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Inflammation meets cancer, with NF-κB as the matchmaker

Yinon Ben-Neriah[1] & Michael Karin[2]

Inflammation is a fundamental protective response that sometimes goes awry and becomes a major cofactor in the pathogenesis of many chronic human diseases, including cancer. Here we review the evolutionary relationship and opposing functions of the transcription factor NF-κB in inflammation and cancer. Although it seems to fulfill a distinctly tumor-promoting role in many types of cancer, NF-κB has a confounding role in certain tumors. Understanding the activity and function of NF-κB in the context of tumorigenesis is critical for its successful taming, an important challenge for modern cancer biology.

In 1863, Rudolf Virchow, the founder of modern pathology, noted leukocytes in neoplastic tissues and made a connection between inflammation and cancer. He suggested that the "lymphoreticular infiltrate" reflected the origin of cancer at sites of chronic irritation. In the dawn of the 20th century, Katsusaburo Yamagiwa showed that repeated painting of coal tar onto rabbits' ears causes carcinomas. Later, in the 1940s, using repeated application of tar or croton oil onto the skin, Peyton Rous and Isaac Berenblum introduced the concept of tumor promotion, a pathogenic process distinct from tumor initiation. The early studies of Yamagiwa on the pathogenesis of gastric carcinoma led to his belief that chronic gastric ulcers have a major role in the development of stomach cancer. In 1911, he established principles that later led him to uphold the irritation theory of cancer. Seventy years later, Barry Marshall and Robin Warren proved that gastritis is caused by infection with *Helicobacter pylori*, now thought to be a major cause of many stomach cancers. Although those classical studies pointed to an association between inflammation and cancer, the mechanistic basis of this relationship emerged subsequently, with the transcription factor NF-κB serving as the major lynchpin. Here we review the function of NF-κB in linking inflammation to cancer. However, rather than providing a detailed summary of the inflammation-cancer connection, this review is focused on certain outstanding issues, such as the relationship between NF-κB activation and abnormal growth signaling, the interaction between the positive and negative roles of NF-κB in the control of inflammatory responses and how these opposing functions affect tumor development and progression. More extensive reviews of the inflammation-cancer field have been published elsewhere[1–5].

[1]Lautenberg Center for Immunology, Institute for Medical Research-Israel-Canada, Hebrew University-Hadassah Medical School, Jerusalem, Israel. [2]Laboratory of Gene Regulation and Signal Transduction, Department of Pharmacology and Cancer Center, School of Medicine, University of California, San Diego, La Jolla, California, USA. Correspondence should be addressed to Y.B.-N. (yinon@cc.huji.ac.il) or M.K. (karinoffice@ucsd.edu).

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Evolutionary linkage of NF-κB and abnormal growth

Inflammation is a manifestation of innate immunity, a fundamental protective response that is conserved in all multicellular animals[6]. The emergence of multicellular life forms required new means for defending these slow-growing organisms from rapidly growing invading pathogens and for preventing the fusion of genetically distinct conspecific organisms[7]. Shortly after the discovery of NF-κB, it was postulated that it 'plays the first violin', if it is not the 'conductor' of inflammatory responses[8,9]. Although inflammation can be induced in the absence of NF-κB[10], that is rarely a physiological occurrence, which possibly reflects the need for the transcription factor not only for amplification and maintenance of inflammation but also for 'tuning down' and curtailing inflammation, to preserve tissue function once the inflammation is no longer needed[11].

The innate immune system is well suited for detecting pathogens and foreign bodies and reacts to them by producing and releasing immune effectors and activated cells that either contain or eliminate the pathogen. An intricate signaling system composed of sensors, signal-processing and signal-transducing elements, and myriad effector molecules, from reactive oxygen species (ROS) and antibacterial peptides to diffusible regulators of immunity (cytokines and chemokines) was constructed for that purpose through evolution. The basic innate immunity scheme is remarkably well conserved both structurally and functionally. Thus, the main classes of pathogen sensors, Nod-like receptors and Toll-like receptors (TLRs) and interleukin 1 (IL-1) receptors, as well as the signal transducers and amplifiers IRAK, MyD88, TRAF and IKK and the transcriptional regulator Rel (NF-κB), are present even in the most primitive metazoans, sponges, sea anemones, hydra and jelly fish[12–15]. Notably, the RIG-I-like receptor family, another major arm of innate immunity that controls viral infection through the interferon response, originated much later than Nod-like receptors and TLRs, possibly only in vertebrates[16].

Given its considerable conservation noted above, innate immunity can be considered a hallmark of multicellularity, one of the following six essential principles of metazoan life: regulated cell replication and growth; programmed cell death; cell-cell and cell-matrix adhesion; regulated developmental processes; cell type specialization; and alloreactivity and

innate immunity[17]. Although NF-κB and inflammation are commonly associated with the last principle, in fact all the principles noted above are affected by NF-κB: it contributes to induction of proliferative genes[18,19]; it regulates genes encoding antiapoptotic molecules[20]; it controls the expression of diverse adhesion molecules[21,22]; it drives and supports developmental processes from lymphocyte differentiation to mammary gland development[23,24]; and it even has a role in cell specialization, as in driving Schwann cells to myelinate[25].

