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NF-κB inhibition: A double-edged sword in cancer?

Eli Pikarsky[a,*], *Yinon Ben-Neriah*[b]

[a]*Department of Pathology, Hebrew University Hadassah Medical School, Ein Kerem Campus, Kiryat Hadassah, Jerusalem 91120, Israel*
[b]*The Lautenberg Center for Immunology, Hebrew University Hadassah Medical School, Ein Kerem Campus, Kiryat Hadassah, Jerusalem 91120, Israel*

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ABSTRACT

Several recent studies of mouse models of cancer have provided direct genetic evidence for the critical role of NF-κB in carcinogenesis. While it has long been known that NF-κB is a key mediator of chemotherapy resistance, it is now clear that the transcription factor also has a major role in tumour development, particularly at its earlier phases. However, the role of NF-κB in tumourigenesis is more complex than anticipated, as in some models NF-κB inhibition blocks, whereas in others it facilitates, tumour development. In this paper we review current knowledge and suggest a general hypothesis that attempts to resolve this apparent paradox. Further cancer model studies should help to clarify this issue, complementing the intensive drug development effort of the pharmaceutical industry around NF-κB.

1. Introduction

NF-κB was identified in 1986 as a nuclear factor that bound to an enhancer element of the immunoglobulin κ light-chain gene in B cells,[1] but it soon became apparent that NF-κB is present in virtually every cell type, but is retained in the cytoplasm in an inactive form bound to specific inhibitors, the IκBs. Nuclear factor-kappa B (NF-κB) is a collective designation for a family of highly regulated dimeric transcription factors. Virtually all vertebral cells express at least one of five Rel/NF-κB members: p50/p105 (NF-κB1), p52/100 (NF-κB2), c-Rel, p65 (RelA) and RelB, which are assembled into homo- and hetero-dimers; most commonly encountered in mammalian cells is the p65/p50 dimer.[1–3] All these proteins share the Rel homology region (RHR), a highly conserved sequence of 300 amino acids. The RHR is responsible for dimerisation, nuclear translocation, DNA binding and regulation of NF-κB through interaction with its inhibitor, IκB. Since some Rel members contain a distinct transactivation domain, combinatorial associations of transactivation-competent Rel proteins with non-competent ones offer flexible regulation over a range of physiological conditions. Numerous gene promoters harbour the 10 bp κB binding motif, to which the NF-κB dimers bind with varying affinities.[1] NF-κB proteins are involved in the activation of an exceptionally large number of genes in response to infection, inflammation and other stressful situations requiring rapid re-programming of gene expression.[1,4–6] Following stimulation, a dedicated kinase complex, IKK, is induced, resulting in phosphorylation-dependent ubiquitination and degradation of all IκB isoforms and proteolytic processing of the precursor NF-κB proteins p105 and

* *Corresponding author:* Tel.: +972 2 6758202; fax: +972 2 6426268.
E-mail address: peli@hadassah.org.il (E. Pikarsky).
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p100.[7] Activation of NF-κB is the hallmark of the innate immune response in the entire animal kingdom, where, through induction of genes encoding cytokines, chemokines, enzymes and anti-microbial peptides, NF-κB helps in building the first line of defence against bacteria and fungi.[6] Mouse models using gene knockouts (KOs), overexpression of Rel family genes and their dominant negative forms, IκBs and IKK components have contributed invaluable data regarding the role of NF-κB in developmental processes and cell survival. RelA KOs die in utero due to massive liver apoptosis.[8] Cells derived from these KOs are susceptible to apoptotic stimuli, such as TNF-α,[9] revealing a major role for NF-κB as an anti-apoptotic regulator. While RelB has a cell-specific function, its absence in some cells results in extensive NF-κB activation and multi-organ inflammation,[10] indicating a complex regulatory relationship among members of the Rel family with both overlapping and unique functional features. Indeed, gene ablation experiments in the NF-κB pathways have revealed a common phenotype in some cases (reviewed,[11,12]), such as liver apoptosis in RelA, IKKβ and IKKγ KOs in males;[13,14]; while at other times, such as in IKKγ X-linked heterozygosity, a unique gender-specific phenotype resembling the human disease incontinentia pigmenti (IP) has been found.[14] Interestingly, in the latter case, the disease is characterised by granulocyte-infiltrated skin lesions and increased keratinocyte apoptosis, emphasising the commonly noticed association between the anti-apoptotic and inflammatory roles of NF-κB.

