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Nuclear factor-κB: a friend or a foe in cancer?

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Abstract

Nuclear transcription factor NF-κB, initially discovered as a factor in the nucleus of B cells that binds to the enhancer of the kappa light chain of immunoglobulin, has since been shown to be expressed ubiquitously in the cytoplasm of all cell types, conserved from Drosophila to man. It translocates to the nucleus only when activated, where it regulates the expression of over 200 genes that control the immune system, growth, and inflammation. The dysregulation of NF-κB can mediate a wide variety of diseases including cancer. Whether NF-κB activation is beneficial or harmful for cancer is controversial. The development of novel therapeutics targeting NF-κB requires full understanding of its role in pathology and physiology. The current review is an attempt to describe two sides of the NF-κB coin; viz, as a friend and as a foe.

Keywords: NF-κB; Apoptosis; Proliferation; Metastasis

1. Introduction

The saying that ''man proposes God disposes'' applies not only to everyday life but also to scientific discoveries. Our group isolated TNF in 1984 for the treatment of cancer, but it turned out to cause cancer (for references see [1]). Similarily, NF-κB, which was discovered by Ranjan Sen and David Baltimore in 1986 as a factor in the nucleus of B cells that binds to the enhancer of the kappa light chain of immunoglobulin [2], has since been shown to be expressed ubiquitously in the cytoplasm of all cell types, conserved from Drosophila to man. It translocates to the nucleus only when activated, where it regulates the expression of over 200 genes that control the immune system, growth and inflammation [3].

It seems that so many things in life are double-edged swords. What determines which edge is functional at any given time, and in what direction, may depend on the inclination of the sword, i.e., the dose, the time, and the environment. For instance, TNF when expressed locally is needed for the function of the immune system [4], its systemic appearance can cause inflammation and tumorigenesis [5]. Similarily, c-myc can mediate apoptosis [6] (acts as tumor suppressor) under some circumstances, whereas it induces cellular proliferation [7] (acts as oncogene) under other conditions. Transcription factor AP-1 has been shown to mediate both proliferation and apoptosis [8], depending on the circumstances. NF-κB is no exception to this dual nature.

That duality is especially striking in relation to cancer. Cancer is a proinflammatory disease [9]. Extensive research during the last few years has shown that most inflammatory agents mediate their effects through the activation of NF-κB and that most anti-inflammatory agents suppress NF-κB activation. Similarily, most carci-

Abbreviations: NF-κB, nuclear factor-kappa B; AP-1, activator protein-1; IκB, IkappaB; IKK, IκB kinase; IL, interleukin; TNF, tumor necrosis factor; PMA, phorbol myristate acetate; EGF, epidermal growth factor; VEGF, vascular endothelial growth factor; MCP, monocyte chemoattractant protein; GM-CSF, granulocyte macrophage colony stimulating factor; NIK, NF-κB-inducing kinase; NEMO, NF-κB essential modulator; TRAF, tumor necrosis factor receptor-associated factor; IFN, interferon; HIV, human immunodeficiency virus; KSHV, Kaposi's sarcoma-associated herpes virus; EBV, Epstein-Barr virus; ICAM, intracellular adhesion molecule; VCAM, vascular cell adhesion molecules; ELAM, endothelial-leukocyte adhesion molecule-1; ATL, adult T cell leukemia; AML, acute myelogenous leukemia; COX, cyclooxygenase; MMP, matrix metalloproteinase; ECM, extracellular matrix; uPA, urinary plasminogen activator; iNOS, inducible nitric oxide synthase; CDK, cell division kinase; IAP, inhibitor of apoptosis; DMBA, 7,12-dimethylbenz(a)anthracene; PDTC, pyridine-2,6-bis(monothiocarboxylic) acid

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nogens and tumor promoters activate NF-κB, whereas chemopreventive agents suppress it, thus suggesting a strong linkage with cancer (for references see [10,11]). Paradoxically, however, most agents including cytokines, chemotherapeutic agents, and radiation, which are known to induce apoptosis, have also been shown to activate NF-κB [12], indicating that NF-κB is a part of the cells' autodefense mechanism and thus may mediate desensitization, chemoresistance, and radioresistance [13,14]. Whether NF-κB activation favors or disfavors tumorigenesis will be addressed in this commentary.