As many of those diverse functions go awry in tumorigenesis, it is interesting to trace the evolutionary origin of the inflammation-cancer link. Two remarkable examples are tumor promotion in *Drosophila* larva, in which hemocyte tumor necrosis factor (TNF) enhances tumor growth and stimulates the invasive migration of cells with mutation of the genes encoding the oncoprotein Ras and the tumor suppressor Scribble[26]; likewise, leukocyte-trophic effects are needed for the promotion of melanoma growth in zebrafish larva[27]. Additional hints of a relationship between the innate response and abnormal cell growth can be found even earlier in metazoan evolution, perhaps as early as corals, which frequently develop abnormal growths resembling tumors[28]. In most coral specimens examined, these malformations are directly attributable to effects of predation or other physical injury. These malformations have many features in common with neoplasms, including failure of natural growth control and breakdown of the normal symmetrical pattern, and overall they resemble adenomatous polyps of the human colon[29,30]. Deep-water corals are repeatedly preyed on by fish and other carnivores, which injure the soft parts of the coral[28]. This results in microbial and viral infections that trigger an inflammatory reaction that promotes regenerative proliferation and abnormal growth. Harold Dvorak described tumors as "wounds that won't heal," pointing to many similarities between the activity of a cancerous tumor growth and the process of wound healing[31]. We thus speculate that NF-κB-orchestrated innate immunity has been entwined with growth control from the early days of multicellularity. If infection is effectively controlled, then the inflammatory response is promptly resolved with no perturbation of tissue growth. Repeated infection, however, may result in tissue loss and a protracted inflammatory response with attempt to restore the lost tissue and, thus, as in damaged corals, may end in abnormal growth.

There is mounting evidence today that many tumors are propagated by means of cancer stem cells, rare cells in tumors with indefinite capacity for self-renewal[32]. Other tumors might arise from normal tissue stem cells or from tissue stem cells that were transformed to become cancer stem cells[33,34]. If that holds true, tissue stem cells should be closely guarded against infectious and chemical genotoxic insults and, at the same time, might be particularly vulnerable to deregulated innate immunity. A notable example is the close proximity of intestinal stem cells to Paneth ($CD24^+$) cells in the small bowel and similar $CD24^+$ cells in the colon[35], the innate immune guardians of the gut epithelium. Indeed, evidence suggests that heterotypic Paneth cell–stem cell interactions have an important role in controlling stem-cell renewal[35]. At the far end of this innate immunity–growth control equation, abnormal growth and cancer may be found, as in the transformation of intestinal crypt stem cells into microadenomas[34]. Moreover, a remarkable synergy has been observed between bacterial infection and oncogenic mutations in *Drosophila* gut that drives abnormal enterocyte growth and dysplasia. Infection of *Drosophila* gut by *Pseudomonas aeruginosa*, a human opportunistic pathogen, induces intestinal damage, apoptosis and compensatory proliferation, which on a background of mutated *Ras* is excessive, with polarity loss, resembling a tumor[36]. We hypothesize that microflora-induced innate immune responses in intestinal stem cells or their niche (composed mainly of $CD24^+$ cells[35]), possibly in conjunction with epigenetic alterations[37], may drive an abnormal proliferative response, which after further mutagenesis may generate tumor-initiating stem cells (**Fig. 1**).

Another striking example of the equivalence of excessive innate immunity activation and abnormal growth signaling is the discovery that deletion of *NFKBIA*, which encodes the NF-κB inhibitor IκBα, is a rather frequent oncogenic event in glioblastoma tumors[38]. The occurrence of this mutation is mutually exclusive with the common glioblastoma amplification of epidermal growth factor receptor (EGFR), which indicates that activation of NF-κB can replace aberrant EGF signaling as an oncogenic factor. Likewise, lung cancer cells with mutant EGFR are particularly sensitive to inhibition of NF-κB, and NF-κB activation through deletion of IκBα rescues EGFR-mutant lung cancer cells from the cytotoxic effects of the EGFR kinase inhibitor erlotinib[39]. Hence, whether innate immunity or a trophic control factor is deranged, the outcome could be similar; that is, abnormal growth.

Pro- and anti-inflammatory functions of NF-κB

Since the realization that NF-κB is an inducible rather than cell type–specific transcription factor that responds to proinflammatory cytokines and microbial products, NF-κB has been thought of as the key regulator of inflammation[8]. Indeed, NF-κB-binding sites have been found in the promoters of most genes encoding cytokines and chemokines[40], and NF-κB activation has been shown to be essential for their induction in response to immune and inflammatory challenges[41]. Although originally NF-κB was associated exclusively with immune and inflammatory cell function, the realization that such transcription factors also have essential roles in epithelial tissues, as in coordinating antimicrobial immunity and maintaining barrier function in the gastrointestinal system, soon followed[42,43]. Furthermore, activated or nuclear NF-κB proteins have been detected in many chronic inflammatory conditions, including inflammatory bowel disease[44,45], rheumatoid arthritis[46] and psoriasis[47]. These diseases respond to anti-TNF therapy[48], and the role of NF-κB in activating *TNF* transcription has been established[10]. Correspondingly, mouse models of inflammatory bowel disease[45,49], rheumatoid arthritis[9,50–52] and other inflammatory diseases respond positively to inhibitors of NF-κB, which has raised enthusiasm about NF-κB and IKKβ as therapeutic targets in chronic inflammation and autoimmunity[53]. Even under acute inflammatory conditions, NF-κB is expected to have an important causal role, as genetic polymorphisms that potentiate NF-κB activation increase mortality due to sepsis[54]. With that in mind, it was a big surprise and a disappointment when inhibition of NF-κB was found to increase or even cause inflammation under some circumstances. One of the earliest alarming observations was greater susceptibility to chemical-induced colitis in mice lacking IKKβ in intestinal epithelial cells (IECs)[55]. An even more severe and spontaneous inflammatory condition has been observed in mice devoid of IKKγ (NEMO) in IECs; these mice have an almost complete loss of NF-κB activity in these cells[56]. Likewise, ablation of IKKγ (NEMO) in mouse keratinocytes results in the development of a psoriasis-like inflammatory condition, which, surprisingly, is dependent on TNF[57]. Initially, those findings were attributed mainly to the absence of NF-κB-mediated cell-survival functions at epithelial surfaces, which serve as barriers that prevent the exposure of underlying tissue macrophages and dendritic cells to commensal bacteria. In support of that interpretation, a variety of genes encoding molecules involved in the maintenance of epithelial layer integrity, in addition to genes encoding standard antiapoptotic molecules, have been found to be under the control of NF-κB[57]. However, the real 'clincher' was provided by studies