2. NF-κB and cancer

In line with its anti-apoptotic activity, the role of NF-κB in cancer has been studied extensively.[15–18] Aberrant sustained activation of NF-κB has been reported in numerous tumours, and was implicated in various stages of tumourigenesis.[18–20] As a potent positive cell cycle regulator on the one hand and a safeguard from apoptosis on the other, it is clear why NF-κB might confer survival benefits on transforming cells. Both v-Rel and c-Rel have been shown to have direct transforming competence.[21] Moreover, NF-κB family members are involved in translocation breakpoints, amplification and other genetic aberrations that are considered to play a causative role in carcinogenesis.[20]

Deregulation of NF-κB due to defective IκB activity was demonstrated in Hodgkin's disease, where loss of function mutations in IκB are sometimes found in the malignant Hodgkin/Reed–Sternberg cells.[22] Human loss of function mutations in CYLD, a de-ubiquitination enzyme limiting NF-κB activation, are associated with tumoural growth of adnexal tissues.[23] In addition, the pivotal role of NF-κB in growth and differentiation of various tissues is closely related to its putative function in their transformation. Most prominent in this context are lymphatic tissues, mammary glands,[24] hepatocytes,[8,25] epidermis[26] and others. Since apoptosis induction is a major mechanism of action of radiotherapy and most chemotherapeutic agents, the anti-apoptotic properties of NF-κB are likely to abrogate the effectiveness of these cancer treatments.[18,27] Whereas some malignant cells possess an inherent protection mechanism through constitutive NF-κB activity, radiation and various chemotherapy drugs induce NF-κB in a wider range of treated cells,[27–29] promoting further resistance.

Two recent works have highlighted the role of NF-κB in inflammation-induced cancer.[30,31] Both focus on the role of NF-κB in the early stages of tumourigenesis, in contrast to most of the existing body of data that has convincingly shown that NF-κB plays a major anti-apoptotic role in established tumours and in tumour metastases. Gretten and colleagues applied a chemical carcinogen to mouse colons, followed with an injurious substance to produce injury and inflammation.[30] When they eliminated IKKβ specifically in the colonic epithelial cells they found that tumour incidence was reduced, without affecting the inflammatory process per se.[30] We used Mdr2 KO mice that spontaneously develop hepatitis, followed with hepatocellular carcinoma (HCC) at a later age.[31] Similar to Gretten's results, we found that inhibiting hepatocyte NF-κB, via expression of an IκB super repressor (IκB-SR), inhibited tumourigenesis. Moreover, using in vivo administration of TNF-α neutralising antibodies, we were able to show that NF-κB activation in hepatocytes was induced by TNF-α originating from adjacent inflammatory cells.[31] NF-κB, in turn, plays an anti-apoptotic role and protects hepatocytes from apoptosis induced by genotoxic stress.[25] In line with these findings, mice lacking the TNF-α receptor type I are resistant to HCC induced by choline deficiency.[32]

Linking chronic inflammation and cancer through NF-κB would almost seem now to be inevitable, suggesting that NF-κB inhibition is an attractive mode of preventing inflammation-induced cancer. However, several lines of evidence suggest that, at least in some cases, NF-κB inhibition may induce tumourigenesis. One would then wonder if NF-κB inhibition could be considered as a means of cancer prophylaxis in predisposed individuals.

3. NF-κB and cancer: another side to the story?

Surprisingly, in some mouse models, NF-κB inhibition induces cancer.[33–38] The most extensive relevant data comes from studies of the role of NF-κB in the skin, where perturbing NF-κB activity induces squamous cell carcinoma (SCC). One possible explanation to this enigma is that the effect of NF-κB inhibition is context-specific: in certain organs NF-κB is anti-tumourigenic and in others it is pro-tumourigenic, yet in our view this is too simplistic. We would maintain that there is no real contradiction: different NF-κB inhibition outcomes result from studying different phases and pathogenic processes of the disease. The complex nature of the interacting forces in animal models (and the human diseases they aim to recapitulate), call for an intricate interpretation of the outcome.

