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Autor(en) des Beitrags: Boutaffala, L; Bertrand, M J M; Remouchamps, C; Seleznik, G; Reisinger, F; Janas, M; Bénézech, C; Fernandes, M T; Marchetti, S; Mair, F; Ganeff, C; Hupalowska, A; Ricci, J-E; Becher, B; Piette, J; Knolle, P; Caamano, J; Vandenabeele, P; Heikenwalder, M; Dejardin, E

Titel des Beitrags: NIK promotes tissue destruction independently of the alternative NF-κB pathway through TNFR1/RIP1-induced apoptosis.

Abstract: NF-κB-inducing kinase (NIK) is well-known for its role in promoting p100/NF-κB2 processing into p52, a process defined as the alternative, or non-canonical, NF-κB pathway. Here we reveal an unexpected new role of NIK in TNFR1-mediated RIP1-dependent apoptosis, a consequence of TNFR1 activation observed in c-IAP1/2-depleted conditions. We show that NIK stabilization, obtained by activation of the non-death TNFRs Fn14 or LT?R, is required for TNF?-mediated apoptosis. These apoptotic stimuli trigger the depletion of c-IAP1/2, the phosphorylation of RIP1 and the RIP1 kinase-dependent assembly of the RIP1/FADD/caspase-8 complex. In the absence of NIK, the phosphorylation of RIP1 and the formation of RIP1/FADD/caspase-8 complex are compromised while c-IAP1/2 depletion is unaffected. In vitro kinase assays revealed that recombinant RIP1 is a bona fide substrate of NIK. In vivo, we demonstrated the requirement of NIK pro-death function, but not the processing of its substrate p100 into p52, in a mouse model of TNFR1/LT?R-induced thymus involution. In addition, we also highlight a role for NIK in hepatocyte...
apoptosis in a mouse model of virus-induced TNFR1/RIP1-dependent liver damage. We conclude that NIK not only contributes to lymphoid organogenesis, inflammation and cell survival but also to TNFR1/RIP1-dependent cell death independently of the alternative NF-κB pathway.