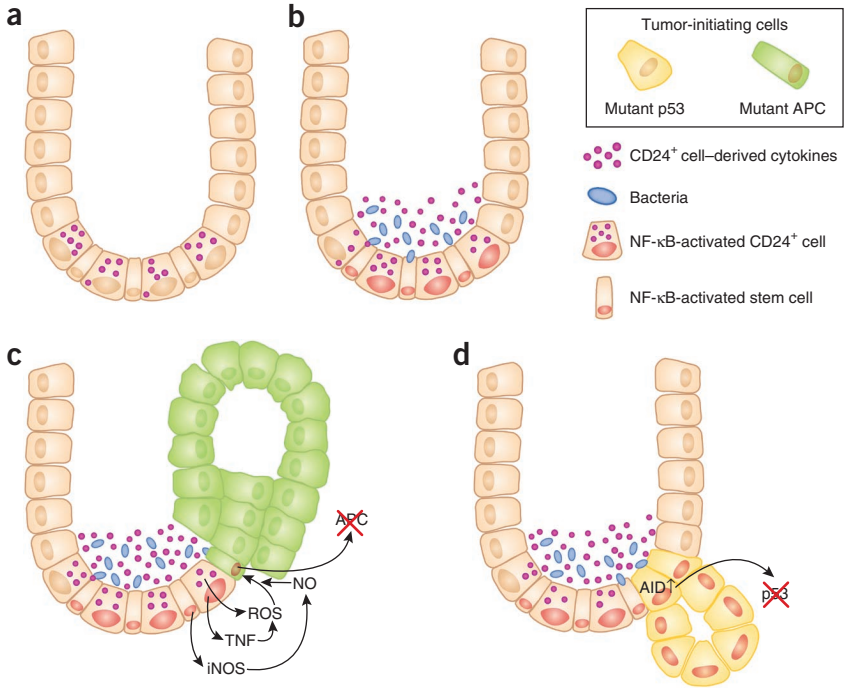

Figure 1 Hypothetical model for the generation of colorectal tumors as a result of interplay among intestinal crypt microflora NF-κB activation, and mutatagenesis mechanisms in intestinal stem cell. Encounters of bacteria with stem cells and their niche (composed mainly of Paneth-like CD24$^+$ cells[35] (granule-filled cells)) at the bottom of the colonic crypts may induce activation of NF-κB in Paneth cells and stem cells. NF-κB activation results in the release of cytokines and the production of ROS and nitric oxide (NO), as well as the upregulation of activation-induced cytidine deaminase (AID) in the stem cells[149], which all results in stem cell mutagenesis. Further activation of NF-κB in tumor-initiating cells supports their survival. (**a**) A normal colonic crypt with CD24$^+$ cells and stem cells (thin columnar cells) at the bottom. (**b**) Bacteria-loaded crypt, which results in NF-κB activation in CD24$^+$ cells and stem cells (red nuclei) and the release of cytokines and enzymes. (**c**) NF-κB-mediated production of ROS and nitric oxide, which results in mutagenesis of the gene encoding adenomatosis polyposis coli (APC) in an intestinal stem cell and adenoma growth[34]. iNOS, inducible nitric oxide synthase. (**d**) NF-κB-induced upregulation of activation-induced cytidine deaminase (AID), which results in mutagenesis of the gene encoding p53, dysplasia and invasion[150], typical of colorectal cancer associated with inflammatory bowel disease[151].

of mice with inducible deletion of the gene encoding IKKβ (IKKβ$^{\Delta}$ mice) in cells responsive to type I interferon, which include myeloid progenitors, mature myeloid cells, lymphocytes, fibroblasts and epithelial cells in tissues in which large amounts of type I interferon are produced. IKKβ$^{\Delta}$ mice are hypersusceptible to septic shock induced by either lipopolysaccharide or bacterial infection[58]. Similar results have been obtained by repetitive treatment of normal mice with a specific IKKβ inhibitor[58]. Even without any challenge, mice treated with an IKKβ inhibitor or IKKβ$^{\Delta}$ mice develop progressive and devastating neutrophilia due to more production of IL-1β by NF-κB-deficient monocytes and macrophages[59]. Such experiments have shown that in addition to its proinflammatory function, NF-κB has a direct anti-inflammatory effect; that is, inhibition of inflammasome-dependent caspase-1 activation[58] (**Fig. 2**). Although the mechanism of inflammasome inhibition by NF-κB is not entirely clear, it is probably related to NF-κB-induced expression of antiapoptotic proteins, such as PAI-2 and Bcl-x_L (refs. 58,59). The IL-1β released by NF-κB-deficient macrophages and monocytes enhances the proliferation of granulocytic progenitors and increases the survival of mature neutrophils[60]. Although the resulting neutrophilia compensates for the loss of NF-κB and allows IKKβ$^{\Delta}$ mice to resist certain microbial infections as well as (or even better than) their wild-type counterparts, it eventually results in the inflammatory destruction of tissues, which can be prevented by inhibition of IL-1β signaling[60]. Although such results seem to suggest that a more effective inhibition of inflammation can be achieved by combining inhibitors of IKKβ and IL-1β, it should be noted that IKKβ$^{\Delta}$ mice that are also deficient in the IL-1 receptor show a complete lack of innate immunity[60] and that the combined use of anti-TNF and anti-IL-1 drugs in humans results in much greater risk of infection[61]. Notably, IL-1β, whose production is subjected to both positive and negative controls by NF-κB, may function as a potent tumor promoter in some types of cancer[62].

