

REVIEW

Aberrant control of NF- κ B in cancer permits transcriptional and phenotypic plasticity, to curtail dependence on host tissue: molecular mode

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ABSTRACT

The role of the transcription factor NF- κ B in shaping the cancer microenvironment is becoming increasingly clear. Inflammation alters the activity of enzymes that modulate NF- κ B function, and causes extensive changes in genomic chromatin that ultimately drastically alter cell-specific gene expression. NF- κ B regulates the expression of cytokines and adhesion factors that control interactions among adjacent cells. As such, NF- κ B fine tunes tissue cellular composition, as well as tissues' interactions with the immune system. Therefore, NF- κ B changes the cell response to hormones and to contact with neighboring cells. Activating NF- κ B confers transcriptional and phenotypic plasticity to a cell and thereby enables profound local changes in tissue function and composition. Research suggests that the regulation of NF- κ B target genes is specifically altered in cancer. Such alterations occur not only due to mutations of NF- κ B regulatory proteins, but also because of changes in the activity of specific proteostatic modules and metabolic pathways. This article describes the molecular mode of NF- κ B regulation with a few characteristic examples of target genes.

KEYWORDS

Cytokine; mucin; chemokine; IL-8/CXCL8; MUC1; NF- κ B; IL-6; TNF α

Introduction

NF- κ B is an inducible transcription factor that recognizes and binds specific DNA sequences. It enables cells to adapt to tissue homeostatic changes by modulating genomic function¹. NF- κ B is a dimer of Rel proteins. These Rel proteins are regulated by assorted post-translational modifications, as well as interactions with other proteins, especially inhibitor of κ B (I κ B). I κ B keeps the Rel dimer in a latent state in the cytoplasm¹. I κ B α is encoded by an NF- κ B-regulated gene, reflecting the spectrum and complexity of NF- κ B effects on the cell. I κ B α may sequester tumor suppressor p53 and operate in the mitochondria by blocking the apoptotic mediator Bax depending on the presence of protein scaffolds^{2,3}. NF- κ B is activated by discrete, cell-specific post-translational modifications, and enters the nucleus and mitochondria to alter the expression of multiple gene clusters⁴⁻⁷.

These clusters include different gene types: those that facilitate drastic changes in cell phenotype, promote cell survival, or initiate cell death. Given the cell lineage and genomic state, NF- κ B target genes change the cell fate depending on the cell's specific contribution to tissue structure and function⁸⁻¹⁰. These changes could be permanent, last over several cell divisions, or be readily reversible depending on the enzymes that accompany transcription factor complexes on chromatin, as well as the ensuing physical or chemical DNA changes. NF- κ B target genes include several potent modulators of the immune system that link tissue homeostasis to all the organism functions¹¹⁻¹⁴. Notably, various NF- κ B target genes participate in negative feedback mechanisms that limit the key functions of NF- κ B and thereby help control inflammation. In cancer, aberrant cellular response to NF- κ B activation alters a cell's phenotype, local microenvironment, and communication with the immune system⁵.

Cycle of NF- κ B activity

Specifically, canonical NF- κ B is composed of a Rel protein dimer, which is maintained in its latent cytoplasmic form by I κ B α ^{15,16}. Cell stress signals and diverse hormonal and

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metabolic mediators induce kinase IKK β to phosphorylate I κ B α . This process commonly leads to the proteasomal degradation of I κ B α . The freed Rel dimer then enters the nucleus and binds to specific DNA sites that function as cell-stress response elements. The Rel dimer also binds to DNA within densely packed heterochromatin¹⁷. The enzymes that are associated with the Rel dimer remodel chromatin and change target gene expression depending on the activities of other transcription factors and the type of post-translational modifications on the Rel dimer itself¹⁸⁻²⁰. In particular, NF- κ B recruits and redistributes proteins that enhance gene expression over a distance, such as MED1, to interact with chromatin and facilitate promoter-enhancer interactions^{7,21}. A cell typically coordinates the expression of differentiation-steering genes through hundreds of distal enhancers that contain dense binding sites to transcription factors. These enhancers are termed as super-enhancers and are extensively replaced during NF- κ B activation; they allow inflammatory gene expression to steer cellular function⁸.