NF-κB is present in all cells in a resting state in the cytoplasm; only when it is activated and translocated to the nucleus is the usual sequence of events generated. Currently, NF-κB consists of a family of Rel-domain-containing proteins; viz., Rel A (also called p65), Rel B, c-Rel, p50 (also called NF-κB1), and p52 (also called NF-κB2). While p100 undergoes phosphorylation-dependent cleavage to form p52 product, p105 is cleaved to form p50. Similarily, a family of anchorin-domain-containing proteins have been identified, that keep NF-κB in its inactive state within the cytoplasm. These include IκBα, IκBβ, IkBγ, IκBε, bcl-3, p105 and p100 (Table 1).

Under resting conditions, NF-κB consists of a heterotrimer of p50, p65 and IκBα in the cytoplasm. The phosphorylation, ubiquitination and degradation of IκBα leads to the release of the p50–p65 heterodimer, which then translocates to the nucleus and binds its specific 10-base-pair consensus site GGGPuNNPyPyCC, where Pu is purine, Py is pyrimidine and N is any base. The individual dimers have distinct DNA-binding specificities for a collection of related κB sites [15,16]. In contrast to this canonical pathway which is activated by multiple stimuli, recently, an alternative NF-κB activation pathway has been described. It involves proteosome-mediated processing of p100 to produce p52 and is activated by B cell-activating factor receptor, lymphotoxin-β receptor, CD40, and latent membrane protein-1 (LMP)-1 of the Epstein-Barr virus (EBV) [17,18].

2. NF-κB as a Foe

Numerous lines of evidence suggest that NF-κB may actually mediate tumorigenesis. In general, it has been found that NF-κB is constitutively active in most tumor cell lines, whether derived from hematopoietic tumors or solid tumors (for references see [10]). NF-κB, however, is rarely found to be constitutively active in normal cells. When in a proliferative state, normal T cells, B cells, thymocytes, monocytes, and astrocytes were found to exhibit activated NF-κB. Constitutively active NF-κB has been identified not only in human cell lines but also in tumor tissues derived from patients; e.g., multiple myeloma [19], acute myelogenous leukemia [20], acute lymphocyte leukemia [21], chronic myelogenous leukemia [22], and prostate [23] and breast cancers [24]. More importantly, suppression of NF-κB in these tumor samples has been shown to inhibit proliferation, cause cell cycle arrest and lead to apoptosis (for references see [11]), indicating the crucial role of NF-κB in proliferation and survival of cells.

What causes the constitutive activation of NF-κB in tumor cells is incompletely understood. Some reported mechanisms include mutation of IκBα, the inhibitor of NF-κB (as reported in Hodgkin's lymphoma) [25], enhanced proteosomal activity (e.g., B cell lymphoma) that induces IκBα degradation [26], or enhanced inflammatory cytokine expression (e.g., T cell lymphoma) [27].

Several carcinogens, such as DMBA and cigarette smoke and tumor promoters, such as PMA, can induce NF-κB activation [28,29]. Numerous studies indicate that TNF, which can also mediate carcinogenesis through induction of proliferation, invasion and metastasis of tumor

Table 1
Genetic deletions of the NF-κB proteins

Gene	Phenotype	Reference
rela	Embryonic lethal; liver apoptosis; sensitivity to TNF	[64]
c-rel	Impaired T and B cell activation; systemic arthritis resistance	[76,78]
relb	Defects in acquired and innate immunity; T-cell infiltration of organs	[83]
nf-κb1	Immune response defects due to abnormal B-cell response; resistance to arthritis	[74]
nf-κb2	Abnormal spleen and lymph node architecture; defective T-cell response	[81,85]
nf-κb1/relB	Lethal 3–4 weeks post-natal; increased organ inflammation	[83]
nf-κb1	Reduced growth; cranofacial abnormalities	[85]
nf-κb2	Bone defects; B-cell defects	[84]
c-rel/rela	Embryonic lethal; early liver apoptosis	[86]
iκbα	Early neonatal lethal inflammatory dermatitis and granulocytosis	[64]
iκbε	Reduction in number of CDD44−CD25+ T cells	[108]
bcl-3	Defects in B- and T-cell responses to antigens	[85]
IKKα	Early neonatal lethal; skin defects	[90]
IKKβ	Embryonic lethal; liver apoptosis; sensitivity to TNF	[69]
IKKγ (NEMO)	Embryonic lethal; liver apoptosis; sensitivity to TNF	[109]
	Heterozygotes are model for incontinentia pigmenti	[110]

cells [30,31], is perhaps the most potent activator of NF-κB. The presence of constitutively active NF-κB in tumor cells is not a co-incidence. Its consequences are enumerated below.

