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Autor(en) des Beitrags: Vier, J; Gerhard, M; Wagner, H; Häcker, G

Titel des Beitrags: Enhancement of death-receptor induced caspase-8-activation in the death-inducing signalling complex by uncoupling of oxidative phosphorylation.

Abstract: Signalling through the death receptor CD95 induces apoptosis by formation of a signalling complex at the cell membrane and subsequent caspase-8 and caspase-3-activation. Treatment of Jurkat T cells with protonophores across the mitochondrial membrane such as 2,4-dinitrophenol (DNP) enhances the death-inducing capacity of CD95. In this study, we show that this enhancement is due to the specific acceleration of caspase-8-processing and activation at the CD95-receptor. DNP-treatment did not affect NF-kappaB-induction by CD95. Immunoprecipitation experiments showed that the amounts of the adapter FADD/MORT1 and pro-caspase-8 at the CD95-receptor were not altered by DNP. Subcellular fractionation studies revealed that the amount of mature caspase-8 but not pro-caspase at the membrane was increased following CD95-stimulation in the presence of DNP. As a consequence of caspase-activation, c-FLIP-levels in the cytosol decreased. In Jurkat cells overexpressing c-FLIPS, DNP was still able to enhance caspase-activation. The enhancing capacity of DNP was seen in some cell lines (Jurkat, CEM and HeLa) but not in SKW6 cells and was also found in mitogen-stimulated human T cells. Furthermore, the enhancement extended to TRAIL-induced caspase-activation. Thus, a mechanism exists by which caspase-8-activation can be
accelerated at death receptors and this mechanism can be triggered by targeting mitochondrial oxidative phosphorylation.