The inflammatory response is a complex physiological host-defense system. In addition to being important for clearing foreign intruders, inflammation is important for the turnover and repair of damaged tissues. To function properly, the inflammatory response must be self-limiting and self-resolving. NF-κB orchestrates both the initiation of inflammation and its resolution[11,63]. In addition, part of the self-limiting nature of the inflammatory response is due to the existence of NF-κB-dependent feedback loops, such as those that entail the induction of IκBα and the ubiquitin-editing enzyme A20 (ref. 64). Thus, although inhibition of NF-κB often attenuates inflammation, under somewhat different circumstance or at a different site it can aggravate or even cause inflammation. The latter outcome often becomes particularly prominent under conditions of tissue injury[65,66].

Pro- and anti-tumorigenic roles of NF-κB in malignant cells

A potential role for NF-κB in oncogenesis was already evident in the discovery of the retroviral oncogene *v-Rel* as the homolog of the gene encoding c-Rel, one of the NF-κB subunits[67]. Subsequently, mutations in genes encoding NF-κB subunits or IκB proteins, most prominent among which were chromosomal translocations in *NFKB2*, were identified in a variety of hematological malignancies[67–70]. However, the number of tumors with activated nuclear NF-κB is much larger than the subfraction of malignancies with confirmed mutations in NF-κB- or IκB-encoding genes. Such observations led to the proposal that some of the NF-κB activation seen in cancer is due to mutations that affect components of signaling pathways that activate NF-κB or is the result of exposure to inflammatory cytokines in the tumor microenvironment[71]. Indeed, upstream mutations that cause NF-κB activation were first detected in MALT lymphomas, a group of tumors that arise through chronic antigenic stimulation of mucosal-associated lymphoid tissue (MALT). Common MALT lymphoma mutations include chromosomal translocations that increase expression of the adaptors Bcl-10 (ref. 72) and MALT1 (ref. 73) and lead to constitutive assembly of the Carma-1–Bcl-10–MALT1 complex, whose normal function is activation of IKK–NF-κB, downstream of antigen receptors[74,75]. Constitutive activation of NF-κB results in greater proliferation

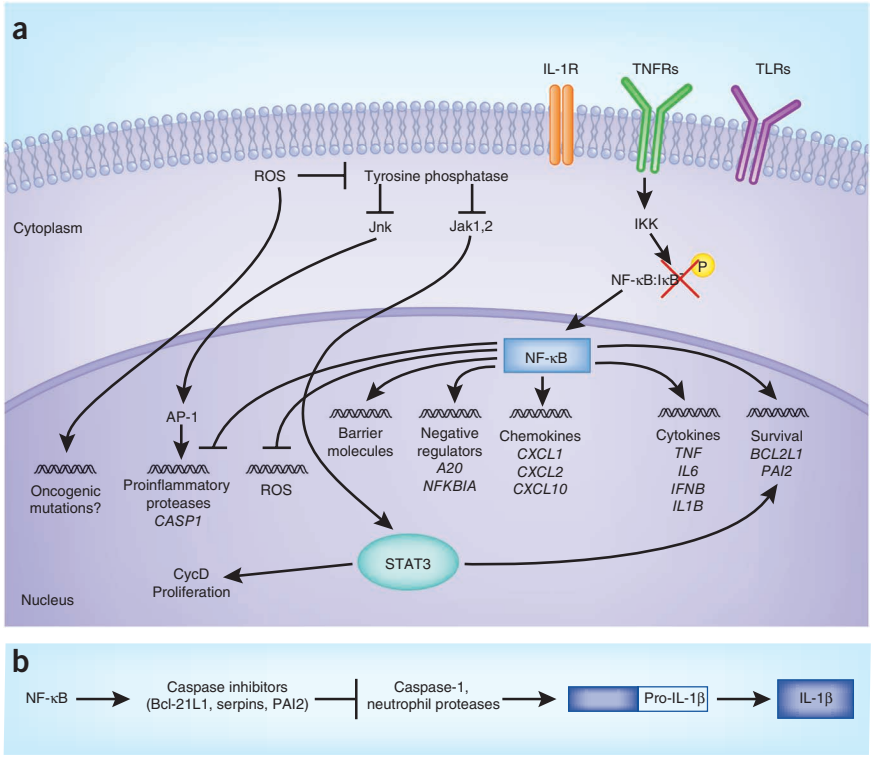

Figure 2 Pro- and anti-inflammatory functions of NF-κB and their relationship to tumorigenesis. (**a**) Activation of NF-κB downstream of TNF receptors (TNFRs), TLRs and the IL-1 receptor (IL-1R) results in the induction of genes encoding prosurvival and pro-proliferative molecules, cytokines and chemokines. The products of such genes contribute to inflammation and tumor development. However, NF-κB activation also promotes tissue integrity through the induction of genes encoding barrier molecules, protease inhibitors and antioxidants. Such molecules can suppress tumor development. By inducing the expression of antioxidant proteins, NF-κB also prevents the accumulation of pro-tumorigenic ROS and can induce DNA damage and genomic instability and lead to the activation of pro-tumorigenic transcription factors, such as STAT3 and AP-1. (**b**) A particularly intriguing NF-κB target gene encodes pro-IL-1β, which is processed by caspase-1 or neutrophil protease to the key proinflammatory and tumor-promoting cytokine IL-1β. Notable, while promoting pro-IL-1β expression, NF-κB negatively controls its processing to mature IL-1β through the induction of various protease inhibitors.