However, NF- κ B also induces the expression of I κ B α , which is encoded by a gene that does not require *de novo* chromatin remodeling. This process generates a negative feedback response that terminates the expression of potent inflammatory mediators^{22,23}. A cell contains several proteolytic systems that can degrade I κ B α . In a cancer cell, cytotoxic drugs induce cell stress, which then changes cellular proteostasis, including I κ B α proteolysis²⁴. Drastic metabolite changes sufficient to alter enzymatic activity in cellular compartments involved in protein turnover induce NF- κ B to facilitate cellular responses to these changes²⁵. Under certain tissue homeostatic conditions, drugs activate NF- κ B dimers that facilitate cell survival, express proteins that protect the cancer cell from the immune system, and enable metastasis²⁶. To add complexity, in some drug-resistant cancer cell types, Rel dimers are induced by noncanonical signaling pathways and control the expression of developmental genes not restricted by I κ B α . In such cases, the main transducer for noncanonical NF- κ B activity is the I-kappa B kinase subunit alpha (IKK α)²⁷. These cells are resistant to drugs that inhibit the upstream inducers of canonical signaling⁵.

To deliver long-term effects, NF- κ B can induce the expression of the methyltransferase DNMT1. DNMT1 can inhibit the expression of tumor suppressor genes over many cell divisions by methylating the CpG islands on the genes²⁸. A tissue regulates inflammation through multiple mechanisms with the following central theme: substances related to infection, injury, or tissue damage by other sources activate the immune system and inhibit tissue function and tissue growth, thereby yielding bioenergetic priority to the

immune response⁷. Inflammatory mediators regulate one another through diverse mechanisms and consequently sustain the immune response in proportion to the stimuli that signal a localized disruption in tissue homeostasis⁸. Finally, inflammatory mediators gradually disappear and local cells activate signals that re-establish tissue function²⁹ (**Figure 1**).

This chain of events is disrupted in cancer, but key control elements may remain functional, as shown by the effects of signal interference on neoplastic tissue^{26,30,31}. Importantly, one must recognize that feedback signaling to NF- κ B in cancer is disrupted to interfere with the fundamental functions of tumor suppressor genes. In brief, cell survival control is not intertwined with tissue homeostasis⁵. Intracellular turnover controls NF- κ B activity, which in turn controls cellular communication with the rest of the organism through cytokines²⁴. Malignant cells increase intracellular turnover, which then enables the NF- κ B-driven expression of antiapoptotic factors and the degradation of pro-apoptotic proteins^{24,32}. This occurrence permits cancer cell survival in abnormal locations, but disrupts the tissue feedback with the immune system essential to optimum tissue growth, development, and function^{5,33}.

Molecular types induced by NF- κ B

In tissue development, NF- κ B interacts with two protein types: inflammatory and tissue regeneration mediators^{10,34}. In oncogenesis, the proteins that regulate inflammation can interact with oncogenes or tumor suppressors. The proteins that mediate tissue regeneration mostly appear in the expression signatures of tumors. However, these proteins may also assume an oncosuppressive role in certain cellular subsets of inflammatory cancers³⁵⁻³⁷.

Specifically, NF- κ B cooperates with transcription factors, such as AP-1, to induce the expression of genes that encode inflammatory cytokines, adhesion molecules, and extracellular proteases (**Figure 2**)³⁸. These gene products serve essential functions during inflammation and may induce apoptosis in tumors. AP-1 proteins function as dimers that form coiled coils upon dimerization; they belong to the broader class of basic leucine zipper (bZip) transcription factors. These bZip transcription factors include the activating transcription factor (ATF) family. ATF dimers regulate cell growth and facilitate the response to cell cycle checkpoint enzymes by activating cyclin gene expression³⁹. This activity of AP-1 and ATF links the progress of processes, such as DNA repair, with cell cycle progression⁴⁰.

