THE MECHANISM OF RESISTANCE TO APOPTOSIS IN TUMOR CELLS

Summary

A most normal cell can die by apoptosis but tumor cells very often have some defects in the apoptotic pathway, leading not only to the increase of tumor mass but also to tumor resistance to chemotherapy. Since chemotherapy and irradiation act primarily by inducing apoptosis, defects in the apoptotic pathway make the therapy less efficient. Generally, there are two pathways of apoptosis. One — mediated by the cell surface death receptors — the extrinsic pathway, the other mediated by the mitochondria — intrinsic pathway. The common element in those two ways is activation of caspase 3. However, in some cases we can observe cell death without activation of this enzyme. One of the often occurring mechanism of resistance to apoptosis is overexpression of the Bcl-2 family antyapoptotic proteins like Bcl-2 and Bcl-XL, or lower expression of proapoptotic proteins like Bax, Bid, Bad. Another mechanism observed in tumor cells is overexpression of apoptosis inhibitors namely IAPs and FLIP. They play an important role in degradation or inactivation of executor caspases and protect cells from apoptosis. A key element in stress-induced apoptosis is p53 protein which can induce the expression of proteins involved in the mitochondrial apoptotic pathway. Mutations in p53 are common in many tumors and affect their ability to undergo cell death. In many tumor cells also the survival signal is stronger than usually and induction of apoptosis is more difficult. One of survival pathways is connected with the PI3K/Akt signalling pathway. Also cells with high expression of Hsp70 protein are protected from apoptosis, especially that leading through mitochondria. Cells with MDR (multidrug resistance) phenotype, expressing proteins from the ABC superfamily on cell surface, are able to exclude many of the drugs (including anticancer drugs) from cytoplasm. There are some evidences that cell possessing membrane transporters are resistant to that form of apoptosis connected with activation of caspase 3. The knowledge of the molecular mechanisms of tumor resistance to apoptosis can improve cancer therapy through resensitization of tumor cells.