PROGRAMMED CELL DEATH AND INHIBITORS OF APOPTOSIS PROTEIN FAMILY (IAP) AND THEIR ROLE IN CANCEROGENESIS

Summary

Apoptosis is a natural physiological process, intended to eliminate some cells. Incorrect, damaged or redundant cells, undergo programmed cell death. Initiation of the apoptosis proceeds under the influence of extracellular factors and activation of membrane receptors or involves mitochondrion activity and a disruption of intracellular homeostasis. A crucial role in regulation of the apoptosis is played by the Bcl-2 family proteins, which include pro- and anti-apoptotic proteins. The relation between these proteins determines which pathway leading to the cell death will be entered. Apoptosis may be inhibited in several ways, for example by heat shock proteins (HSP) or by inhibitors of apoptosis (IAP). IAP inhibit initiation of the process by binding to effector proteins of the execution phase of apoptosis or by leading them to the proteasomal degradation. Genes of IAP were identified for the first time in baculoviruses. In a human, eight IAP proteins, grouped into three classes, were isolated. Common feature of all members of the family is the presence of at least oneBIR domain. BIR domains and contiguous regions are responsible for binding IAPs to caspases, leading to inhibition of their activity. Other domains, common for specific members of IAP family, are responsible, among others, for: degradation of proteins through ubiquitination (RING, UBC domains) or association with other proteins (CARD domain). Besides controlling apoptotic pathways, IAPs take part in degradation of proteins not involved in the programmed cell death, in control of the cell cycle and regulation of transcription factors.

Avoidance by a cell of the control mechanisms of cell proliferation and death may lead to its cancer transformation. A frequently observed phenomenon in cancer cells is an increased expression of IAP proteins, hence their function can be compared to that of the oncogenes. In many types of cancers cells exhibit the presence of translocation or amplification of genes encoding apoptotic inhibitors. This decreases cancer's sensitivity to pro-apoptotic stimuli. The level of IAP proteins in a cell may serve as a marker of developing cancer and a prognostic factor. IAP proteins are thus attractive goal of research underlying cancer therapies, mainly those involving the use of IAP inhibitors and interfering RNA.