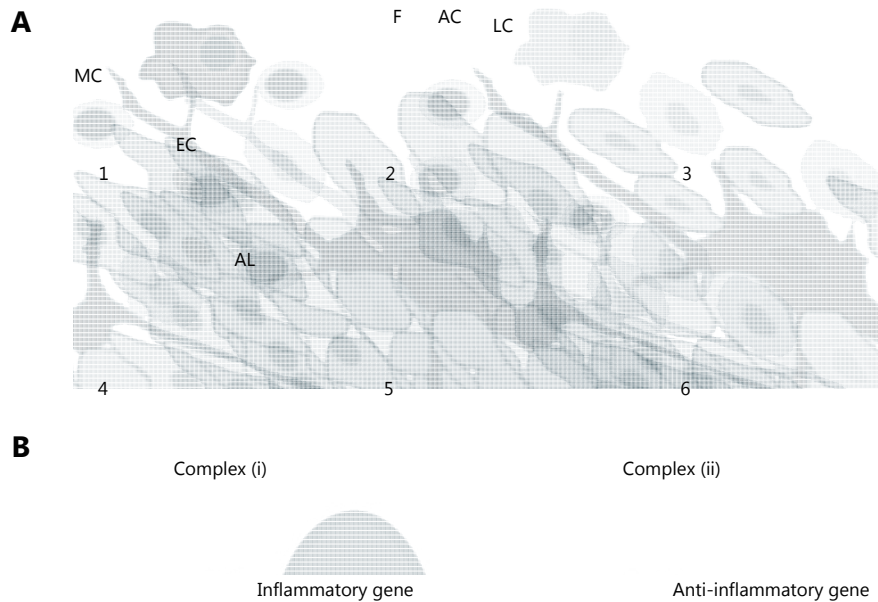


Figure 1 (A) Tissue response to internal or external insult followed by the activation of different cell types based on experimental evidence. The different cell types activated include several types of leukocytes (LC), resident macrophages (F), groups of resident cells in apoptosis (AC), and circulating components of the immune system migrating in successive waves (1-3). Selected groups of resident cells, such as epithelial cells (EC), undergo dedifferentiation into mesenchymal cells (MC) and re-epithelialization. Several mediators of immunosuppression are expressed. The immune response subsides, some leukocytes undergo apoptotic death (AL), and tissue function resumes (4-6). Accumulating data from molecular studies suggest that this succession of events is regulated by a chain of changes in the activity of sequence-specific transcription factors. In particular, factors that interact with Rel family proteins alter the gene selection activated by the Rel-domain proteins. This occurrence results in cell-specific patterns of gene expression and determines the function of each cell type during inflammation. (B) Simplified view of transcriptional regulation. Normally, transcription factor complex (i) is produced during inflammation, whereas complex (ii) appears during inflammatory resolution. After complex (ii) resolves, chromatin returns to its basal state, and the cell expresses genes depending on its typical function in the tissue. The cell is then prepared to induce complex (i) formation upon inflammatory stimulation. In cancer, pro- and anti-inflammatory mechanisms may be activated. The cancer cell may survive this occurrence by increasing the activity of intracellular turnover systems. Under the simultaneous expression of pro- and anti-inflammatory genes, a cancer cell is endowed with survival mechanisms under inflammation and sends mixed signals to its microenvironment.

bZip can form numerous potential dimers, where each monomer may be activated by discrete members of the mitogen-activated protein kinases. These kinases include the extracellular signal-activated kinases (ERK) and the stress-activated protein kinases [p38 and c-Jun kinase (JNK)], which promote cell apoptosis⁴¹. A tumor may activate an appropriate survival mechanism, such as degrading a key apoptotic mediator. In this case, NF- κ B-induced inflammatory genes may facilitate metastasis by permitting cancer cells to overcome tissue barriers to invasion and express molecules that enable cancer cell adaptation in the metastatic niche^{42,43}.

Cells may be stimulated by signals that induce later stages of inflammation, as well as ensuing tissue regeneration. In this case, NF- κ B cooperates with transcription factors, such as STAT3, to induce the expression of genes that encode

proteins mediating cellular transdifferentiation, resident stem-cell proliferation, immune cell apoptosis, and tissue protection from the immune system⁴⁴. These proteins collectively operate to enable a tissue to return to a functional state. A cell will undergo apoptosis or survive depending on whether proteins that interact with the Bcl-2 family are expressed. NF- κ B drives the expression of several antiapoptotic genes of the Bcl-2 family⁴⁵. Cell stress can induce the NF- κ B-dependent expression of protein p62, which sequesters proteins to the proteasome and lysosome, to clear protein aggregates²⁵. In cancer, altered pace and selection of protein removal enables malignant cells to neutralize attacks from the immune system and consequently survive in niches that would normally reject the differentiated progeny of their parental cell lineage^{5,37,46}. A comprehensive list of genes regulated by NF- κ B is provided

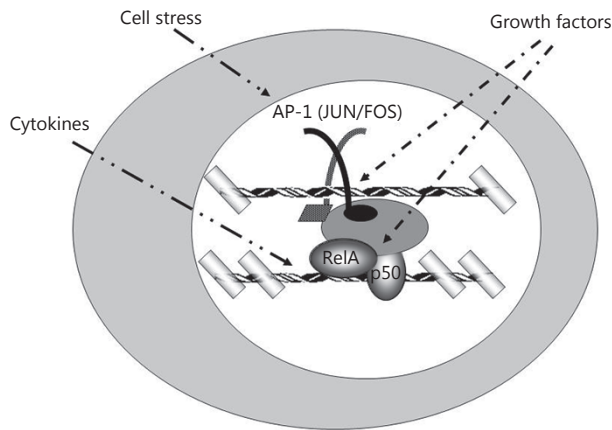


Figure 2 Interaction between transcription factors NF- κ B and AP-1, which bind to their respective DNA target sequences and facilitate chromatin remodeling. In the nucleus, NF- κ B binds to cognate sites and synergistically interacts with proteins to redistribute chromatin remodeling complexes on chromosomal DNA. This change affects the cellular developmental fate by altering protein occupancy in the proximal and distal gene regulatory regions in a cell-specific and gene-specific fashion.