2.1. NF-κB proteins are oncogenes

Certain members of the NF-κB family have been shown to be oncogenic. Gilmore et al. showed that, among the Rel/NF-κB family members, c-Rel consistently transforms cells in culture. In addition, c-rel is activated by a retroviral promoter insertion in an avian B-cell lymphoma, and amplifications of REL (human c-rel) are frequently seen in Hodgkin's lymphomas, diffuse large B-cell lymphomas, and some follicular and mediastinal B-cell lymphomas [32]. The avian Rev-T retrovirus encodes the v-Rel oncoprotein. v-Rel induces a rapidly fatal lymphoma/leukemia in young birds, and v-Rel can transform and immortalize a variety of avian cell types in vitro. v-Rel is frankly oncogenic in animal model systems. The potent oncogenicity of v-Rel is the consequence of a number of mutations that have altered its activity and regulation [33].

Tumors with *rel* amplification have an increased frequency of chromosomal aberrations, a condition previously associated with tumor progression, suggesting an oncogenic effect of amplified *rel* in B-lymphoid cells that already contained a transforming genetic lesion. *rel* amplification is frequent in diffuse lymphoma with a large cell component and probably constitutes a progression-associated marker of primary extranodal lymphomas [34]. The *rel* proto-oncogene has been mapped to chromosome region 2p11.2-14, a site associated with non-random rearrangements in non-Hodgkin's lymphoma. Lu et al. characterized an abnormal rel mRNA from a cell line derived from a diffuse large cell lymphoma in which the evolutionarily conserved N-terminal half of the *rel* coding region was fused with the C-terminal coding region of an unrelated gene. In addition, rearrangement or amplification of the *rel* locus was found in the lymphomatous tissue of two follicular and one diffuse large cell lymphoma. The findings suggest involvement of rel in the pathogenesis of large cell lymphoma [35].

2.2. NF-κB activation can induce cellular transformation

Several oncogenes have been identified that mediate their effects through activation of NF-κB. For instance oncogenic Ras, which is constitutively active in several tumor types [36,37] including prostate [38] and colon cancer, has been shown to activate NF-κB. Similarily c-myc, which can mediate tumorigenesis [39], has been shown to be regulated by NF-κB. Pim-2, which is a transcriptionally regulated oncogenic kinase, promotes cell survival through activation of NF-κB [40]. Various viral proteins that mediate tumorigenesis also signal through NF-κB activation. For instance, Kaposi's sarcoma-associated herpes virus (KSHV), implicated in Kaposi's sarcoma, primary effusion B cell lymphomas, and multicentric Castleman's disease, has been shown to induce cellular transformation through p21-activated kinase 1(Pak 1)-mediated activation of NF-κB [41]. EBV, a ubiquitous herpes virus present in over 90% of the world's population, infects the oral epithelium and is then transmitted to adjacent B cells, leading to lymphoid and epithelial malignancies such as Burkitt's lymhoma, Hodgkin's disease, posttransplant lymphoma, gastric carcinoma and nasopharyngeal carcinoma. It mediates its effects through LMP-1 which is a potent activator NF-κB [42]. LMP-1 induced NF-κB activation has been shown to be essential for the transformation of B cells and fibroblasts. Another example is human T lymphocytic leukemia virus (HTLV)-1, which causes adult T cell leukemia (ATL): it mediates its effects through a protein called tax that is a potent activator of NF-κB [43]. All these examples indicate that transformation of cells from normal to tumorigenic phenotype is in part mediated through the activation of NF-κB.

2.3. NF-κB activation mediates cellular proliferation

Numerous cytokines that are regulated by NF-κB have been shown to be growth factors for tumor cells. These include IL-1, TNF, and IL-6. While IL-1β has been shown to be growth factor for AML, TNF is growth factor for Hodgkin's lymphoma, cutaneous T cell lymphoma, and gliomas [3]. Similarily, IL-6 has been shown to be a growth factor for a wide variety of tumors including multiple myeloma [44]. Both IL-1 and TNF have been shown to mediate their proliferative effects through activation of NF-κB [45]. EGF, a growth factor for many different solid tumors, has also been shown to activate NF-κB [46]. HER2, a growth factor receptor, overexpressed in breast, prostate and other cancers; it too mediates its effects in part through NF-κB activation [47,48]. Thus both cytokines and cytokine receptors either are regulated by NF-κB or mediate proliferation through activation of NF-κB. Also, certain cell cycle proteins, such as cyclin D1, needed for entry of cells from G1 to S phase are also regulated by NF-κB.

