# The NF?B-mediated Control of RS and JNK Signaling in Vitamin A-treated Cells: Duration of JNK/AP-1 Pathway Activation may Determine Cell Death or Proliferation.

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NF?B has emerged as a crucial regulator of cell survival, playing functions in cellular resistance to oxidants and chemotherapeutic agents. Recent studies showed that NF?B mediates cell survival through the suppression of the accumulation of reactive species (RS) and the control activation of the Jun-N-terminal kinase (JNK) cascade. This work was undertaken in order to evaluate the role of NF?B in modulating the pro-oxidant effects of supplementation with Vitamin A (retinol) in Sertoli cells, a major retinol target. In this work, we reported that retinol increases mitochondrial RS formation leading to a redox-dependent activation of NF?B. NF?B activation played a pivotal role in counteract RS accumulation in retinol-treated cells, since NF?B inhibition with DNA decoy oligonucleotides (ODNs) or pharmacological inhibitors (BAY-117082) potentiated retinol-induced RS and oxidative damage. In the presence of NF?B inhibition, retinol-induced oxidative stress, promoted a prolonged activation of the JNK/AP-1 pathway and induced significant decreases in cell viability. Inhibition of JNK/AP-1 with ODNs to AP-1 or JNK inhibitor SP600125 prevented the decreases in cell viability. Antioxidants blocked the persistent JNK/AP-1 activation, cell oxidative damage and the decreases in cell viability induced by NF?B inhibition. Finally, our data pointed that NFkB-dependent induction of SOD2 acts as a potential antioxidant factor mediating NF?B protective effects against retinol-induced oxidative stress. Thus, data suggest that NF?B mediates cellular resistance to the pro-oxidant/cytotoxic effects of retinol by preventing or avoiding RS accumulation and the persistent and redox-dependent activation of JNK/AP-1 pathway.

Keywords: Retinol, NF?B, oxidative stress, and JNK-AP1.
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