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NF-κB and Cancer — Identifying Targets and Mechanisms

Willscott E Naugler[1] and **Michael Karin**[2]

[1]*Department of Medicine, Division of Gastroenterology and Hepatology, Oregon Health and Sciences University, Portland* [2]*Laboratory of Gene Regulation and Signal Transduction, Departments of Pharmacology, Pathology and Cancer Center, University of California, San Diego*

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Though there is growing evidence for a critical connection between inflammation and carcinogenesis, the mechanistic links between the two are just beginning to emerge. Nuclear factor-κB (NF-κB) transcription factors are important in integrating multiple stress stimuli and regulating innate and adaptive immune responses seen in states of inflammation[1]. With the recognition that inflammatory conditions are often associated with or preceed cancer, it was natural to suspect a link between NF-κB and cancer, as was first suggested several years ago[2]. Since that time, experimental evidence revealing specific mechanisms by which NF-κB influences cancer initiation, promotion, and progression has been mounting at a dizzying pace. This review will focus on new data that has emerged over the last couple of years implicating NF-κB its signaling pathways and downstream targets in carcinogenesis.

One of the founding fathers of modern pathology, Rudolf Virchow, observed leukocytes in neoplastic tissue over a hundred years ago, and first suspected that inflammation might support or promote cancer[3]. This notion has re-emerged in the last decade in part because of the recognition that many chronic infectious diseases are associated with development of cancer. Approximately 15% of the global cancer burden has been attributed to chronic infections and the accompanying inflammatory reaction[4], and 15–20% of cancer deaths arise from preventable infections[5]. Likewise, many non-infectious conditions of chronic inflammation increase the risk and accelerate the progression of diverse cancers[6]. The common denominator in these conditions is the presence of chronic inflammation, invariably associated with activation of NF-κB and its effector pathways.

NF-κB was first discovered as a protein bound to the kappa immunoglobulin gene enhancer in the nuclei of B cells[7], and was thought to be restricted to these cells. Ironically, the name “NF-κB” applied to these transcription factors is no longer descriptive: the factors generally reside in the cytoplasm of resting cells, when activated bind to a large array of enhancer sequences (over 150 genes), and are present in most (if not all) cells. A detailed description of NF-κB regulation is beyond the scope of this article (see recent reviews[8, 9], and Figure 1).

*To whom correspondence should be addressed: 9500 Gilman Road, Mail Code 0723, University of California, San Diego, San Diego, CA 92093, USA.

Briefly, mammalian NF-κB transcription factors consist of 5 homologous subunits (RelA/p65, c-Rel, RelB, p50/ NF-κB1, and p52/ NF-κB2) which dimerize and are held in the cytoplasm by specific proteins, the inhibitors of NF-κBs (IκBs). Immediately upstream from the IκB-bound NF-κB dimers is the IκB kinase (IKK) complex, comprised of two catalytic (IKKα and IKKβ) and one regulatory (IKKγ/NEMO) subunits[10]. Several pathways of cell stimulation converge to activate the IKK complex, which then phosphorylates the IκBs, targeting them for ubiquitination and degredation by the 26S proteosome[11]. The liberated NF-κBs travel to the nucleus and engage transcriptional programs.

Though there is a broadening complexity to NF-κB signaling, the two most recognized pathways are the so-called “canonical” and “non-canonical.” The former depends on NEMO, IKKβ activation, nuclear localization of RelA/p50 dimers, and is associated with inflammation, while the latter depends on IKKα activation probably via the upstream kinase NIK, nuclear localization of p52/RelB dimers, and is important in lymphoid organogenesis[8]. Both pathways of NF-κB activation have now been implicated in carcinogenesis[12, 13].

Activation of NF-κB (usually assessed by presence of nuclear RelA) has been observed in many cancers, including but not limited to breast cancer[14], melanoma[15], lung cancer[16], colon cancer[17], multiple myeloma[13], pancreatic cancer[18], esophageal adenocarcinoma[19], and various types of leukemia[20–22] and lymphoma[23, 24]. The presence of activated NF-κB in tumors does not, however, establish a causal link. Only with the advent of recent advances in experimental mouse models of cancer have investigators been able to tie specific functions of NF-κB activation to the carcinogenesis process, as well as tumor progression and metastatogenesis. A synopsis of cellular processes which contribute to cancer development and progression include self-sufficiency in growth signals, insensitivity to growth-inhibitors, evasion of apoptosis, limitless replicative potential, tissue invasion and metastasis, and sustained angiogenesis[25]. NF-κB activation has been linked to most of these cancer cell intrinsic processes, but most importantly has also been established to be a major mediator of influences that are extrinsic to cancer cells but nonetheless are critical to most aspects of tumorgenesis. This review will focus on the role of NF-κB in these processes and the development or progression of cancer.

