

Apoptosis-Based Therapies for Neoplastic Diseases

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Abstract

Defects in the regulation of apoptosis (programmed cell death) make important contributions to the pathogenesis and progression of most cancers and hematological malignancies, and also figure prominently in resistance to chemotherapy, radiotherapy, and immune-based treatments. Apoptosis is caused by activation of intracellular proteases, known as “caspases”, which are responsible directly or indirectly for the morphological and biochemical events that characterize the apoptotic cell. Numerous proteins that regulate these cell death proteases have been discovered, including proteins belonging to the Bcl-2, IAP, CARD, Death Domain (DD), Death Effector Domain (DED) families). These caspase-regulating proteins provide mechanisms for linking environmental stimuli to cell death responses (e.g. DNA damage, microtubule disruption; cytokine stimulation) or to maintenance of cell survival (e.g., growth factors; cell adhesion receptors; oncoproteins). Alterations in the expression and function of several apoptosis-regulating genes have been demonstrated in cancer, suggesting targets for drug discovery. Knowledge of the molecular details of apoptosis regulation and the 3-dimensional structures of apoptosis proteins have revealed new strategies for identifying small-molecule drugs that may one day yield more effective treatments for malignancy. Apoptosis-regulating genes are also beginning to find utility as targets for antisense oligonucleotides or as apoptosis inducers for use in cancer gene therapy. Moreover, knowledge about the signal transduction pathways that control the expression of apoptosis gene can be exploited for altering the balance of pro- and anti-apoptotic gene expression so that apoptosis sensitivity is restored to tumor cells, using protein kinase inhibitors, regulators of steroid/retinoid-family transcription factors, and other approaches. Some of the key molecules responsible for aberrant regulation of apoptosis in cancer will be described and strategies for clinical intervention presented.