2.4. NF-κB activation can mediate cellular invasion

Tumor invasion is a critical component of tumor metastasis. This process is regulated by numerous gene products including matrix metalloproteinases (MMP), urinary plasminogen activator (uPA), interleukin-8 (IL-8) and other chemokines, all regulated by the NF-κB [49–51].

MMPs promote angiogenesis by increasing the bioavailability of proangiogenic growth factors. They also regulate invasion and migration by degrading structural extracellular matrix (ECM) components in particular by cleaving laminin-5. It has been reported that MMP-9 expression is

regulated transcriptionally through NF-κB elements within the MMP-9 gene [49]. Bond et al., using an adenovirus that overexpresses the inhibitory subunit IκBα, found that NF-κB activation was an absolute requirement in upregulation of MMP-9.

uPA is another critical protease involved in tumor invasion and metastasis. Transcriptional activation of the uPA gene by PMA, IL-1, and TNFα requires the induction of NF-κB activity and the decay of its short-lived repressor protein, IκBα [51]. Wang et al. reported that uPA was overexpressed in pancreatic tumor cells and that its overexpression was induced by constitutive RelA activity [52]. The uPA promoter contains an NF-κB binding site that directly mediates the induction of uPA expression by RelA. Treating the pancreatic tumor cell lines with the NF-κB inhibitors dexamethasone and *n*-tosylphenyalanine chloromethyl ketone (TPCK) abolished constitutive RelA activity and uPA overexpression. These results showed that uPA is one of the downstream target genes induced by constitutively activated RelA in human pancreatic tumor cells and suggested that constitutive RelA activity may play a critical role in tumor invasion and metastasis.

Recent studies have shown that constitutively active PI 3-kinase controls cell motility by regulating the expression of uPA through the activation of NF-κB [53]. In a very recent study, Mahabeleshwar et al. demonstrated that activation of Syk, a protein-tyrosine kinase, suppressed cell motility and NF-κB-mediated secretion of uPA by inhibiting phosphatidylinositol 3′-kinase activity in breast cancer cells [54]. Thus, one of the ways to block the invasion of tumors is to target NF-κB and thus its activation of genes involved in cancer progression.

2.5. NF-κB activation can mediate angiogenesis

Angiogenesis is a process of blood vessel formation and has been found to be critical for the growth of solid tumors. Various growth factors that regulate angiogenesis have been identified. These include chemokines (e.g., MCP-1, IL-8), and growth factors (e.g., TNF, VEGF) produced by macrophages, neutrophils, and other inflammatory cells [55]. The production of these angiogenic factors has been shown to be regulated by NF-κB activation [56].

NF-κB has been shown to mediate the up-regulation of IL-8 and VEGF expression in bombesin-stimulated PC-3 cells [57]. NF-κB expression has been implicated in VEGF expression and microvessel density in human colorectal cancer [58]. Immunohistochemical expression of NF-κB, VEGF, and CD34 was detected on paraffin-embedded colorectal adenocarcinoma tissue sections. NF-κB and VEGF were significantly overexpressed and associated with increased microvessel density in colorectal cancer. These results suggest that increased expression of NF-κB contributes to tumor angiogenesis in colorectal cancer and that VEGF may play an important role in mediating the NF-κB angiogenic pathway.

Highly metastatic melanoma cells express high levels of constitutive NF-κB activity that is suppressed by transfection with mutant IκBα (IκBαM). In one study, suppression of constitutive NF-κB activity inhibited tumor growth, prevented lung metastasis, and decreased microvessel density (angiogenesis), which correlated with a decrease in the level of interleukin-8 expression [59]. These studies further underscore the role of NF-κB activation in mediating angiogenesis.

2.6. NF-κB activation can mediate metastasis

The metastasis of cancer requires the migration of cancerous cells both into and out of the vessel walls that transport them to other parts of the body. The ability to penetrate vessel walls is mediated by specific molecules expressed on the endothelial cells of the blood vessels in response to a number of signals from inflammatory cells, tumor cells, etc. Metastasis is mediated through the expression of various adhesion molecules including ICAM-1, VCAM-1, and ELAM-1 [60]. All these adhesion molecules are also regulated by NF-κB. The inducible nitric oxide synthase (iNOS) has also been closely linked with metastatic ability of the tumor [61]. The expression of this protein once again is regulated by NF-κB.