by the Gilmore Lab at <http://www.bu.edu/nf-kb/gene-resources/target-genes/>

Operating mode of NF- κ B

Inflammation activates successive waves of inducible transcription factors that enter the nucleus and bind to specific DNA sequences to modulate gene expression. Inflammation is elicited by the molecules released by dying cells or expressed on parasite surfaces. These molecules bind to specific cell surface transmembrane receptors, such as the TLR family or the RAGE, which in turn activate the expression and release of cytokines, such as TNF, IL-1, or CCL2⁴⁷⁻⁵¹. The released cytokines then stimulate other cells to express additional cytokines and surface receptors until adequate combinations of feedback repressors for inflammation are produced. At this point, tissue function resumes⁵². Although some transcription factors share few functions within a given gene cohort, the interactions among NF- κ B and proteins of the AP-1 and STAT families have been the most studied operating system for inflammatory gene promoters^{19,23,53,54}.

In most cells, the transcription factors of the NF- κ B family appear in latent cytoplasmic forms. Under signals that induce either the phosphorylation or proteolysis of their inhibitor I κ B, the transcription factors enter the nucleus almost instantly, whereas the most potent Rel protein, RelA (p65),

which is phosphorylated on the Serine 536 residue, induces the expression of the I κ B α gene to produce a timely negative feedback to NF- κ B. Meanwhile, the expression of inflammatory genes depends on oxidative stress¹. In this manner, gene expression induced by reactive oxygen species (ROS) is rapidly restrained by I κ B α resynthesis. RelA serine 536 phosphorylation occurs mainly from the IKK complex and possibly through the contribution of other enzymes, such as protein kinase C isoforms delta and zeta⁵⁵⁻⁵⁷. Increased oxidative stress then induces RelA phosphorylation on serine 276 and concurrently preconditions the chromatin of inflammatory genes for NF- κ B binding. Specifically, ROS promotes oxidative modifications on DNA, such as 7,8-dihydro-8-oxoguanine (8-oxoG), which induces the 8-oxoguanine DNA glycosylase1 (OGG1)-initiated base excision repair pathway. OGG1 strengthens NF- κ B binding on DNA⁵⁸. NF- κ B activity on inflammatory genes is hence limited, and depends on ROS and the produced 8-oxoG base lesions. The activities of other transcription factors are then stimulated, and these factors can interact with NF- κ B and modulate the expression of common target genes.

In particular, the c-Jun factor of the AP-1 family is transcribed and translated rapidly upon phosphorylation of factors that activate its own promoter⁵⁹. As a result, the c-Jun protein becomes available to regulate transcription. AP-1 recruits the chromatin remodeling complex SWI/SNF⁶⁰. STAT proteins can then be activated by JAK family kinases to fine tune the time course of inflammation in a tissue⁶¹. STAT proteins help recruit histone acetyltransferases through NF- κ B⁶². Changes in the acetyltransferase abundance on cell-function-related chromatin elements are critical for cell fate. For example, STAT3 increases the abundance of p300 on super-enhancers of genes characteristic to T-helper type 17 (Th17) cell function; this increase marks the genes critical for this cell type⁶³.

The interactions among NF- κ B, AP-1, and STAT proteins depend on the expression of different proportions of their subunits in different cell types. Stimulus-induced post-translational modifications enable rapid inflammatory control. In primary epithelial cells, oxidized palmitoyl-2-arachidonoyl-sn-glycero-3-phosphorylcholine activates tyrosine kinase JAK2, which in turn phosphorylates STAT3 on residue 705. This series of activations enables STAT3 binding to the sequence flanking the consensus γ -interferon activation sequence (GAS) in the promoter of the gene IL-8 encoding the cytokine IL-8/CXCL8⁶⁴. IL-8 binds to cognate transmembrane receptors that activate the chemotactic movement of neutrophils and monocytes across concentration gradients. Therefore, IL-8 significantly

influences local tissue inflammation⁶⁵. However, the prolonged stimulation of immortalized cells by cytokine IL-6 can increase the expression of STAT3 without JAK2-catalyzed phosphorylation. STAT3 then activates the expression of the cytokine CCL5 by interacting with the p65 NF- κ B bound to its target site on the gene promoter⁶⁶.

