PYRIN and CARD Domains of the Apoptosis-associated Protein ASC: Structure and Interdomain Mobility

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Human ASC [1], a 195 amino acid-long protein abundantly expressed in epithelial cells and leukocytes, is intimately involved in the immune response system and plays a key role in apoptosis. ASC modular structure contains a caspase recruitment domain (CARD) and an N-terminal pyrin death domain (PYR), both known to act as protein-protein binding domains and therefore having pivotal functions in the regulation of apoptosis and inflammation. For instance, ASC participates in apoptotic pathways by acting as an adaptor of the protein Bax and by interacting with several caspases [2]. Additionally, ASC constitutes part of a multiprotein complex named the inflammasome, which stimulates caspase-1 activation. The relevance of ASC physiological role is manifested by mounting evidence that connects the silencing of ASC expression to several types of human cancer (breast, brain and ovarian) [3].

The biological functions of ASC are linked to its capacity of forming protein complexes and to self-associate, therefore, a key step towards the understanding of ASC role in apoptosis, cancer and inflammation is to study its structure and interdomain dynamics. Multidimensional, triple-resonance NMR techniques have been used to determine the structure of ASC, which is compared to the structures of isolated PYR and CARD domains of other apoptosis-related proteins, highlighting structural differences and similarities relevant to the protein function. Information on interdomain mobility and interface has been obtained from magnetic relaxation experiments and chemical shift perturbation data.

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