NF-κB in malignant proliferation

Promotion of cell growth is a necessary feature of any cancer, and can be achieved either through abnormally activated or deregulated signaling pathways involved in cell cycle regulation, or quite often (but usually neglected) abnormal growth signals outside the malignant cell. NF-κB target genes regulating proliferation include CyclinD1, CyclinE, CDK2, and c-Myc, while growth signals include GM-CSF and interleukin-6 (IL-6)[26]. Activating mutations involving NF-κB pathways which lead to cancer are thought to be rare, but this may be a result of simply not understanding what to look for. A recent survey of 155 patient samples of multiple myeloma found 20% of them to have NF-κB-activating mutations, the most common of which was inactivation of TRAF3[12]. A second study confirmed the presence of activating NF-κB mutations in 368 patient samples, and found that an IKKβ inhibitor induced death in cell lines established from these samples[13]. A similar study found that IKKβ inhibition in human multiple myeloma blocked cell cycle progression[27]. Cancer growth inhibition via NF-κB inhibition has similarly been shown in several flavors of human neoplasia, including breast[28], lung[16], melanoma[15], colon[29], and B-cell lymphoma[23].

An insightful study of metastatic colon cancer revealed that stimulation of the inflammatory system by lipopolysaccharide (LPS) injection caused increased growth of the metastatic cancer, dependent on NF-κB signaling, which, when abolished, paved the way for TRAIL-dependent

tumor regression[30]. This study confirmed that NF-κB-induced inflammation is directly linked to growth stimulation of malignant cells.

Genetic manipulation of NF-κB signaling in mice has proved most illuminating in dissecting the mechanisms which link inflammation to carcinogenesis. In a mouse model of colitis-associated cancer, genetic deletion of IKKβ in enterocytes, which are the cells that undergo malignant progression in this model, significantly reduced tumor multiplicity compared to controls, directly implicating NF-κB signaling in early tumor promotion during the initiation stage[31]. Interestingly, when IKKβ was deleted in myeloid cells (which control the inflammatory response but do not undergo any genetic alterations), tumor size was markedly reduced, suggesting that the inflammatory cells were elaborating growth signals which aided in the promotion of neoplastic growth[31]. Indeed, known growth factors such as IL-6 were dramatically decreased when NF-κB signaling was disrupted in myeloid cells. Although one study confirmed the contribution of IL-6 to colitis-associated cancer[32], we find that the actual role of IL-6 in this malignancy is rather complex, and that canonical NF-κB activation in myeloid cells is likely to act via additional growth factors (unpublished results). Using the same model of colitis-associated cancer Rigby et al. found that deletion of SOCS3 (suppressors of cytokine signaling-3) led to increased NF-κB signaling, an increase in intestinal crypt cell proliferation, and more and larger tumors than wildtype (WT) counterparts[33]. Both of these studies point to a direct role for NF-κB-directed increased intestinal cell proliferation leading ultimately to cancer.

A third model of intestinal cancer directly linked the Toll-like receptor (TLR) adaptor protein MyD88 to increased spontaneous tumorigenesis in APC^{min} mutant mice[34]. MyD88 is an adaptor used by several TLRs as well as IL-1 receptor (IL-1R), and its activation integrates signals from the innate immune system. Genetic ablation of MyD88 in this study significantly reduced the number of intestinal tumors. Not surprisingly, the transcription factors through which MyD88 signals are NF-κBs, and several NF-κB target genes, including COX-2 and IL-6 were down-regulated in the MyD88-deficient mice who demonstrated reduced carcinogenesis[34].