and survival of B lymphocytes, which leads to their uncontrolled accumulation even after the initiating antigenic stimulus has disappeared. Activating mutations in *CARD11* (which encodes Carma-1) have been detected in activated B cell–like diffuse large B cell lymphoma, another B cell malignancy[76,77]. Such mutations generate constitutively active Carma-1 that associates with the Bcl-10–MALT1 complex without antigenic stimulation, which results in persistent activation of NF-κB[78]. A mutation that modifies the TLR adaptor MyD88 and promotes constitutive TLR signaling has been found in diffuse large B cell lymphoma of the activated B cell–like type. The L265P MyD88 variant promotes lymphoma cell survival by spontaneously assembling a protein complex containing the IRAK1 and IRAK4, leading to kinase activity of IRAK4, phosphorylation of IRAK1, signaling by NF-κB, activation of the transcription factor STAT3 mediated by the kinase Jak, and secretion of IL-6, IL-10 and interferon-β[79]. Other mutations that lead to constitutive activation of the kinase NIK and result in the activation of both classical and alternative NF-κB signaling have been detected in multiple myeloma, another type of B cell malignancy[78,80–82]. Multiple myeloma–associated mutations include those in *NFKB2*, *BTRC*, *CARD11*, *CYLD*, *IKBIP*, *IKBKB*, *MAP3K1*, *MAP3K14*, *RIPK4*, *TLR4*, *TNFRSF1A*, *BIRC2*, *BIRC3*, *TRAF2* and *TRAF3*. *BTRC* encodes β-TrCP, the substrate-recognition subunit of the IκB ubiquitin ligase[83]. Products of the *BIRC2*, *BIRC3*, *TRAF2* and *TRAF3* loci form a ubiquitin-ligase complex responsible for degradative, Lys48-linked ubiquitination of NIK that keeps the concentration of this kinase below a critical threshold required for its autoactivation; and mutations and deletions of these genes affect this process. Other multiple myeloma–linked mutations have been found in *NIK* itself that affect the binding site for TRAF3, which connects NIK to the complex of TRAF2 and the ubiquitin ligases cIAP1 and cIAP2 (refs. 80,84,85). These mutations cause the inhibition of NIK turnover, which results in its autoactivation and the subsequent phosphorylation of IKKα, the key kinase responsible for activation of NF-κB2 processing and the generation of alternative dimers of the p52 and RelB subunits of NF-κB[85,86]. NIK can also be overexpressed as a result of gene amplification or chromosomal translocations, which also occur in multiple myeloma[78]. By analogy to B cell lymphomas in which NF-κB2 is constitutively processed as the result of its truncation because of chromosomal translocation[70], multiple myeloma has been proposed to depend on NIK-driven NF-κB2 activation[80,81]. Given those expectations, it was rather surprising when NIK-driven IKKβ activation turned out to be more important for the survival of multiple myeloma cells than is NIK-driven activation of IKKα[87].

The bulk of NF-κB-positive tumors, however, are solid malignancies derived mainly from epithelial cells. NF-κB-activating mutations are extremely rare in carcinomas, although mutations and gene fusions of *IKKA* and *IKBKB* have been detected through genomic sequencing of breast and prostate cancer, respectively[88,89]. In addition, the IKK-like kinase IKKε has been identified as a contributor to the malignant activity of breast carcinoma cells[90]. However, the role of IKKε in the activation of NF-κB is not well established and, therefore, its oncogenic activity may be NF-κB independent. A role for IKKα in the self-renewal of breast cancer progenitors has been demonstrated in a mouse model[91], and IKKα has been shown to be responsible for the tumor-promoting effect of progesterone in breast cancer, which is mediated through induction of the IKKα-activating cytokine RANKL in mammary epithelial cells[92,93]. IKKα activation is also important for the metastatic spread of breast cancer; this depends on the production of RANKL, which in advanced and progesterone-independent tumors is produced by tumor-infiltrating regulatory T cells rather than carcinoma cells[94]. NF-κB activation is also involved in the *in vitro* formation of breast cancer stem cells in response to activation of the Src tyrosine kinase[95]. However, the oncogenic functions of IKKα in breast or prostate cancers[96,97] are not mediated through either classical or alternative NF-κB signaling and instead depend on the nuclear functions of IKKα[97]. Notably, in the bulk of carcinomas in which classical NF-κB signaling is activated and may provide the cancer cell with a survival advantage, the actual cause of NF-κB activation remains to be identified and is probably microenvironmental factors rather than genetic alterations.

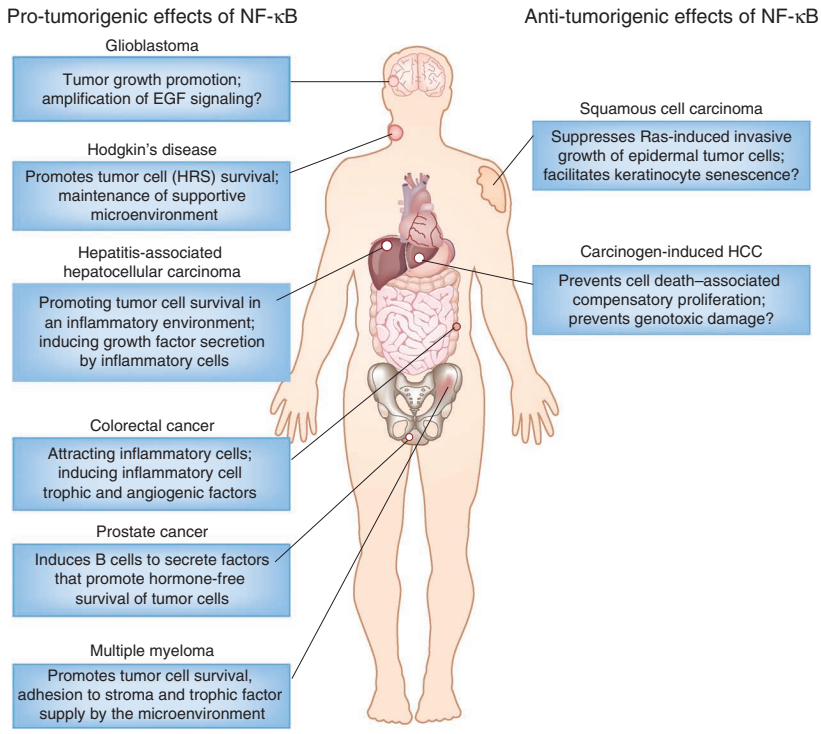

Figure 3 Pro- and anti-tumorigenic effects of NF-κB activation in cancer cells and their microenvironment. Opposing NF-κB inhibition effects are found in distinct cancer types, yet also in cancers of a similar type, depending on the mechanism of carcinogenesis. Hence, whereas NF-κB inhibition suppresses inflammation (hepatitis)-associated liver cancer (HCC), it facilitates carcinogen-induced HCC.