Helbig et al. have demonstrated that NF-κB regulates the motility of breast cancer cells by directly up-regulating the expression of chemokine receptor, CXCR4 [62]. They showed that the NF-κB subunits p65 and p50 bind directly to sequences within the −66 to +7 region of the CXCR4 promoter and activate transcription. They also showed that the cell surface expression of CXCR4 and stromal-derived factor-1α (SDF-1α)-mediated migration are enhanced in breast cancer cells isolated from mammary fat pad xenografts compared with parental cells grown in culture. A further increase in CXCR4 cell surface expression and stroma-derived factor-1α (SDF-1α) migration was observed with cancer cells that metastasized to the lungs. These results implicate NF-κB in the migration and organ-specific homing of metastatic breast cancer cells. Fujioka et al. showed that inhibiting constitutive NF-κB activity by expressing IκBαM suppressed liver metastasis [63]. The evidence indicates that NF-κB could mediate metastasis.

3. NF-κB as a friend

While all the above evidence indicates that activation of NF-κB could lead to tumorigenesis, suppressing NF-κB, in some situations, could also prove harmful. Several studies over the past few years on mouse models with a deletion of one or more of the genes that code for specific Rel/NF-κB proteins (termed ‘knockout mice’) have provided a valuable insight into the function and relevance of various NF-κB gene products. Overall, individual knockouts have

caused either mild to severe immune-related deficiencies (e.g., p105/p50, p100/p52, Rel A, Rel C, IκBα), liver apoptosis (Rel A), or various other developmental abnormalities (e.g., IκBα, IKK). Knocking out the Rel A subunit caused embryonic lethality as a result of fetal liver cell apoptosis and granulopoiesis [64]. This implicates Rel A in cell survival, specifically in response to the cytotoxic effects of TNF via induction of IκBα. Also, Rel A has been shown to be important in induced lymphocyte proliferation and isotype switching but not basal transcription [65].

Knocking out the major inhibitory subunit IκBα in mice produces severe runting (one-third of normal weight) despite normal development, death by day 8 of life due to widespread dermatitis and granulocytosis, scaly skin with significant sloughing, extensive post-natal granulopoiesis, small spleen size caused by depletion of cells of erythroid and lymphoid lineages (but not myeloid), and elevated levels of NF-κB in hematopoietic tissues and some NF-κB-dependent target genes (implying that additional transcriptional factors are involved) [66–68]. Recently, experiments with IKK and IKK knockout mice have demonstrated that IKK is the major subunit involved in NF-κB activation in response to a majority of stimuli (i.e., pro-inflammatory cytokines) [69,70] (Fig. 1).

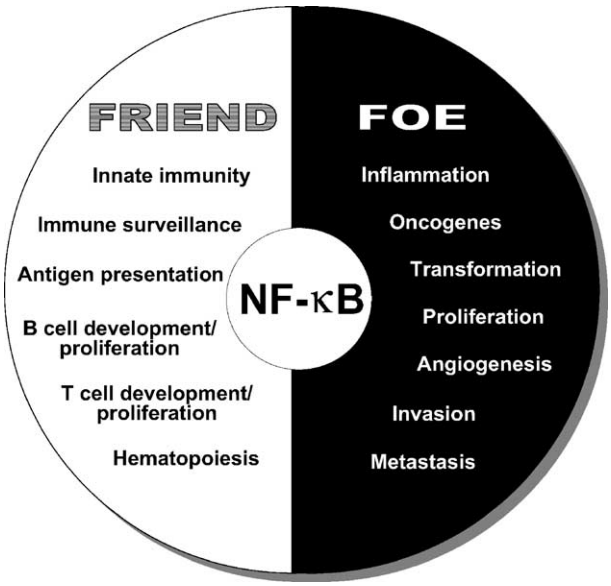

Fig. 1. The beneficial and harmful roles of NF-κB.

3.1. NF-κB activation is needed for immune function

NF-κB is required for the normal functioning of the immune system. Cytokines and their corresponding receptors are key mediators of the immune system that are crucial for immune cell communication and efffector functions during an active immune response. NF-κB plays key roles in regulating the expression of many cytokine genes. Studies on *c-rel*-deficient mice have demonstrated that *c-rel* is essential for IL-2, IL-3, GM-CSF, γ-IFN expression in T lymphocytes, IL-6 expression in B cells, TNF-α expression in macrophages, and IL-12 expression in dendritic cells [66,71–73] (Fig. 2).