Hepatocyte-specific deletion of IKKβ in a murine model of chemically-induced hepatocellular carcinoma (HCC) resulted in a remarkable increase in the number of tumors[35]. Molecular mechanisms underlying increased HCC development included augmented hepatocyte injury (due to accumulation of ROS, which prolongs JNK activation in the absence of NF-κB signaling[36]), leading to increased compensatory proliferation and hepatocarcinogenesis[35, 37]. In a remarkable turnabout, when IKKβ was deleted in both hepatocytes and immune cells in the liver, the number and size of HCC tumors was greatly diminished, lower even than in WT littermates[35]. The mechanism was found to be through reduction of Kupffer cell (liver macrophage)-produced and NF-κB-regulated IL-6, which limited both liver injury and compensatory proliferation[38].

In a follow-up study using the same model, canonical NF-κB regulation of IL-6 at the level of the Kupffer cell was confirmed to be necessary for development of HCC[38]. Genetic ablation of IL-6 markedly attenuated chemically-induced liver injury, subsequent compensatory proliferation, and development of HCC. These 2 studies[35, 38] in which NF-κB-regulated IL-6 production contributes to hepatic injury suggest a mechanism by which chronic inflammation in the liver leads to perpetuation of injury, compensatory proliferation, and ultimately HCC development.

Hepatocyte-specific deletion of the regulatory IKKγ/NEMO subunit abolishes all NF-κB signaling in the liver, and induces a state of chronic steatohepatitis, leading ultimately to HCC in all male mice at 12 months of age[39]. However, mice with hepatocyte-specific IKKβ deletion

develop normally, without features of steatohepatitis or any signs of liver damage[40]. Although ablation of IKKγ/NEMO results in more complete inhibition of canonical NF-κB signaling than IKKβ ablation[41], it is possible that the hepatic damage in the conditional IKKγ/NEMO knockout mice is due to a yet-to-be-identified infection. Indeed, hepatic injury in hepatocyte-specific IKKγ/NEMO-deleted mice is dependent on accumulation of ROS, and is completely blocked by administration of an antioxidant, previously found to inhibit DEN-induced injury in hepatocyte-specific IKKβ knockout mice[35]. Together these studies paint a picture in which NF-κB signaling in hepatocytes prevents ROS-induced damage, thereby reducing compensatory hepatocyte proliferation and diminishing HCC development. Kupffer cell NF-κB signaling on the other hand (which can be activated by products of hepatocyte death, among other things[38]) creates inflammatory signals which amplify liver damage as well as increase compensatory proliferation and hepatocarcinogenesis. (Figure 2 outlines inflammation-associated hepatocarcinogenesis and NF-κB involvement)

In the breast, mammary gland development and proliferation through cyclinD1 expression is dependent on IKKα activation[2]. Genetic introduction of a non-activateable IKKα mutant into the Neu/ErbB2-driven mouse model of breast cancer significantly retarded breast tumor development[42]. Of interest, inactive IKKα inhibited breast cancer development only in the ErbB2/Her2 model, but had no effect in a breast cancer model driven by the Ha-Ras oncogene. This finding is important, as the subset of human breast cancers which are estrogen receptor (ER)-negative (and unresponsive to hormonal therapies) often depend on ErbB2/Her2 upregulation, and were shown to be responsive to treatment with NF-κB inhibitors *in vitro*[43]. Interestingly, the inactivation of IKKα blocks the ability of Neu/ErbB2-induced tumors to generate secondary tumors upon orthotopic transplantation, as it inhibits the self-renewal capacity of breast cancer progenitors[42]. This suggests that IKKα may be targeted in ErbB2/Her2-dependent breast cancer to prevent emergence of metastases after resection or chemo-ablation of primary tumors.

NF-κB and prevention of apoptosis

Inhibition of apoptosis is perhaps the most obvious way through which NF-κB signaling promotes the development of cancer, and NF-κB activation has long been known to suppress apoptosis[44]. Numerous NF-κB target genes prevent apoptosis, a normal mechanism by which immune and genomic surveillance mechanisms can eliminate pre-malignant or malignant cells. Some of these genes include Bcl-2 family members such as Bcl-xL, IAPs (inhibitors of apoptosis), and c-FLIP[6]. NF-κB also indirectly prevents mitochondrially-mediated apoptosis though neutralization of ROS (through induction of manganese superoxide dismutase or ferritin heavy chain). Several of the studies discussed above have documented decreased apoptosis in response to NF-κB activation (in addition to promoting proliferation).