The role of NF-κB in the tumor microenvironment

Notably, the presence of activated NF-κB in a tumor is not necessarily causal, and even when it is of importance, just like in inflammation, NF-κB can influence tumor development and progression both positively and negatively (**Fig. 3**). The first two examples of a critical positive role for NF-κB in linking inflammation with tumor development were colitis-associated colon cancer (CAC) and hepatitis-associated liver cancer[55,98]. In CAC, a classical inflammation-driven cancer that accounts for about 5% of sporadic colorectal cancers, it has been shown by conditional ablation of IKKβ that the activation of NF-κB in IECs, in which β-catenin signaling has been activated via mutation, provides premalignant progenitors with a survival advantage through the induction of antiapoptotic genes, such as that encoding Bcl-x_L (ref. 55). NF-κB in myeloid cells, most probably lamina propria macrophages, also makes an important contribution to tumor growth and progression through the transcriptional activation of genes encoding growth factors that enhance the proliferation of premalignant IECs and their transformed derivatives[55]. Many inflammatory cytokines, including TNF, IL-6 and IL-23, produced by lamina propria macrophages and dendritic cells, as well as by tumor-associated macrophages, have been identified as the main drivers of CAC growth[99–101]. Although TNF activates NF-κB in IECs and other epithelial cells, it should be noted that ablation of IKKβ in myeloid cells, which prevents TNF production, does not affect NF-κB or the survival of premalignant IECs[55]. Thus, the actual cause of NF-κB activation in IECs remains to be identified. TNF produced by activated liver inflammatory cells, however, is probably responsible for NF-κB activation in hepatocytes of *Mdr2*$^{-/-}$ mice, which experience chronic low-grade inflammation caused by phospholipid accumulation due to absence of the MDR2 phospholipid pump[98]. Inhibition of hepatocyte NF-κB through expression of a nondegradable variant of IκBα blocks the development of hepatocellular carcinoma (HCC) in *Mdr2*$^{-/-}$ mice and enhances the apoptosis of premalignant hepatocytes[98]. Similar results have been obtained by the administration of nonsteroidal anti-inflammatory drugs (NSAIDs) or anti-TNF drugs to *Mdr2*$^{-/-}$ mice[98], yet the effects of long-term treatment with these agents on hepatocarcinogenesis are yet to be demonstrated. On the basis of analysis of a CAC model in which tumor initiation depends on metabolic activation of the mutagen azoxymethane (AOM), it was concluded that NF-κB activation promotes tumor development after the initiation stage, most probably during early tumor promotion[71,74]. Although the actual tumor-initiation event in *Mdr2*$^{-/-}$ mice is not known, NF-κB probably also acts during the tumor-promotion stage by protecting premalignant cells from apoptotic elimination. Another important mechanism through which NF-κB contributes to tumor promotion as well as tumor progression is enhanced cell proliferation. At least in CAC, in which this aspect has been investigated in some detail, the proliferative function of NF-κB is indirect and is mediated through IL-6 and related cytokines produced by myeloid cells that lead to the activation of STAT3 in IECs[55,99]. Ablation of STAT3 in IECs also inhibits CAC development, affecting both cell survival and cell proliferation[99].

The relationships between NF-κB and STAT3 are complex (**Fig. 2**). In many cell types and circumstances, NF-κB and STAT3 control the expression of a similar repertoire of antiapoptotic genes[102,103]. NF-κB and STAT3 can both interfere with synthesis of the tumor suppressor p53 and attenuate p53-mediated genomic surveillance[104]. STAT3 controls the expression of c-Myc and cyclin D[103,105]. Although NF-κB may control expression of those pro-proliferative factors in some cell types, ablation of IKKβ in IECs has no effect on cell proliferation[55], and in hepatocytes initiated by diethylnitrosamine (DEN), inhibition of NF-κB enhances cyclin D expression and cell proliferation[106]. This seemingly paradoxical effect is probably due to the activation of STAT3 in IKKβ-depleted HCC cells[107], an outcome of NF-κB inhibition that is also observed in neutrophils[60]. However, in other tumor types, NF-κB potentiates STAT3-mediated transactivation of genes encoding distinct inflammatory and pro-proliferative molecules in cells of the immune system present in the tumor microenvironment[103]. Furthermore nonphosphorylated STAT3 is reported to activate the transcription of genes encoding cytokines and growth-promoting molecules via NF-κB[108].

The microenvironmental functions of NF-κB are widespread and complex. In addition to promoting the expression of inflammatory cytokines, NF-κB seems to be involved in the polarization of tumor-associated macrophages[109]. Inhibition of NF-κB in such cells converts them from the M2 tumor-promoting phenotype to the M1 cytotoxic phenotype, thereby augmenting tumor regression[110]. Interestingly, the p50 subunit of NF-κB is a key regulator of M2-driven inflammatory reactions *in vitro* and *in vivo*. It has been shown that p50 inhibits NF-κB-driven M1 polarization, and p50-deficient mice have exacerbated M1-driven inflammation and a defective ability to mount allergy- and helminth-driven M2-polarized inflammatory reactions[111]. NF-κB also acts in cancer-associated fibroblasts, in which it promotes the expression of a proinflammatory gene signature, important for

macrophage recruitment, neovascularization and tumor growth[112]. Although some of those activities are mediated through inflammatory cytokines, others are mediated via chemokine expression. NF-κB activation in cancer cells can also lead to the upregulation of chemokines that initiate and maintain the tumor microenvironment through the recruitment of immune-response and inflammatory cells, as well as of progenitors of cancer-associated fibroblasts[3]. In addition, NF-κB can affect epithelial-to-mesenchymal transition through induction of the transcription factors twist and snail[113,114], but these effects need to be confirmed *in vivo*. In summary, NF-κB is involved in most if not all aspects of tumorigenesis, and many of its important activities are exerted in the tumor microenvironment.

