

Constantinou C, Papas KA, Constantinou AI. **Caspase-independent pathways of programmed cell death: The unraveling of new targets of cancer therapy?** *Current Cancer Drug Targets* 2009 9(6):717-728.

In the past few years, accumulating evidence in the literature supports the existence of pathways of caspase-independent programmed cell death (CI-PCD). These pathways are likely to be acting as 'death backup systems' that ensure effective removal of defective cells from the organism. Similar to classical apoptosis i.e. caspase-dependent programmed cell death (CD-PCD), the mitochondrion is the main organelle orchestrating the series of events which are required for the induction of CI-PCD. In addition, the pro-apoptotic proteins Bax and Bid are also key participants in CI-PCD. However, contrary to CD-PCD, CI-PCD involves executioners other than the caspases which include the cathepsins, the calpains and serine proteases. The protein AIF may also play an important role in the induction of CI-PCD. In this review we report current knowledge on CI-PCD and provide evidence for its regulation by chemotherapeutic agents currently used in the clinic and under investigation in clinical trials. Lastly, we discuss how the study of natural and synthetic agents triggering CI-PCD may help in the pharmacological design of a new generation of more effective chemotherapeutic drugs. The use of such drugs activating both CD-PCD and CI-PCD pathways should achieve a more successful eradication of carcinogenic cells and the attainment of lower levels of tumor resistance.