Deciphering the functional properties of non-metazoan caspase homologues

P-02.3-05

M. Klemenčič[I], V. Štrancar[I], N. Goršek[I], P. Huesgen[II]

[I]University of Ljubljana, Faculty of Chemistry and Chemical Technology, Department of Biochemistry, Ljubljana, Slovenia, [II]Forschungszentrum Jülich, Juelich, Germany

Caspases are enzymes, indispensable for execution of apoptosis in metazoa. However, no caspases were yet identified in other eukaryotes. Instead, structurally highly homologous proteins were identified and termed metacaspases and paracaspases. Additionally, caspase homologues were also found in prokaryotes and were termed orthocaspases. All members of this caspase superfamily contain the p20 domain, with the His-Cys dyad needed for hydrolysis of the peptide bond. Despite high structural similarities between the p20-containing proteins, only caspases cleave their substrates after negatively charged amino acid residues, while paracaspases, as well as type I/II metacaspases and orthocaspases favour the Arg or Lys at the position P1.

No information was until recently available for orthocaspases and type III metacaspases, which are found in prokaryotes and algae, respectively. We have recently shown that genes for both types code for proteolytically active enzymes, which have the preference for cleavage after basic amino acid residues. The activity of type III metacaspases, just like for type I and type II metacaspases, strongly depends on the presence of calcium. Additionally, we show high functional relatedness of type III metacaspases to type I metacaspases and propose a new function of the p10 domain. This domain contains a well-conserved N-terminal region, which can only be found in type I/II/III metacaspases, but is absent in caspases and calcium-independent caspase homologues, which explains their calcium-independent activity. Despite their similar structural properties, the three metacaspase types exhibit remarkably contrasting activation, autoprocessing and proteolytic properties and vary in their substrate preferences, as we have determined by performing Proteolytic Identification of Cleavage Sites (PICS).