Mechanisms of apoptosis-induction by rottlerin: therapeutic implications for B-CLL.

Abstract:
Constitutively activated signaling pathways contribute to the apoptosis-defect of B-CLL cells. Protein kinase C-delta is a permanently activated kinase and a putative downstream target of phosphatidylinositol-3 kinase in B-CLL. Blockade of protein kinase C-delta (PKC-delta) by the highly specific inhibitor rottlerin induces apoptosis in chronic lymphocytic leukaemia (CLL) cells. By co-culturing bone marrow stromal and CLL cells, we determined that the proapoptotic effect of rottlerin is not abolished in the presence of survival factors, indicating that a targeted therapy against PKC-delta might be a powerful approach for the treatment of CLL patients. The downstream events following rottlerin treatment engage mitochondrial and non-mitochondrial pathways and ultimately activate caspases that execute the apoptotic cell death. Herein we report that the inhibition of PKC-delta decreases the expression of the important antiapoptotic proteins Mcl-1 and XIAP accompanied by a loss of the mitochondrial membrane potential Deltapsi. In addition, we discovered that ZAP-70-expressing cells are significantly more susceptible to rottlerin-induced cell death than ZAP-70 negative cells. We finally observed that rottlerin can augment cell toxicity induced by standard chemotherapeutic drugs.

Conclusively, PKC-delta is a promising new target in the combat against CLL.