

THE BH3-ONLY PROTEIN NBK/BIK INDUCES APOPTOSIS VIA AN ER SIGNALLING PATHWAY

B. Gillissen¹, D. Güner¹, P. Hemmati¹, G. Forro¹, F. Essmann², B. Dörken¹, P. T. Daniel¹

¹Department of Hematology, Oncology and Tumor Immunology, University Medical Center Charite, Humboldt University, Berlin, Germany

²University of Düsseldorf, Institute of Molecular Medicine, Düsseldorf, Germany

Besides the extrinsic and intrinsic apoptosis signalling pathways, a third pathway for activating apoptosis has been identified which involves the endoplasmic reticulum. The pro- and anti-apoptotic members of the Bcl-2 family are key regulators of the mitochondrial and ER pathway and their deregulation have been implicated in the development of diverse malignancies. The pro-apoptotic subgroup of so called BH3-only proteins share homology in only one of the four conserved regions termed Bcl-2 homology (BH) domains 1 to 4. BH3-only proteins continuously sense the cellular integrity at various subcellular levels. Activation of these proteins by distinct upstream signals triggers activation of the proapoptotic multidomain proteins Bax and Bak and consequently induction of apoptosis by release of proapoptotic factors from the mitochondrial intermembrane space into the cytosol. The BH3-only protein Nbk/Bik (Natural born killer /Bcl-2 interacting killer) acts via an entirely Bax dependent pathway and causes a conformational switch and translocation of Bax to the outer mitochondrial membrane, but it neither interacts nor colocalizes with Bax (Gillissen et al. EMBO J 2003, 22, 3580). Activation of Bax by Nbk coincides with loss of the mitochondrial membrane potential and release of cytochrome c from the mitochondrial intermembrane space into the cytosol. Here we show that despite activation of the mitochondria in Nbk induced apoptosis, Nbk does not colocalize with mitochondria but with the endoplasmic reticulum. Consequently, targeting of the antiapoptotic protein Bcl-2 to either of these subcellular organelles, the mitochondria as well as the ER, protects cells from Nbk induced apoptosis. Thus activation of the mitochondria in Nbk-induced apoptosis occurs via an indirect mechanism that is regulated by the ER.