Studies of human SCC and several murine models of SCC show frequent NF-κB activation, as well as upregulation of many of its targets[39,40] and a likely pro-tumourigenic role for NF-κB in skin carcinogenesis,[41–43] indicating that, sometimes at least, NF-κB facilitates a skin neoplastic process. Furthermore, inactivating NF-κB in PAM-LY-2 cells (an aggressive murine SCC cell line) inhibited malignant phenotypic features including proliferation, cell survival, migration, angiogenesis and tumourigenesis.[39] So why is NF-κB inhibition promoting skin cancer in other studies? Toftgard's group developed mice,

which constitutively express the IκB-SR in the epidermis using the epidermis specific K5 promoter.[35,36,44] These mice develop a chronic inflammatory skin disease characterised by massive dermal infiltration by neutrophils, followed with epidermal hyperplasia and eventually SCC. They also showed that NF-κB inhibition in this model induces upregulation of TNF-α in the skin, suggesting that in this model NF-κB inhibition promotes cancer by inducing inflammation. In a follow-up study, Toftgard and colleagues show that when the same mice are bred onto a tumour necrosis factor receptor 1(TNFR1)-KO background, both the inflammatory and the tumourigenic responses are blocked.[44] Interestingly, reconstitution of lethally irradiated K5-IκB-SR/TNFR1-KO mice with TNFR1(+/−) bone-marrow does not induce the inflammatory or the tumourigenic phenotype, indicating a critical dependence on TNFR1-mediated signalling in skin cells or non-haematopoietic cells. Moreover, even though there is no inflammatory reaction in the K5-IκB-SR/TNFR1KO mice, TNF-α levels are increased compared with wild-type (wt) skin. These results indicate that the target of TNF-α, and perhaps its source as well, are the keratinocytes themselves. Interestingly, TNF-α upregulation in K5-IκB-SR mice induces activation of jun N-terminal kinase (JNK) and cJun signalling in keratinocytes, which could be the immediate underlying cause of the carcinogenic response, particularly as it was shown that upregulation of cJun is necessary for SCC development.[45,46] Thus, the emerging picture is that NF-κB inhibition in the skin induces upregulation of TNF-α, followed by JNK and cJun activation in keratinocytes, which concomitantly with the inflammatory process leads to development of cancer. Similar data was reported by Pasparakis and colleagues,[37] who generated mice with epidermis-specific deletion of IKK2. These mice develop a severe inflammatory skin disease shortly after birth, mediated by TNF-α. Yet, whether TNF-α is targeting the NF-κB-deficient keratinocytes themselves is not always clear. Triple knockout skin lacking cRel, RelA and TNF-α receptor1 transplanted by Gerondakis and colleagues into an immunodeficient mouse underwent extensive TNF-α-dependent keratinocyte hyperproliferation, indicating that in this case the TNF-α-dependent proliferation was not a cell-autonomous effect.[47] Therefore, the common theme that transpires from these models is that inhibition of epidermal NF-κB results in upregulation of TNF-α, which is normally expressed at low levels by keratinocytes. TNF-α then induces an inflammatory response and keratinocyte hyperproliferation, which eventually develops into SCC. NF-κB inhibition in the skin can thus be viewed as a form of inflammation-induced cancer, supporting the hypothesis that inflammation promotes hyperproliferation and cancer via TNF-α signalling, whether directly at the keratinocytes, or indirectly via an unknown mediator.