Many investigators have observed that resistance to apoptosis in human cancer cell lines may be dependent on activation of NF-κB because when NF-κB is inhibited apoptosis can be triggered more readily[28, 43, 45–50]. NF-κB-induced apoptosis resistance has been implicated in chemotherapeutic failures in cancer treatment, and this topic is currently under intense investigation.

An elegant study linking NF-κB activation to inhibition of apoptosis (and carcinogenesis) utilized a mouse model with genetic deletion of the Mdr2 gene. Mdr2 knockout mice develop cholestatic hepatitis and ultimately HCC[51]. Suppression of NF-κB signaling early in $Mdr2^{-/-}$ mice had no effect on HCC initiation, but suppression of late NF-κB signaling diminished dramatically the size of HCC. The differences seen in HCC development were directly related to NF-κB-mediated prevention of apoptosis in transformed hepatocytes[52]. The difference between this model and the DEN model in which NF-κB inhibition in hepatocytes

accelerates HCC development[35] is due to the fact that DEN-induced carcinogenesis is highly dependent on hepatocyte death which is prevented by NF-κB, whereas the Mdr2$^{-/-}$ model is mainly dependent on chronic inflammation which is promoted by NF-κB. Indeed, as long as NF-κB is activated for only 48 hours after DEN application HCC development is suppressed (Y. Ben-Neriah, personal communication).

A causal link between NF-κB activation and prevention of apoptosis in B-cell lymphomagenesis was recently shown: transgenic introduction of a mutant NF-κB2 ("p80HT", a mutant form of p100 found in a human lymphoma) into mice caused high level TRAF1 expression, suppressing apoptosis and leading to B cell lymphomas[24]. Sodium salicylate (asprin) has long been known to inhibit NF-κB activation[53], and use of this agent decreases NF-κB activation and high levels of cFLIP expression in leukemic cells, causing apoptosis[20].

Genotoxic stress, an event that can lead to cancer-initiating mutations, was recently found to activate the NF-κB pathway through activation of IKKγ/NEMO, causing resistance to apoptosis[54], and this mechanism of IKK activation was found to inhibit apoptosis in the myelodysplastic syndrome, leading to acute myeloid leukemia[49]. Lastly, ROS have been implicated in genetic alterations which could lead to cancer, and NF-κB signaling was found to decrease ROS accumulation within cells and diminish associated apoptotic and necrotic cell death[35, 36].

NF-κB and metastasis

Progression from local to metastatic cancer signifies late stage tumor progression, and the molecular mechanisms underlying this important process are just coming to light. Canonical NF-κB activation was recently implicated[55] in epithelial-mesenchymal transition (EMT), a change thought to herald tissue invasion and prophesize metastatic potential. Activation of a so-called mesenchymal program (involving genes such as MMP2/9, VCAM-1, ICAM-1, Cathepsins B and Z[56]) was found to be dependent on NF-κB activation in a breast cancer model, and reversal of EMT was triggered by NF-κB inhibition[55]. E-cadherin was newly added to the list of genes regulated by NF-κB, and its repression by NF-κB enhances EMT in breast cancer[14]. NF-κB activation of Bcl2 was also been shown to promote EMT in breast cancer, leading to a more malignant phenotype[57]. Another important regulator of EMT is the transcription factor TWIST[58]. It was recently suggested that NF-κB may promote EMT and metastasis through transcriptional activation of TWIST[59].

The most specific linkage of IKK signaling to cancer metastatic potential comes from a model of prostate cancer, in which IKKα activation represses expression of the metastasis suppressor gene maspin[60]. Genetic inhibition of IKKα kinase activation was shown to result in higher levels of maspin expression in advanced prostate adenocarcinomas where its expression is normally repressed during metastatic progression by activated IKKα via an NF-κB-independent mechanism. This repression correlates with accumulation of activated IKKα in nuclei of prostatic carcinoma cells, something that is also seen in advanced human prostate cancer[60]. Altough the mechanism responsible for activation of nuclear IKKα remains to be identified, it correlates with infiltration of prostate cancers with T cells that express RANK ligand (RANKL), a known activator of IKKα. A knockdown of maspin expression in IKKα mutant tumors restores metastatic potential[60].