Immortalized untransformed cells differ from carcinoma in protein kinase C activity. During cancer progression, protein kinase C may be activated by the tumor promoting agent phorbol 12-myristate 13-acetate (PMA)^{67,68}. In a different fashion, stimulating epithelial carcinoma cells with cytokine IL-1 and not IL-6 may lead to the tethering of STAT3 without JAK2-catalyzed phosphorylation. This tethering is achieved through the interaction of STAT3 with the p65 NF- κ B bound to its target site on gene promoters that activate the expression of IL-8/CXCL8 and other inflammatory genes⁶⁹. Independently from synergy with IKK-induced NF- κ B, starved cancer cells, activating ROS, autophagy, and kinase Rac1, enable unphosphorylated STAT3 to activate IL6 (IL-6) gene expression in synergy with NF- κ B and independently from IKK⁷⁰. Meanwhile, autophagy can activate the p65 phosphorylation on serine 536 by protein kinase C zeta independently from IKK⁵⁶.

For feedback inhibitors, genes that encode inflammation-related proteins can be divided into those that depend on RelA (p65) phosphorylation on residue 276 or residue 536²³. The former genes encode potent inflammatory initiators, which are induced by oxidative stress and repressed by I κ B α . Thus, these initiators are switched off by antioxidants and glucocorticoids⁷¹. By contrast, the latter genes encode proteins that modulate inflammation in a cell-specific manner. The presence of acetylases is critical for the genes driven by RelA phosphorylation on residue 536. The synergy of proteins, such as STAT3, facilitates the expression of genes that ultimately terminate immune response⁷². STAT3 interacts with multiple proteins that respond to organelle dynamic changes and consequently helps optimally regulate tissue postnatal development^{73,74}. However, this optimum function requires strict limits on acetylase activity⁶¹. Tissues are protected from uncontrolled inflammation by synthesizing inhibitors, including I κ B α ⁷⁵.

Protein complexes involved in the coordination between DNA repair and cell survival influence the regulation of NF- κ B activity. Upon oncogene activation, tumor suppressor ARF induces the ATR- and Chk1-dependent phosphorylation of the RelA transactivation domain at threonine 505 that represses cell survival gene expression⁷⁶. Furthermore, this phosphorylation on residue threonine 505 of RelA transforms NF- κ B into an apoptotic gene activator and

autophagy inhibitor. These functions are essential to limiting cell proliferation and migration and helps balance the supply of cellular components for tissue regeneration⁷⁷. Consistently, knock-in mice with RelA T505A mutation develop normally but exhibit aberrant hepatocyte proliferation following liver partial hepatectomy or carbon tetrachloride (CCl₄) induced damage. The role of T505 as an oncogenic inhibitor was then confirmed when the RelA T505A mice exhibited early cancer onset in the N-nitrosodiethylamine model of hepatocellular carcinoma⁷⁸.

NF- κ B activity can be steered also by nuclear receptors that are activated by metabolic products. For example, proteins of the peroxisome proliferator-activated receptor (PPAR) family are activated by free fatty acids, affect NF- κ B subunit phosphorylation, and can promote NF- κ B-driven apoptosis^{79,80}. However, PPAR proteins possess multiple interaction partners in a cell, and their effects on cancer cells depend on many factors, including the cell's metabolic activity⁸¹. Hence, PPAR activity may become either oncogenic or oncosuppressive^{82,83}.

Loss of feedback to NF- κ B affects tissue homeostatic coordination

Hypoxia normally limits NF- κ B activity when NF- κ B induces the expression of hypoxia-induced factor 1 (HIF1), which restricts the expression of NF- κ B target genes, under physiological conditions. This process contributes to the regulation of extracellular milieu^{84,85}. However, in contrast to normal pancreatic tissues or nontumorigenic cell lines, NF- κ B is constitutively activated in most (>70%) human pancreatic cancer cells and primary tumor specimens. Molecular analysis shows a p65-HIF1 cooperation that drives epithelial-mesenchymal transition (EMT) and resistance to chemotherapy⁸⁶. The analysis shows that N-cadherin, vimentin, Snail, and Twist overexpression, as well as E-cadherin suppression, induces striking morphological changes to loss of cell polarity, acquisition of mesenchymal phenotype, and resistance to gemcitabine.