Another skin model in which epidermal NF-κB inhibition induces SCC has been described by Khavari and colleagues.[33,34,48] They transplanted foetal skin from RelA$^{-/-}$ mice to adult nude mice. Similarly to other studies, the RelA$^{-/-}$ grafts develop keratinocyte hyperplasia followed by SCC. However, in contrast to the results of Toftgard and Pasparkis, these mice do not develop dermatitis. Thus, inflammation cannot account for the development of SCC in this case. To study the role of TNF-α in this model, they crossed the RelA$^{-/-}$ mice with TNFR1 KOs and generated skin grafts from these double knockouts.[48] In the double knockouts no tumours were formed, suggesting that in this model as well, TNF-α signalling is responsible for the malignant conversion. Recently, however, it has been shown that c-Rel is expressed in the skin, playing an important role in epidermal development in conjunction with RelA.[47] Possibly, in RelA-deficient skin, there is compensatory upregulation of c-Rel and consequently TNF-α, an NF-κB target gene, is induced in skin grafts from RelA$^{-/-}$ mice. Perhaps this is the source of the more general skin response in Khavari's model, while other models of NF-κB deficiency in skin produced tumours only in specific locations. An alternative explanation is that the grafting procedure per se has important implications on the process of epidermal carcinogenesis. In a different set of experiments, Balkwill's group has convincingly shown that TNF-α is a key mediator of epidermal carcinogenesis.[49–51] Absence of TNF-α, or its receptor TNFR1, conferred resistance to skin carcinogenesis.[50,52] TNF-α did not influence the initiation phase of carcinogenesis; DNA adducts and the initiating h-ras mutation occurred in its absence. However, epidermal induction of TNF-α was a critical mediator of tumour promotion, acting via a PKCα- and AP1-dependent intracellular signalling pathway in epithelial cells.[46] In the absence of TNF-α, epithelial induction of other cytokines and proteases thought to be important in skin carcinogenesis and tumour-stroma communication was delayed and/or inhibited. Thus again, the pro-tumourigenic effect of NF-κB inhibition in the skin could be due to an indirect effect, i.e. upregulation of TNF-α – a key player in epidermal carcinogenesis and a common denominator of the different models – rather than to a direct anti-neoplastic effect of NF-κB itself. TNF-α would in turn induce JNK activity, cJun and possibly CDK4[48] expression, leading to keratinocyte hyperproliferation and tumourigenesis.

It is noteworthy that the perplexing role of NF-κB in tumourigenesis is not unique to skin models. A surprising paper indicates that inhibiting NF-κB in the liver in the course of a chemical carcinogenesis model involving acute injury accelerates tumourigenesis that is induced by diethylnitrosamine (DEN).[38] This is apparently in direct contradiction to the studies reported by Pikarsky and colleagues and Greten and colleagues in inflammation-induced cancer.[30,31] It is possible that the opposing results have to do with the mechanism of tumourigenesis underlying the different models used. In chronic inflammation models, such as in the Mdr2 KO hepatitis model, NF-κB is activated over prolonged periods of time. Using an inducible super-repressor in the Mdr2 KO mouse, we showed that the effect of blocking NF-κB is mostly important at the promotion phase and not the initiation phase of the experimental model. In contrast, in the DEN liver carcinogenesis model, NF-κB activation is limited to the acute injury phase following administration of the carcinogen. Blocking NF-κB at this phase results in accelerated apoptosis and compensatory hyperproliferation of mutated, thus cancer-prone hepatocytes.[38] Perhaps this mode of carcinogenesis would even favour induction of hepatocyte mutations that obviate the need for NF-κB activation for tumour promotion. Thus, as in skin, the context of NF-κB inhibition would determine the tumourigenesis outcome: if inhibition is inducing inflammation and/or TNF-α induction, as in skin, or extensive tissue

