Activation and Homeostatic Control of IKK and NF-kappaB in oncogenesis and development

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NF-κB and IκB kinases (IKK) serve to transmit signals in diverse biological contexts to affect apoptosis, proliferation and morphogenic processes, as well as other functions. In a growing number of tumor entities, including Hodgkin lymphoma, the first two biological functions are of prime importance and hence IKK pathways are pharmacological targets. Proteomic analyses of IKK-associating components have revealed a number of proteins, including Hsp90 and the co-chaperones Cdc37 and FKBP51, that interact with IKK complexes. For its efficient inducibility and homeostasis in tumor cells, the IKK complex requires the ATPase activity of the chaperone Hsp90. Analogues of the HSP90 ATPase inhibitor geldanamycin, which inhibit IKK activation by pro-inflammatory cytokines, are under clinical evaluation. However, how chaperones regulate IKK pathways is not known. An analysis of the interaction of chaperone molecules with IKK and the differential functional requirement for IKK activation, prevention of co-translational IKK ubiquitination and post-translational folding will be presented. In addition to the activation of IKK and NF-B triggered by signaling emanating from the cytoplasm, the DNA-damage response (DDR) activates a nuclear signaling cascade that results in activation of cytoplasmic IKK complexes. The identification of a novel component of nuclear IKK complexes and its role in nucleus to cytoplasm signaling and IKK activation will be presented. Besides for activating of genes in various immune responses and inflammation, NF-κB is involved in developmental processes as well. Investigations of the physiological and pathological functions of NF-κB were performed with transgenic NF-κB superrepressor mice, that allow systemic and conditional NF-κB suppression and with NF-κB reporter mice. We show how NF-κB is integrated into epidermal morphogenic signaling cascades that are formed by Wnt, EdaA1/EDAR and Shh modules and are required for embryonic appendice placode formation. Like in tumor cells, an ultimate prime function of NF-κB activation in epidermal development is the transcriptional induction of D-type cyclins. The utility of NF-κB superrepressor mice for the investigation of NF-κB-dependent functions in other disease models, such as cardiac hypertrophy, will be presented.