

**THE MOLECULAR BASIS OF RESISTANCE TO APOPTOSIS IN
CALCITRIOL DIFFERENTIATED CELLS**

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The induction of monocytic differentiation by 1,25-dihydroxyvitamin D₃ (calcitriol) confers the ability to resist drug-induced apoptosis to human promyelocytic leukemia cells (HL-60). Though analogs of calcitriol were proposed to be candidates for anti-cancer drugs, this property could be a limiting factor in their application. The molecular basis of this phenomenon is still unclear. The evasion of apoptosis by differentiated cells may depend on changes in the susceptibility to death signals or changes in the cell survival machinery. Our results show that changes detected in the CD95 (APO-1/Fas) receptor/ligand system of HL-60 cells are of no significance in the mechanism of this phenomenon. Undifferentiated and calcitriol-differentiated HL-60 cells express low levels of the CD95 receptor. We speculated that the apoptosis resistance of differentiated HL-60 cells might be caused by an increased sensitivity to growth factors present in fetal calf serum (FCS). We showed that calcitriol-differentiated HL-60 cells undergo apoptosis in serum-free conditions but a low concentration of FCS is enough to prevent them from apoptosis. We also observe that insulin is a component of fetal calf serum which can prevent the serum-free cell death of differentiated cells. The antiapoptotic activity of insulin in calcitriol-differentiated HL-60 cells is phosphatidylinositol 3-kinase dependent. Moreover, the results of our experiments reveal that resistance to apoptosis concerns not only cells differentiated by calcitriol, but also by its side-chain modified analogs, as long as they retain strong cell-differentiating-properties.