Antitumorigenic effects of NF-κB

The role of NF-κB in cancer is not always positive (**Fig. 3**). Thus, blockade of NF-κB via overexpression of IκBα promotes oncogenic Ras-induced invasive epidermal growth resembling squamous cell carcinoma[115]. Although the mechanism of this phenomenon is not obvious, it might be related to the role of NF-κB in oncogene-induced senescence[116]; blocking NF-κB might abolish Ras-induced senescence. In mice given DEN, hepatocyte-specific ablation of IKKβ strongly enhances the development of HCC[106]. A similar enhancement of DEN-induced HCC development has been found after hepatocyte-specific ablation of the inflammation-responsive protein kinase p38α[117,118]. Although IKKβ and p38α do not control a common set of target genes, they both maintain hepatocyte viability by suppressing ROS accumulation[118]. Indeed, the ability of IKKβ and p38α to suppress HCC development is related to their ability to prevent DEN-induced cell death that otherwise triggers compensatory proliferation, which is critical for the transmission of oncogenic mutations, as mature hepatocytes with such mutations do not proliferate unless the liver is damaged. Hepatocyte-specific ablation of IKKγ[119] or TAK1 (refs. 120,121), which are both required for the activation of IKK and NF-κB, results in spontaneous liver damage, hepatocyte death, liver fibrosis and spontaneous development of HCC. In this case, however, the cause of the oncogenic mutations that are propagated via compensatory proliferation is unknown. Liver damage and subsequent HCC development in mice lacking hepatocyte IKKγ is related to ROS accumulation, as both can be prevented by administration of the potent antioxidant butylated hydroxyanisole, which has been found to suppress the enhanced HCC development in mice lacking hepatocyte IKKβ[106]. One further clue to the putative antitumorigenic activity of NF-κB is provided by a mouse model of stomach-specific overexpression of IL-1β, whose endogenous production is negatively regulated by NF-κB[59,60]. Mice with transgenic expression of IL-1β develop gastric inflammation and cancer, possibly due to the recruitment of myeloid-derived suppressor cells to the stomach[122].

The tumor-suppressive function of hepatocyte NF-κB applies only to situations in which the main driver of liver inflammation is hepatocyte death, which results in release of IL-1α, thereby triggering protumorigenic NF-κB signaling in Kupffer cells[118]. In another model of chronic liver inflammation that depends on NF-κB activation in hepatocytes, this one driven by ectopic expression of the TNF family member lymphotoxin, ablation of hepatocyte IKKβ prevents HCC development[123]. Furthermore, even in the DEN model, ablation of IKKβ in Kupffer cells inhibits HCC development[106], which is also inhibited by ablation of the IL-1 receptor and MyD88, both of which are required for activation of NF-κB in Kupffer cells[118]. Activated Kupffer cells produce the critical tumor-promoting cytokine IL-6, whose ablation almost completely prevents the induction of HCC by DEN[124]. As in CAC, IL-6 acts via STAT3, whose hepatocyte-specific ablation also inhibits DEN-induced HCC[107]. Ablation of IKKβ causes STAT3 activation as a result of enhanced ROS accumulation, and inverse relationships between the activation of NF-κB and STAT3 have also been observed in human HCC[107]. IKKβ ablation also enhances the activation of Jnk family members[106], including Jnk1, which contributes to HCC development[118] (**Fig. 2**).

Another interesting example of a cell type–specific role for NF-κB in tumor progression is castration-resistant prostate cancer[96]. In this case, it has been found that IKKβ activation in B cells is required for the production of lymphotoxin composed of two subunits encoded by target genes of NF-κB; this lymphotoxin activates IKKα in prostate carcinoma cells. Whereas IKKβ ablation in prostate carcinoma cells has no effect on the development or recurrence of tumors, ablation or inactivation of IKKα delays or inhibits the development of castration-resistant cancer[96]. Furthermore, IKKα, not IKKβ, is required for the metastatic spread of prostate cancer in mice[97]. It should be noted, however, that this pro-metastatic function of IKKα is NF-κB independent and requires nuclear translocation of IKKα.

Blocking NF-κB for cancer prevention and therapy

It is conceivable that if indications for NF-κB inhibition as means of cancer treatment had to be prioritized, such a list would be headed by tumors bearing NF-κB-activating mutations[78], followed by tumors in which NF-κB activation is linked to a bad prognosis[125] and those with NF-κB activation due to microenvironmental factors[126]. For some time, the first group consisted almost completely of hematological malignancies, lymphomas, leukemias and multiple myeloma, in which a variety of mutations in genes encoding components of the NF-κB pathway have been found[79,81,127], yet deletions of IκBα have now also been identified in brain tumors[38]. When treatment for such cancers is considered, the strategy should be tailored to the patient, depending on the nature of the activating mutation; hence, it would not be wise to use IKK inhibitors to treat Hodgkin's disease and glioblastoma tumors that have deletion of IκBα, as the main substrate of those reagents is missing, but RelA-specific NF-κB decoys[51] would be a logical choice. It should be noted, however, that even tumors bearing activating mutations of the gene encoding NF-κB in cancer-initiating stem cells, such as multiple myeloma, diffuse large B cell lymphoma and Hodgkin's lymphoma, often also benefit from NF-κB activation in the microenvironment[114]. Thus, blocking the activation of NF-κB in the microenvironment may compromise tumorigenesis regardless of the activating mutation; it may even be advantageous because of the relative genomic stability of the cells in the surrounding microenvironment and their likely lower tendency to develop drug resistance.

