CHAPTER 9

Molecular Basis of Oncogenesis by NF-κB: From a Bird's Eye View to a RELevant Role in Cancer
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Abstract

The Rel/NF-κB transcription factors are renowned for their fundamental contribution to normal immune, inflammatory and acute phase responses. A growing body of evidence also underscores their important role in the control of cellular gene expression, cell proliferation and apoptosis. Thus, it comes as no surprise that sustained Rel/NF-κB activity has emerged as a hallmark of many human cancers. Experimental evidence indicates a strong correlation between the transcriptional activity of Rel/NF-κB and its role in malignant cell transformation. The important role of NF-κB in the control of the apoptotic response also supports its participation in the resistance of tumor cells to therapeutic treatment. This review focuses on the mechanisms that underlie the contribution of Rel/NF-κB to cancer and highlights how appreciation of its role in this context has evolved from a bird's eye view to a true recognition of its RELevant function in oncogenesis.

Introduction

The Rel/NF-κB transcription factors have been the focus of numerous studies aimed at elucidating their role in the development and function of the immune system and at unveiling the signaling pathways that control their activity (see accompanying chapters by M. Karin, S.C. Sun, R. Sen, U. Siebenlist, H.C. Liou, Y. Chen, and C. Hunter). In recent years, there has been considerable progress in appreciating their contribution to oncogenesis and in understanding the mechanisms involved. Inappropriate Rel/NF-κB activity is observed in many different types of human cancers. Hyperactivation of the NF-κB signaling cascade, mutations that inactivate the inhibitory kB subunits or chromosomal aberrations involving various rel/nf-κb genes have been noted in many human tumors.1,2 Consistent with the transforming activity of the viral Rel/NF-κB oncoprotein v-Rel and its cellular homologue c-Rel in primary cells and in animal models, NF-κB is also critically involved in malignant cell transformation by viruses such as the human T-cell leukemia virus type I (HTLV-1) and Epstein-Barr virus (EBV).3 Collectively, these findings justify the vast body of literature exploring the molecular basis for the role of Rel/NF-κB in cancer. Important findings center on its ability to regulate cellular gene expression, to affect cell proliferation and survival, and on important regulatory mechanisms that control its activity - all of which have important consequences for effective anti-cancer therapy.4,7

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Constitutive Rel/NF-κB Activity Is a Hallmark of Many Human Cancers

Sustained activation of NF-κB is a feature of many human leukemia, lymphoma and solid tumors. Immunohistochemistry, gel mobility shift assays and gene expression profiling of primary tumor specimens and tumor-derived cell lines have highlighted the persistent nuclear localization of NF-κB subunits compared to normal controls (for example see refs. 8-11). The dimer comprised of the p50/p65 subunits is the most frequently reported NF-κB complex to be activated in human cancer, although there is evidence that clearly implicates c-Rel-containing complexes in certain tumor types, like breast cancer. The important implication of sustained NF-κB activity for the survival and proliferation of tumor cells is underscored by the growth arrest and rapid onset of apoptosis observed in many tumor-derived cell lines upon introduction of a degradation-resistant form of IκB (IκB super-repressor) to inhibit endogenous NF-κB activity (for example see refs. 12,13).

Activation of the NF-κB Signaling Cascade

Persistent activation of the NF-κB pathway is observed in many different human cancers. By virtue of its ability to trigger the N-terminal phosphorylation of the NF-κB inhibitory subunit IκBa on serines 32 and 36, the IKK kinase complex promotes degradation of IκB via the ubiquitin/proteasome pathway. This enables NF-κB dimers to accumulate in the nucleus where they promote transcription of specific gene programs. Although the detailed mechanisms responsible for sustained IKK activation in many human tumors remain unknown, there are several potential mechanisms (Table 1).

IKK Complex Activation

Since no mutation has yet been identified to affect IKK subunits in human tumors, unremitting activation of NF-κB is likely to result from alterations in upstream signaling components. In many types of cancer, sustained IKK activation is achieved via autocrine loops involving cytokines and growth factors that activate the NF-κB pathway and are themselves transcriptional targets of NF-κB (Tables 1, 2). For instance, IL-1 activates NF-κB in pancreatic carcinoma cell lines and is in turn induced by NF-κB. Likewise CD40, the receptor for CD40 ligand, constitutively activates NF-κB in malignant Reed-Sternberg (H/RS) cells of Hodgkin's disease (HD) and is upregulated in these cells. Another mechanism for constitutive activation of the IKK complex involves deregulation of TRAF adaptor proteins in human tumors. TRAF2 is a critical component of receptor-triggered signaling pathways involving NF-κB, JNK and p38. Recent work showed that loss of the TRAF2- and IKKγ/NEMO-interacting tumor suppressor protein CYLD, a de-ubiquitinating enzyme for TRAF2, leads to constitutive activation of IKK coincident with increased cell resistance to apoptosis. Loss of CYLD causes cylindromatosis, an autosomal dominant syndrome that predisposes patients to benign tumors of hair follicles and sweat and scent glands.

Interestingly, recent work unveiled a new NF-κB-independent role for IKK in cancer. IκKB expression in primary breast cancer specimens is correlated with poor survival and studies in primary breast cancer cell lines showed that IKK negatively regulates the forkhead transcription factor FOXO3a, independent of NF-κB activation. Indeed, IKK-mediated phosphorylation of FOXO3a promoted its nuclear export and proteolysis via the ubiquitin proteasome pathway to promote cell growth and tumorigenesis. It will be interesting to see if the newly reported abilities of IκKα and IκKγ/NEMO to localize to the nucleus and respectively modify histones and interact with CBP to regulate NF-κB gene expression imply that these subunits can also act on other nuclear targets to affect oncogenesis.

Activation by Other Kinases, Oncogenes and Viruses

Other means to constitutively activate NF-κB signaling in human tumors entail various kinases other than IKK, as well as oncogenes and viruses (Table 1). One example involves the