NF-κB and angiogenesis

Formation of new blood vessels is essential for tumor progression, as the growing tumor mass quickly exceeds the capacity of the native blood supply. Many of the signals which orchestrate angiogenesis are elaborated by tumor-associated macrophages (TAM), most of which are

dependent on NF-κB signaling[3]. The NF-κB-coordinated inflammatory cytokines TNFα, IL-1, and IL-6 can stimulate expression of vascular endothelial growth factor (VEGF), one of the main regulators of angiogenesis, and VEGF is itself an NF-κB target gene, along with other angiogenic regulators such as CXCL 1, 8 and IL-8[56]. Study of the relationship between NF-κB and angiogenesis has probably been impaired by the near-universal decrease in tumor growth upon NF-κB inhibition. In the setting of reduced cancer growth, independent reduction in angiogenesis is difficult to evaluate. However, more solid evidence tying NF-κB activation to angiogenesis was just provided in a study identifying JunB upregulation as the hypoxia-induced NF-κB activation target which induces VEGF expression[61]. Deletion of JunB in teratocarcinomas severely impaired angiogenesis. Interestingly, oxygen tension controls the extent of IKK activation such that normoxia limits IKKβ activity through proline hydroxylation whereas hypoxia favours it by preventing IKKβ proline hydroxylation[62]. These results suggest that macrophages and even epithelial cells in the hypoxic core of tumors are more likely to undergo IKK and NF-κB activation.

Summary

The perceived hypothetical role of inflammation in carcinogenesis has been bolstered by epidemiological observations linking infections and chronic inflammatory conditions to cancer. Given their place as master regulators at the center of inflammation, NF-κB transcription factors were natural suspects in providing a mechanistic link between inflammation and carcinogenesis. Indeed, the inflammation-cancer field has moved quickly from descriptive observations that activated NF-κB is present in many tumors to biochemical and genetic studies performed to elucidate the causal effects of NF-κB signaling in specific processes considered hallmarks of carcinogenesis (Figure 3 outlines potential NF-κB targets for the prevention and treatment of cancer). Of major importance is the recognition that various effects of NF-κB on cancer initiation, promotion, and progression are cell-type, tissue and context specific, ascertainment of which was only possible due to recent advances in genetically dissectable mouse models of inflammation-linked cancer. These advances are rapidly paving the way to new insights into the origin and treatment of human cancers.

Annotations to references for COGEDE-D-07-00059

1 NF-κB discovered and first described, thought to act solely in B cells

2 First suggestion that NF-κB may be a mechanistic link between cancer development to inflammation

3 Tumor progression directly linked to NF-κB activation for the first time

4 First study to show that NF-κB may have differing (and opposing) effects on carcinogenesis depending on the cell type (myeloid versus epithelial) in which it is active

5 Important study showing that innate immune mechanisms (as exemplified by the TLR adaptor MyD88) act upstream of NF-κB to promote cancer

6 Mechanism revealed by which NF-κB opposes JNK activation and cell death

7 NF-κB regulated IL-6 production in liver macrophages found to increase hepatic injury

8 Seminal study showing that TNF-alpha-induced apoptosis is opposed by NF-κB activation

9 NF-κB pathway (through IKKβ) found to oppose necrotic and apoptotic cell death by decreasing ROS accumulation

10, 11 Well-done studies showing that mutations involving the NF-κB signaling pathway occur and are responsible for a subset of human multiple myelomas

12 Excellent review on the processes of cancer development which gives framework for mechanistically studying carcinogenesis

13 NF-κB found to be important for promotion, but not initiation of inflammationassociated liver cancer

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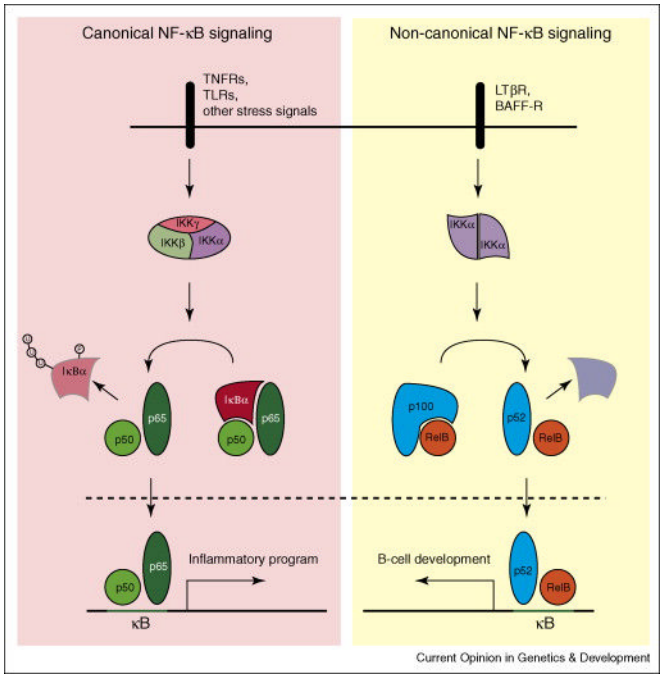