Aberrant NF- κ B activity bestows cancer cells with the capacity to overrun the natural control of cell bioenergetic and survival functions that normally depend on cell-specific interactions with the host tissue. Specifically, NF- κ B simultaneously controls many molecules involved in cell communication with the rest of the organism. Interfering with NF- κ B regulation is thus critical for virtually any type of aggressive cancer; this capacity enables unrestricted movement and survival in the presence of apoptotic inducers³². Unrestricted movement becomes possible by

synthesizing chemotactic mediators, such as IL-8, producing enzymes that break down molecules that restrict movement, and inactivating pathways that cause cell death in an aberrant niche⁵. Every category of these NF- κ B target genes has multiple functions that simultaneously control many aspects of the activity they regulate in a cell-specific and coordinated fashion^{87,88}.

Cell specificity is attained through the differences in the proportions of cytokine receptors, as well as the specific assortments of intracellular signal transducers⁸⁹⁻⁹¹. The persistence of both chronic inflammation and cancer requires loss of feedback to NF- κ B. However, in cancer, the loss of feedback allows independence from tissue phenotype control and enables cancer cells to grow in an aberrant niche microenvironment⁵. The tissue control normally limits the phenotype change possible for a cell; this control functions through the regulation of cell death, immune recognition of cell surface antigens, and effects of secreted cytokines on the signals that control stemness/differentiation of a cellular lineage⁹²⁻⁹⁵.

Surface antigen changes indicate that cancer cells may increase the expression of inflammatory mediators and enzymes that remodel the extracellular matrix without becoming a target for the immune system. Enhanced permeability would help activate immune response; however, cancer cells are not recognized by the immune system in a manner that allows effective tumor clearance.

Interacting agents of NF- κ B direct immune system activity

The ultimate barrier to carcinogenesis is the immune system. The effects of the immune system depend heavily on the precise cell communication with all the components of the innate and adaptive immunity⁹⁶. Defects in the cellular response to cytokines and adhesion molecules deprive the immune system of essential guidance in resolving infections and eliminating life-threatening developmental aberrations in host tissue cells⁹⁷.

Changes are observed after oncogene activation in animal models. These changes suggest that cancer develops aberrant signals that suppress antitumor immunity on the basis of the normal signals that regulate inflammation and the ensuing partial tissue regeneration. Genes induced in cohorts during inflammation mediate the propagation and, ultimately, the termination of inflammatory processes to restore and protect host tissue. In mammals, two main cancer types occur, as follows: the solid tumor, which requires disruption of tissue adherence to metastasize, and the immune cell tumor, which

readily forms under few molecular aberrations⁵. Immune cells of the myeloid lineage readily proliferate under innate immune response triggers. These cells possess redundant mechanisms for organelle turnover and NF- κ B activation. By contrast, lymphoid cells can sustain survival and proliferation only under precise development and functional fidelity of the modules for acquired immunity⁹⁸. Consequently, lymphoblastic leukemia develops NF- κ B-driven chemoresistance far less often than myeloid leukemia^{99,100}.

Inflammation through NF- κ B interferes with postnatal tissue development and function by altering the activities of multiple enzymes in the nucleus. Macroscopically, inflammation interferes with tissue function¹⁰¹. Microscopically, groups of cells either die or reprogram their functions. Toward the end of inflammation, dead cells are replaced by reprogrammed resident cells, as well as by circulating cells that possess compatible differentiation capacity. At the molecular level, this interference between inflammation and tissue development becomes possible through shared cofactors between NF- κ B and nuclear receptors that mediate the hormonal control of cell function within the tissue¹⁰². Cofactors of this type include zinc-finger LIM-domain proteins^{103,104}.

The critical role of NF- κ B regulation is evident in the control of the interaction between the cells of the monocyte-macrophage lineage and the circulating T-cells in the bone marrow. T-cells secrete the receptor activator of NF- κ B ligand (RANKL), which induces osteoblasts to differentiate into the monocytic lineage and give rise to osteoclasts that contribute to bone remodeling. Deregulation of RANKL can cause bone loss¹⁰⁵.

In certain cancer cell categories, overexpressing proteins of the AP-1 and STAT families increases the recruitment of acetylases and impedes the function of the negative feedback loop on NF- κ B. This occurrence then redirects the NF- κ B activity on immunosuppressive genes¹⁰⁶. In agreement with this effect, high STAT3 abundance results in a statistically increased risk of poor cancer prognosis¹⁰⁷. The same is true for the combined NF- κ B/STAT3 target gene that encodes cytokine IL-6¹⁰⁸. STAT3 is critical for the function of super-enhancers that regulate switching between Th1-, Th2-, and Th17-driven immunity⁶³.

