Chapter 11
Regulation of Programmed Cell Death by NF-κB and its Role in Tumorigenesis and Therapy

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Abstract The Rel/NF-κB transcription factors are key regulators of programmed cell death (PCD). Their activity has significant physiological relevance for normal development and homeostasis in various tissues and important pathological consequences are associated with aberrant NF-κB activity, including hepatocyte apoptosis, neurodegeneration, and cancer. While NF-κB is best characterized for its protective activity in response to proapoptotic stimuli, its role in suppressing programmed necrosis has come to light more recently. NF-κB most commonly antagonizes PCD by activating the expression of antiapoptotic proteins and antioxidant molecules, but it can also promote PCD under certain conditions and in certain cell types. It is therefore important to understand the pathways that control NF-κB activation in different settings and the mechanisms that regulate its anti- vs pro-death activities. Here, we review the role of NF-κB in apoptotic and necrotic PCD, the mechanisms involved, and how its activity in the cell death response impacts cancer development, progression, and therapy. Given the role that NF-κB plays both in tumor cells and in the tumor microenvironment, recent findings underscore the NF-κB signaling pathway as a promising target for cancer prevention and treatment.

Keywords Rel/NF-κB, apoptosis, necrosis, transcription factor, cancer, therapy

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1 Introduction

The Rel/NF-κB family of proteins is comprised of homologous transcription factors that mediate the cellular response to various exogenous or endogenous stimuli including infection, inflammation, stress, or injury (reviewed in Bonizzi and Karin, 2004; Hayden and Ghosh, 2004). This multimember family consists of the vertebrate c-Rel, RelA, RelB, p105/p50 NF-κB1, and p100/p52 NF-κB2 subunits, the viral oncoprotein v-Rel, Xenopus X-Rell, and the Dorsal, Dif, and Relish factors from Drosophila. Rel/NF-κB proteins share a highly conserved Rel homology domain (RHD) at their N-terminus that allows them to engage in homodimer or heterodimer formation, enter the nucleus, and bind to consensus GGGRNNYYCC NF-κB DNA sites. It also enables them to associate with inhibitory IκB molecules that act in an autoregulatory feedback fashion to terminate the activation process. The C-terminal domains of NF-κB factors are more divergent across the family and impart transcriptional activation properties to c-Rel, RelA, RelB and v-Rel proteins, or inhibitory properties to p105/NF-κB1 and p100/NF-κB2 that contain ankyrin-repeats akin to those found in IκB proteins.

In resting cells, cytosolic NF-κB dimers are inactive and typically bound to IκB proteins that prevent their nuclear translocation and binding to consensus NF-κB DNA-binding sites. Two distinct NF-κB activation cascades that respond to different stimuli have been documented (Fig. 11.1). The canonical (or classical) NF-κB pathway is activated by proinflammatory and mitogenic stimuli such as cytokines, bacterial lipopolysaccharides (LPS), interleukin-1 (IL-1), and antigens. This pathway commonly converges upon activation of the IκB kinase complex (IKK complex), a large multisubunit entity comprised of the catalytic IKKα and IKKβ subunits and the regulatory subunit IKKγ/NEMO. Phosphorylation of IκBα on serines 32 and 36 targets it for ubiquitination at lysines 21 and 22 by the E3 ligase SCF-βTrCP. Degradation of polyubiquitinated IκBα by the 26S proteasome frees NF-κB dimers, like the classical p50/p65 complex, enabling their entry into the nucleus where they bind to NF-κB DNA sites. This commonly results in the transcriptional activation of genes important for immune and inflammatory responses, cell proliferation, and/or suppression of apoptosis. Among the many genes that NF-κB regulates, transcriptional activation of its inhibitor IκBα generates an autoregulatory feedback loop that terminates the activation process. Consequently, activation of the NF-κB pathway is normally a regulated and transient process that is important for normal innate and adaptive immunity, inflammatory and acute phase responses and for embryonic development, organogenesis, and homeostasis. In contrast, sustained activation of the NF-κB pathway is implicated in a wide variety of pathological conditions including immune system disorders, chronic inflammation, and cancer.

The noncanonical (or alternative) NF-κB signaling cascade is characterized by the tightly regulated processing of the p100/NF-κB2 precursor protein into a mature p52 subunit and is commonly involved in the preferential activation of RelB/p52