Figure 1.
NF-κB signaling pathways

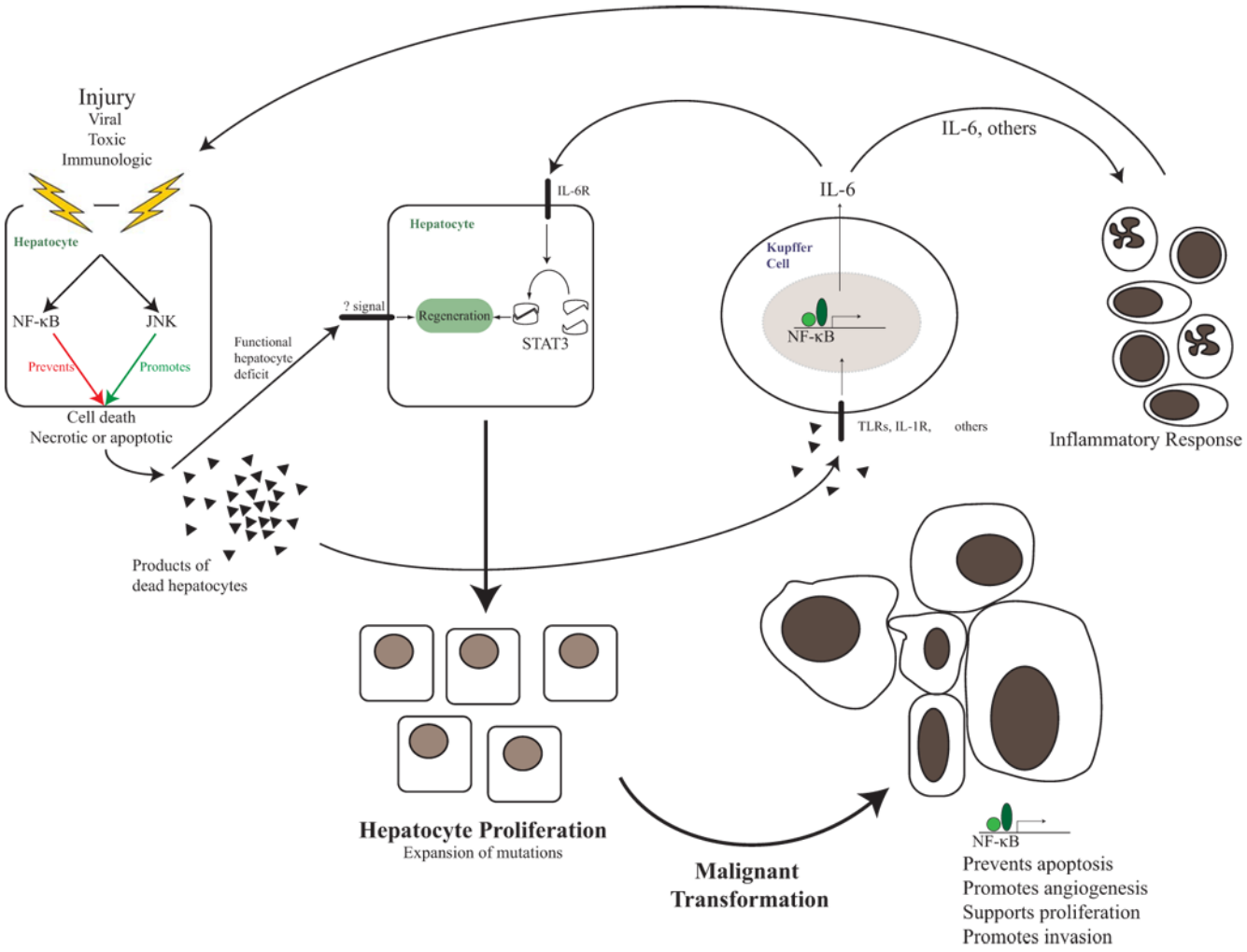

Figure 2.
NF-κB in hepatocarcinogenesis