STAT3 and NF- κ B enable macrophages to secrete the ligand PD-L1 that inhibits T-cell activity by binding to their PD-1 surface receptor¹⁰⁹. NF- κ B-driven PD-L1 expression is increased after stimulating cells with TNF α , TGF β , or EGF, or constitutive activation of the EGFR that in cancer can accompany EMT, and increased vascular permeability; PD-L1 apparently protects cancer cells that enter circulation and

remain in circulation¹¹⁰⁻¹¹². Interestingly, tumor-associated macrophages can capture therapeutic monoclonal antibodies raised against PD-1 from T-cell surfaces. This observation demonstrates the effect of macrophages on acquired immunity¹¹³. Macrophages can promote tumor evasion of immune response through multiple mechanisms that affect T-cell activity.

T-cells and macrophages are two key cell categories involved in immunity and respond promptly to cytokine changes¹¹⁴. T-helper cells secrete cytokine cocktails that direct acquired immunity. Macrophages, which are abundant in the organism, bind to microbial and other disease-related antigens and secrete more cytokines to recruit neutrophils, while presenting antigen to facilitate cooperation between cells of innate and adaptive immunity¹¹⁵. The critical role of the interaction between the cells of the monocyte-macrophage lineage and the circulating T-cells is demonstrated in the bone marrow. T-cells secrete RANKL, which induces osteoblasts to differentiate into the monocytic lineage, giving rise to osteoclasts. Besides loss of bone, the formation of an effective premetastatic niche may occur in the bone marrow because of RANKL deregulation. This effect is achieved because the osteoclast is inefficient in antigen presentation¹⁰⁵.

For the cytokine modulation of T-cell activity, several viruses secrete homologs of human cytokines such as IL-10, to impede antiviral immunity¹¹⁶. The limits of cytokine expression in macrophages and T-cells, are largely dependent on the regulation of NF- κ B^{75,117}. NF- κ B is also involved in the expression of the anti-inflammatory glycoprotein MUC1 by epithelial cells¹¹⁸. MUC1 induction shows how inflammatory stimuli in normal tissue help restrain excessive inflammation during infection.

To summarize, the organism uses the immune system to control the activity of tissue-residing cells and phenotypes of circulating cells. This control is mainly achieved by secreting specific cytokine combinations. These combinations change depending on the availability of feedback regulators of NF- κ B in each cell. These feedback regulators not only control internal cell functions but also determine the cell interaction with the rest of the organism (a comprehensive list of proteins that interact with NF- κ B is presented in <http://www.bu.edu/nf-kb/physiological-mediators/interacting-proteins/>).

Intracellular and extracellular cancer processes

In cancer, different modules of protein turnover show

excessive activity because of cell stress from mutational burden and the need for bioenergetic adaptation in cells that deviate from tissue function^{5,119}. Depending on the cell growth state, neoplastic development stage, and malignant cell location in the metastatic or primary niche, several regulators of protein synthesis and degradation can operate beyond the limits of normal cells. Protein synthesis control pathways include the signal cascade PI3K/AKT/mTOR, which controls the activation of ribosomal subunits and polyribosome formation, to allow protein translation¹²⁰. Growth factors FL, EGF, PDGF, and IGF-1, activate AKT signaling^{121,122}. Cancer cells may activate AKT kinase, and ribosomal activity concurrently with NF- κ B¹²³⁻¹²⁵. Interestingly, the androgen receptor in renal cell carcinoma can enhance AKT/NF- κ B activity to induce CXCL5 expression and endothelial cell recruitment, which in turn facilitate metastasis¹²⁶. The AKT/S6/NF- κ B pathways also allow cytokine-independent growth and hence afford malignant cells with substantial plasticity^{127,128}.

Malignant cells can grow independently from mTOR signaling and the classical NF- κ B cofactor BRD4 by activating autophagy. For example, in acute myeloid leukemia (AML), treating with the BRD4 inhibitor JQ1 activates AMPK and hence autophagy in cell populations with leukemia-initiating capacity¹¹⁹. Conversely, AML cells with mutations on the cytokine FL receptor FLT3 tyrosine kinase domain gain resistance to tyrosine kinase inhibitors through BRD4¹²⁹.