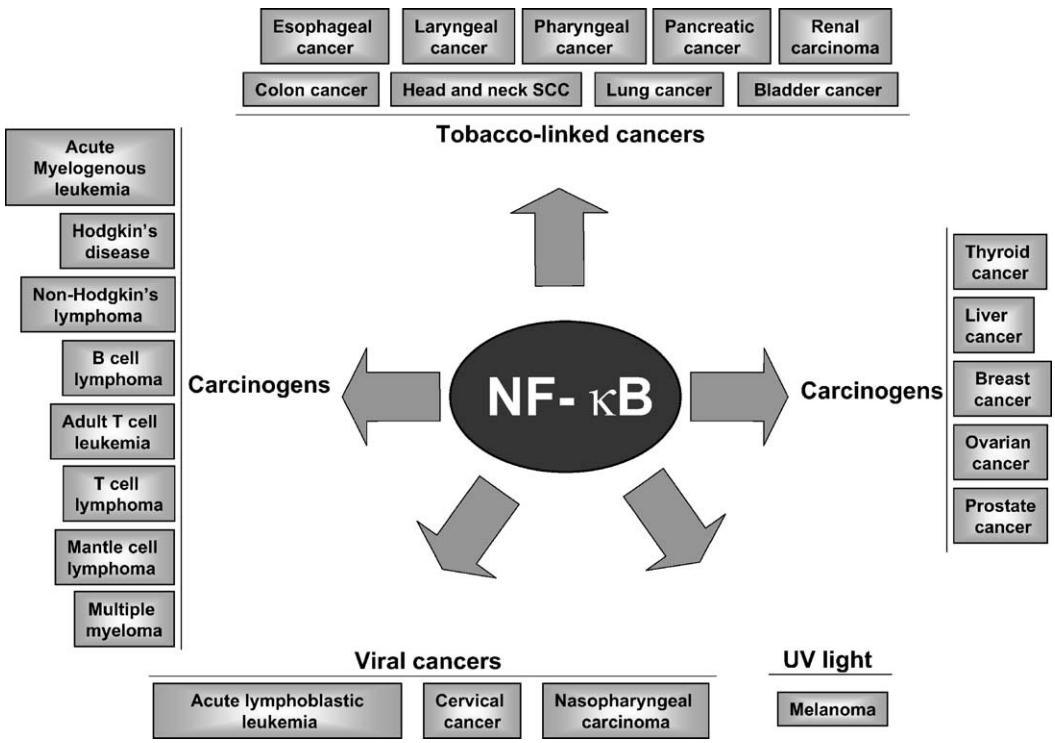

Fig. 2. Cancers that have been linked with constitutive activation of NF-κB.

When p105/p50 is knocked out, functional defects in the immune system appear despite otherwise normal development and phenotype [74]. More specifically, p105/p50 is essential for the survival of non-activated B cells but not for all B cell-activated pathways [75–77]. For example, p50-deficient mice are susceptible to *Listeria monocytogenes* and *Streptococcus pneumoniae* infections and do not proliferate in response to LPS but do respond to *Haemophilus influenzae* and *Escherichia coli*. *c-rel* knockout mice show normal development but have B and T cell deficiencies [78]. Specifically, *c-rel*-deficient B cells cannot proliferate in response to immunogens due to a cell cycle block at G1 and have increased activation-induced apoptosis due to a failure to upregulate A1 (homologue of Bcl-2), a prosurvival protein [76,79]. c-Rel has also been shown to cause a tissue-specific deficiency of various cytokines and growth factors in T cells and macrophages affecting both innate and humoral immune responses in the host [66,80]. Mice deficient in the NK-κB2 gene (p100/p52) mainly have defects in lymph node and splenic architecture, although development is normal [81]. This leads to antigen presentation impairment from accessory cells such as dendritic cells and macrophages but does not affect B or T cells directly [82]. All these studies emphasize the significance of NF-κB in normal development and functioning of the immune system.

3.2. NF-κB activation is needed for haematopoiesis

NF-κB is crucial for hematopoiesis. This is supported by the observation that $p65^{(-/-)}$ derived fetal liver cells have severe deficits in lymphopoiesis, but relatively normal development of myeloid and granulocyte lineage. By comparison, deletion of both p65 and c-Rel led to defect in lymphopoiesis, reduced colony forming unit progenitors for myeloid cells, impaired erythropoiesis, and expansion of granulocytes.

