occurs inside a closed chamber is reminiscent of the proteasome structure and for that reason we introduced a new term: the peptidasome. The chamber has no obvious opening for the substrate to enter; yet a bound peptide is found inside and amino acids separated by almost 800 residues in sequence form the active site. The structure suggests a novel mechanism for access to the active site, involving hinge-bending motions that cause the peptidasome to open and close in response to substrate binding.

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