

# THE I $\kappa$ B KINASE (IKK) AND THE CONTROL OF IMMUNITY, INFLAMMATION AND CANCER

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Mammals express five NF- $\kappa$ B proteins: NF- $\kappa$ B1, NF- $\kappa$ B2, RelA, RelB and c-Rel. These proteins can assemble into a variety of homo- and heterodimers that bind to  $\kappa$ B sites on DNA and induce transcription of genes whose products play key roles in activation of innate and adaptive immune responses, inflammation and prevention of apoptosis. NF- $\kappa$ B1 and NF- $\kappa$ B2 require proteolytic processing to produce the mature p50 and p52 NF- $\kappa$ B subunits that can associate with any of the other Rel proteins. Once formed, NF- $\kappa$ B dimers are stored in the cytoplasm through interaction with the I $\kappa$ B proteins, which need to be degraded via the 26S proteasome before NF- $\kappa$ B can enter into the nucleus and regulate transcription (1).

Ubiquitin-dependent degradation of I $\kappa$ Bs requires their phosphorylation by the I $\kappa$ B kinase (IKK) complex, whose activity is rapidly stimulated in response to microbial and viral infections, proinflammatory cytokines and ionizing radiation. IKK is composed of two related catalytic subunits IKK $\alpha$  and IKK $\beta$  and a regulatory subunit IKK $\gamma$ /NEMO, that is essential for activation of the complex (2). We found that IKK $\alpha$  and IKK $\beta$  differ in their substrate specificities and as a result have distinct biological functions. Whereas IKK $\beta$  is a true I $\kappa$ B kinase, IKK $\alpha$  is a poor I $\kappa$ B kinase and instead is an efficient NF- $\kappa$ B2 kinase, whose activity is required for production of p52. As a result, IKK $\beta$  is required for general NF- $\kappa$ B functions, including activation of innate immune responses, inflammation and protection of cells from TNF-induced apoptosis, whereas IKK $\alpha$  is required for p52-specific functions, such as B cell maturation and formation of secondary lymphoid organs (3, 4, 5). IKK $\alpha$  kinase activity is also required for inducing the proliferation of mammary epithelial cells in response to a TNF family member called RANK ligand. In this case, however, it is required for the canonical NF- $\kappa$ B activation pathway, which depends on I $\kappa$ B degradation. These findings reveal that IKK $\alpha$  and IKK $\beta$  may be differentially engaged by different members of the TNF receptor family.

We used mice that lack IKK $\beta$  in defined cell types to study the physiological functions of the classical NF- $\kappa$ B activation pathway that depends on its activity. The results indicate that IKK $\beta$  plays a critical role in macrophage activation and inhibition of macrophage and neutrophil apoptosis in response to bacterial encounter (6). IKK $\beta$  is also important for prevention of IL-1 $\beta$  secretion, although it is required for induction of *IL-1 $\beta$*  gene transcription. In addition to its role in the control of inflammation, IKK $\beta$  also plays an important role in carcinogenesis. We found that in a model of colitis-associated cancer the activation of IKK $\beta$  in intestinal epithelial cells suppresses the apoptosis of preneoplastic cells, whereas the activation of IKK $\beta$  in myeloid cells promotes the proliferation of transformed epithelial cells through a paracrine mechanism. Thus, IKK $\beta$  may provide a mechanistic link between inflammation and cancer. In addition, we have found that the IKK/NF- $\kappa$ B pathway is involved in inflammation-induced progression and

metastatic growth. Inhibition of NF- $\kappa$ B activation in cancer cells converts inflammation-induced tumor growth to inflammation-induced tumor regression (7).

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