Deletion of both p50 and RelB genes in mice affects lymphoid lineage development which may in part result from a defective stromal environment. The p50/RelB double knockout mice have impaired development of $B220^{+}$ cells in bone marrow, traced to stages as early as pre-B or pro-B stage [83]. These mice reveal thymic atrophy and lack a $CD4^{+}$ $CD8^{+}$ DP thymocyte population. Deletion of both p50 and p52 affects further maturation of committed progenitors of the lymphoid and osteoclast lineages [84,85]. The B cell development is arrested in the discrete immature T1 stage because the double knockout mice are unable to form germinal centers in response to antigen challenge. The p50/p52 double knockout mice have no detectable peripheral T cells, but the defect is not intrinsic to T cell development. Rather, it is due to impaired thymic and splenic architectures. Thus, p50- and p52-containing complexes (which may include RelB) play major roles in the development, differentiation, and trafficking of medullary epithelial cells and dendritic cells. Deletion of both p65 and c-Rel appears to only affect later developmental stages of the lymphoid lineages. Together, these studies suggest that the role of p50 and c-Rel is primarily restricted to mature lymphocytes, especially for mediating antigen-induced clonal expansion, cytokine production, effector function, and terminal differentiation that are necessary for germinal center immune responses.

NF-κB/Rel plays a role in myeloid differentiation, as deletion of both p65 and c-Rel affects early common myeloid progenitors, leading to reduced colony forming unit progenitors, impaired erythropoiesis, aberrant expansion of granulocytes, and macrophage apoptosis [86]. The double-knockout macrophages also have defects in the production of IL-6 and GM-CSF, suggesting that p50/p52 is also required for macrophage activation. RelB knockout mice have defective development of thymic medullary epithelial cells and of dendritic cells. These reports demonstrate that p50/p65 are required for proper development of both lymphoid and myeloid dendritic cells [87].

3.3. NF-κB activation mediates apoptosis

Although rare, there are systems in which NF-κB plays a pro-apoptotic role in addition to its more common anti-apoptotic role. Examples of its pro-apoptotic effects in cells include those found in B-cells, T-cells, neuronal cells, and endothelial cells. The opposing effects of NF-κB are thought to be cell type-specific and/or dependent on the inducing signal (e.g., IL-1, TNF, and UV radiation). Different activation pathways of NF-κB may cause the expression of proteins that promote apoptosis (e.g., Fas, c-myc, p53) or inhibit apoptosis (e.g., TRAF2, IAP proteins, Bcl-2-like proteins). In addition, NF-κB activation variably controls the regulation of cell cycle proteins (e.g., cyclin D1 and CDK2 kinase) and the interaction with various cellular components (e.g., p300 and p53) that promote or induce apoptosis (for references see [88]).

NF-κB activation mediates TNF-induced apoptosis in murine clonal osteoblasts [89]. The suppression of the growth of $CD34^{+}$ myeloid cells by TNF also correlates with the NF-κB activation [90]. Apart from this, Fas activates NF-κB and induces apoptosis in T-cell lines by signaling pathways that are distinct from those induced by TNF [91]. Human melanoma cells are protected against UV-induced apoptosis through the down-regulation of NF-κB activity and Fas expression [92]. Oxidative stress induces apoptosis in human aortic endothelial cells through the downregulation of bcl-2, translocation of bax, and up-regulation of p53, which probably takes place through NF-κB activation. Oxidative stress may play an important role in endothelial apoptosis that is mediated by hypoxia through the activation of NF-κB [93]. The activation of NF-κB is required for apoptosis, as has also been shown for other inducers such as H_2O_2 [94]. Similarly, H_2O_2-induced apoptosis is not suppressed by hyperoxia-induced NF-κB