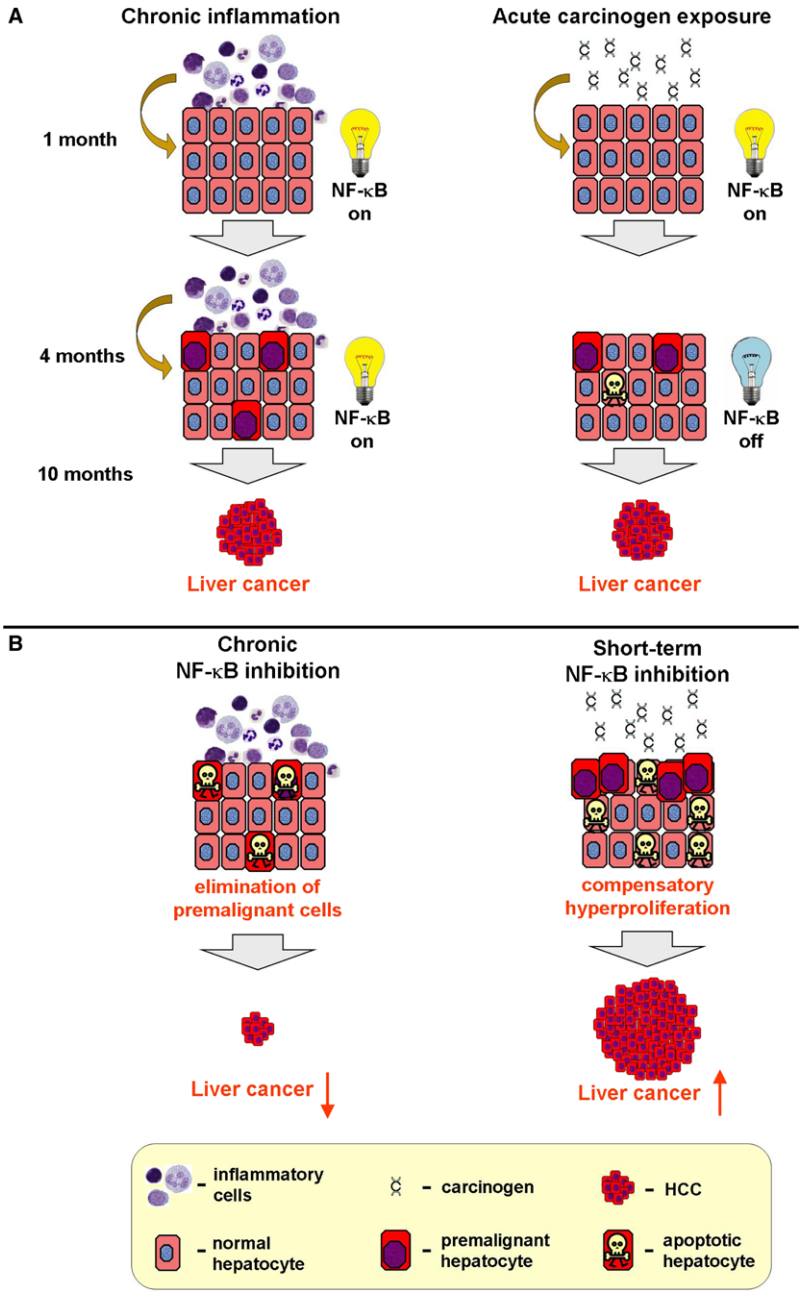

Fig. 1 – The role of NF-κB in two different pathogenetic processes. (A) In both chronic inflammation and carcinogen exposure the end result is liver cancer. However, different mechanisms operate in each scenario, both eventually culminating in hepatocellular carcinoma (HCC). It is notable that, while in chronic inflammation, the NF-κB activating signal is present throughout the disease progression, in acute carcinogen exposure NF-κB is activated only in the acute phase. (B) The difference in the duration of NF-κB activation in the two states dictates a difference in the duration, and hence outcome, of NF-κB inhibition. As a result, the endpoint of NF-κB inhibition is opposite in the two situations. In both states NF-κB acts as a prominent anti-apoptotic regulator in hepatocytes. In chronically inflamed livers, NF-κB is activated for prolonged periods and protects cancer prone hepatocytes from innate mechanisms that eliminate mutated cells. Therefore, NF-κB inhibition may prevent tumour emergence in the chronically inflamed liver. In the acute disease NF-κB inhibition causes massive apoptosis of many hepatocytes. This, in turn, results in clonal expansion of hepatocytes, thus selecting for the propagation of transformed clones.

injury requiring intensive mending, as in carcinogen liver damage, it would facilitate tumourigenesis. If, on the other hand, NF-κB inhibition compromises the survival of transformed cells, as in the chronic inflammation models and relevant human diseases predisposing to cancer, it will abolish or slow tumourigenesis (Fig. 1).

4. Conclusion

Based on numerous basic and clinical observations, NF-κB inhibition is often viewed as a necessary future addition to the armamentarium of cancer therapy.[17,27,53] Recently, however, this proposal has been challenged by several tumour models, mostly, but not exclusively, in skin cancer, in which NF-κB activation has been postulated as a safeguard against tumourigenesis. Due to the importance of this issue, it would be necessary to understand the basis for this contradiction and its medical implications, i.e. the consequences of NF-κB inhibition in different pathological contexts. Perhaps under acute insults, such as ultraviolet UV burn of the skin, liver intoxication by carbon tetrachloride, or even following radiochemotherapy damage to a normal tissue, NF-κB inhibition would aggravate the damage and promote tumourigenesis. In contrast, during chronic tissue damage, such as chronic hepatitis or *Helicobacter* infection of the stomach, NF-κB inhibition will deprive the survival needs of emerging tumour cells and slow tumourigenesis. It is hoped that further cancer model studies will help to clarify this critical issue, complementing the intensive NF-κB-based drug development efforts of the pharmaceutical industry.

Conflict of interest statement

None declared.

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