Which therapeutic means are available clinically or experimentally for targeting NF-κB oncogenic pathways? To our best knowledge, although many IKK inhibitors have been developed and have been found to exert antitumor effects in a variety of experimental cancer models, ranging from lymphoma to melanoma[128–131], at present no such drug has been clinically approved. The fairly limited success of IKK inhibitors, like that of many other targeted cancer therapeutics when they are used as single agents, has prompted studies seeking to stratify failure versus success or combining targeted therapeutics with traditional chemotherapy. IKK inhibitors, for example, should be effective in sensitizing cancer cells to standard chemotherapy-induced death, given the suppression of NF-κB-dependent genes encoding antiapoptotic molecules[132] and antioxidant molecules (such as ferritin heavy chain)[133]. An alternative strategy that has attracted growing interest is a new class of compounds known as multitarget drugs[134].

These compounds were selected to improve therapeutic efficacy by targeting diverse regulatory pathways essential for the proliferation and survival of cancer cells. Data-driven computational modeling techniques aim to find key vectors that represent signal combinations that contain information necessary for the prediction of cell responses to various perturbations[134]. Among the promising roads located by this approach is a combination of blockers of the heat-shock protein hsp90 and inhibitors of histone deacetylases and the ubiquitin-proteasome system[135–137]. Combinations of bortezomib, a proteasome inhibitor that can block NF-κB activation, and various inhibitors of histone deacetylase have already found their way into advanced clinical studies. The most extensively studied is a combination of bortezomib and vorinostat (inhibitors of histone deacetylase). A phase III trial of this pair is being conducted in patients with relapsed and/or refractory multiple myeloma after a very good response in a third of the patients who failed to respond to bortezomib monotherapy (US National Institutes of Health Clinical Trials identifier NCT00773747)[138]. An interesting new addition to the arsenal of ubiquitin-proteasome-system inhibitors is MLN4924, which inhibits the NEDD8-activating enzyme and blocks NF-κB signaling in primary diffuse large B cell lymphoma, resulting in tumor regression[139]. NEDD8-activating enzyme facilitates the addition of the ubiquitin-like protein NEDD8 to Cul-1; this is required for activity of the Skp1–Cul1–F-box complex $SCF^{\beta\text{-}TrCP}$, an IκB–E3 ubiquitin ligase, which promotes several NF-κB signaling steps[140]. By itself, the F-box protein β-TrCP is a likely target for NF-κB inhibition[141], yet no effective small molecules targeting this enzyme have been reported.

Although there is a rational for inhibiting NF-κB in tumors with constitutive or chemotherapy-induced NF-κB activation, caution should be taken with other types of cancer in which NF-κB activation could be a homeostatic switch, possibly limiting genotoxic damage[142] or toning down an inflated innate immune response[58]. Such cases, so far apparent only in experimental cancer systems, should be taken into account when an NF-κB-blocking therapeutic regimen is being considered, and this should possibly handled with a drug combination that will rebalance the adverse effects of NF-κB inhibition. Thus, if inhibition of NF-κB promotes enhanced the secretion of IL-1β and neutrophilia[60], anti-IL-1 therapy may reverse this possible pro-tumorigenic effect, albeit at the high cost of greater susceptibility to infection.

Another issue is prevention and prophylactic therapy. Will long-term suppression of smoldering inflammation result in a lower cancer risk? As NF-κB inhibitors have not yet entered clinical practice, the information available is limited to the long-term effects of NSAIDs, mostly aspirin. Daily aspirin use at doses as low as 75 mg per day for 5 years or longer has been found to diminish death due to several common cancers, with 55–75% lower risk of death for the main types of cancer, such as colorectal, pancreatic and lung carcinomas[143]. For colorectal cancer, this effect is probably not, as previously thought, due to selective inhibition of cyclooxygenase 2 (COX-2), as adjuvant therapy with the selective COX-2 inhibitor rofecoxib does not improve overall survival, nor does COX-2 expression correlate with prognosis nor can it be used to predict the effectiveness of COX-2 inhibitors[144]. Thus, although the specific target of NSAID-based cancer chemoprevention remains unknown, its remarkable preventive effect suggests that low-grade inflammation may be a far more important factor than previously appreciated. It has been suggested that 20% of all cancers are linked to inflammation[145], but this figure is probably actually much higher[146]. Systems biology–type studies should be helpful in identifying critical nodes of inflammation signaling for drug targeting. Nevertheless, it is probably safe to predict that NF-κB will emerge as an important hub in any inflammation network, which should motivate the development of effective inhibitors of the NF-κB pathway, particularly those that evade the proinflammatory side effects discussed above. NF-κB-targeting drugs may eventually prove more effective and possibly safer than NSAID use for cancer chemoprevention and therapy.

Concluding remarks

Tumor-promoting inflammation has finally been recognized as one of the hallmarks of cancer[147]. Carcinogenesis is a multistage process, and although in the classical sequence of chemical carcinogenesis, tumor initiation is followed by tumor promotion[148], inflammation represents an inverse carcinogenesis program: tumor-promoting inflammation may precede tumor initiation, creating a favorable microenvironment in which cells with cancer-causing mutations thrive. Human epidemiology and animal model studies indicate that chronic, smoldering inflammation may be a far more widespread ground for cancer development than previously thought, and NF-κB activation, as one of the pillars of inflammation, may have a promoting role in most cancers. Twenty-five years after the discovery of NF-κB, much (and yet not enough) has been learned about its signaling and transcriptional targets, and taming NF-κB activity will remain an important challenge for modern cancer biology.

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