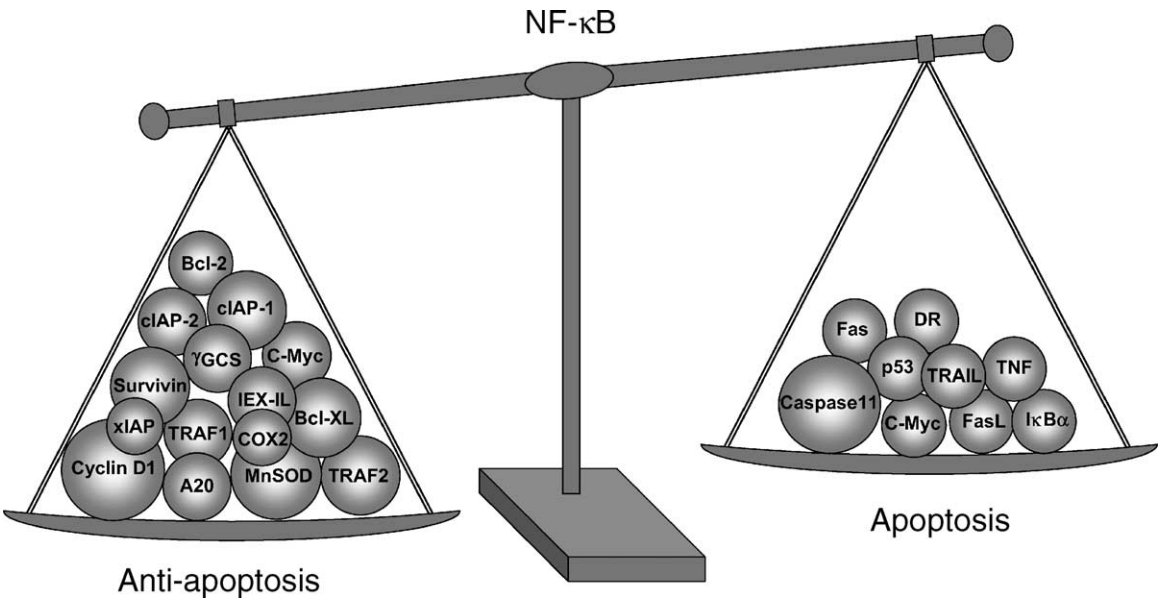

Fig. 3. Role of NF-κB regulated gene products in apoptosis.

activation [95]. In pancreatic islets, A20 inhibits both apoptosis and the NF-κB activation that is induced by cytokines. This suggests that NF-κB may actually mediate apoptosis [96] (Fig. 3).

Apoptosis in HL-60 cells that is induced by chemotherapeutic agents, such as etoposide or 1-β-D-arabinofuranosylcytosine was also found to require NF-κB activation: the suppression of NF-κB by PDTC blocked apoptosis [97]. Recently, Stark et al. demonstrated that aspirin induces cell death by an active apoptotic process that involves the nuclear translocation of NF-κB [98]. The inhibition of breast cancer cell growth by mullerian inhibiting substance also takes place through NF-κB mediated pathway [99]. The activation of NF-κB is essential for the cytotoxic effects of doxorubicin and its analogues [100,101]. Similarly, cellular resistance to vincristine has been shown to suppress TNF-induced NF-κB activation [102].

Lin et al. showed that NF-κB can be proapoptotic or antiapoptotic, depending on the timing of the modulating NF-κB activity relative to the death stimulus [103]. How NF-κB mediates apoptosis is unclear, but p53 and c-myc induction play a role [6]. In addition, NF-κB is required for the anti-CD3-mediated apoptosis of double-positive thymocytes through a pathway that involves the regulation of the anti-apoptotic gene bcl-XL [104]. c-myc has also been implicated in the survival of certain cells such as hepatocytes [7]. These observations suggest that NF-κB activation both negatively, and positively regulates apoptosis, thereby further strengthening the idea that NF-κB activation may be advantageous in overcoming certain kinds of cancer.

3.4. NF-κB activation prevents tumorigenesis

NF-κB has also been implicated in epidermal squamous cell carcinoma in mice [105]. Seitz et al. showed that blockade of NF-κB predisposes murine skin to squamous cell carcinoma [106]. Dajee et al. have shown that NF-κB blockade triggers invasive human epidermal neoplasia [107]. Thus these reports suggest that suppression of NF-κB could be tumorigenic under some conditions.

4. Conclusion

NF-κB is activated in response to oncogenes, viral proteins, carcinogens, tumor promoters, and inflammatory stimuli. Its activation controls the expression of genes that mediate transformation, proliferation, invasion, angiogenesis, and metastasis on one hand and apoptosis, immunity, and hematopoiesis on the other. While NF-κB is required for the normal function of the immune system and for hematopiesis, its deregulation has been implicated in a variety of cancer in which NF-κB is overexpressed. While numerous pharmaceutical companies are developing inhibitors of NF-κB for the treatment of cancer, these inhibitors should be tested with caution in view of the dual nature of NF-κB, in which either its activation or inactivation may lead to tumorigenesis, depending upon circumstances. Cancer is a proinflammatory disease is also indicated by the fact that aspirin, an established NF-κB blocker and an anti-inflammatory agent, has now shown promise in the treatment of certain cancers. Blockers of NF-κB, that are non-toxic such as plant polyphenols, should be beneficial in not only prevention but therapy of cancer as well.

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