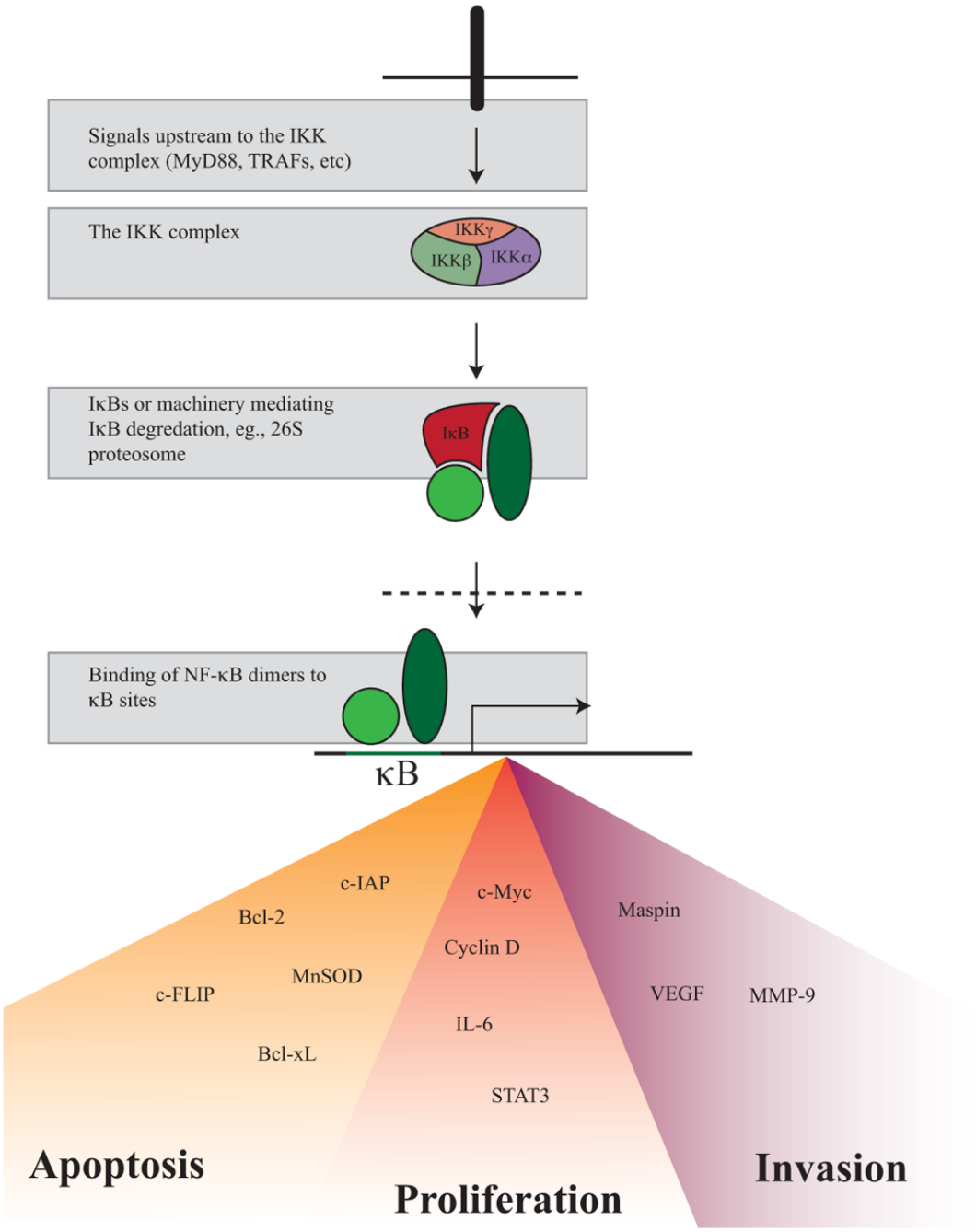

Figure 3.
Targeting potential NF-κB contributors to carcinogenesis