Cytokine-independent growth is important because it allows a cancer cell to deviate from the extracellular signaling code of a tissue by secreting cytokines at time points and concentrations unrelated to normal tissue needs. Specifically, the range of effects enabled by this deviant secretion allows cancer cells to modulate their microenvironment, which includes fibroblasts and endothelial cells. As a result, stromal cell function is modified in both cancer primary and metastatic niche^{126,130-132}. NF- κ B activates the expression of metalloproteases, as well as chemokines, which enable the malignant cell to overcome tissue-specific restrictions in cellular motility¹³³⁻¹³⁵. Changes in the feedback-induced regulation of NF- κ B activity allow cancer cells to activate several cytokines and modulators of cell development to recruit and alter cells of the monocyte/macrophage lineage¹³⁶. Macrophages constitute a critical part of cytokine-secreting cells in a tissue, especially under low-oxygen tension and inflammation⁸⁴. In pancreatic cancer, cultured M2-polarized macrophages significantly increase the migration rate of pancreatic ductal adenocarcinoma cells¹³⁷.

Poor patient prognosis is possibly associated with the T-helper type 1 immune response (Th1) in non-small cell lung

cancer (NSCLC). This relation is an example of extreme deviation from the regular cytokine code. Typically, the Th1 response is needed against tumors and viral infections. In the above-mentioned case, the T-cell-inactivating ligand PD-L1 on CD45+CD14+ monocytes/macrophages was more abundant in tumor tissue than in the adjacent nontumor tissues¹³⁸. This observation can be reconciled with at least two possible scenarios. On one hand, inflammatory stimuli in the presence of glucocorticoids, TGF β , and IL-10 can generate macrophages with an immunosuppressive M2-profile¹³⁶.

However, the tumor cells may secrete PD-L1 themselves, especially when stimulated by PI3K/AKT activators (e.g., insulin, IGF, niche-homing SDF1/CXCR4 signals) or by IL-6-induced STAT3 activation to undergo EMT¹³⁹⁻¹⁴². The Th1 response allows EMT through the following observation. In NSCLC specimens, discrete zones of Th2, Th17, and Th1 were found. These zones distinguished the tumor nest from the tumor boundary, adjacent normal lung tissue, or corresponding lymph node tissue¹³⁸. IL-17 activates STAT3 and induces EMT in lung cancer cells *in vitro*. IL-17 also correlates with EMT in human lung cancer specimens¹⁴³. TNF α and TGF β enhance p65-driven expression of Twist1 and the self-renewal of “cancer stem cells (CSC),” which are malignant clones with established capacity to initiate tumors¹⁴⁴. EMT-activated p65 can induce the expression of the TGF β -family member Activin, which in turn induces EMT master-switch regulators and self-renewal factors that can sustain CSC and enable metastasis¹⁴⁵. The cytokines secreted in the vicinity of cancer cells can thus permit the propagation of clones that function as CSCs through the positive feedback activation of EMT.

On one hand, these defects in feedback restriction of NF- κ B activity allow proliferating cancer cells to survive. On the other hand, these defects cause tumor stroma and tumor nest to interact aberrantly with the immune system and cripple the immune response within the tumor microenvironment. In other words, several control molecules for the immune response can establish immunosuppressive niches for the cancer cells, which would then be difficult to detect macroscopically.

Modulation of the microenvironment to “license” cancer: many processes initiated by a few genes

Proteins directly regulated by NF- κ B at the transcriptional level include many NF- κ B transcriptional cofactors. Several of these proteins are also regulated by STAT3, as well as by STAT3 synergy with NF- κ B depending on the cell state. Such

important proteins can be encountered on the chromatin of the chemokine IL-8, which facilitates leukocyte and endothelial cell movement and reprogramming. IL-8 also contributes to inflammation-induced tissue remodeling and vascularization¹⁴⁶. Notably, IL-8 does not exert ubiquitous effects in all cell types. For instance, it cannot initiate extracellular matrix remodeling in the nucleus pulposus cells of the human intervertebral disc¹⁴⁷.

The interaction of NF- κ B with the *il8* gene promoter can integrate regulation through different types of transcription factors, including AP-1, EGR1, helicase WRN, STAT3, and MUC1^{16,64,148-151}. β -catenin also mediates IL8 gene expression after receiving signals that activate WNT or TLR4^{152,153}. TLR4 activates phosphorylases p38 and ERK¹⁵⁴. p38 and ERK activate MSK1, which phosphorylates RelA on Ser276¹⁵⁵. TLR4 by activating p38, induces NF- κ B to bind chromatin DNA in the nucleus¹⁵⁶. NF- κ B recruits bromodomain proteins such as BRD4, which enable chromatin remodeling in synergy with acetyltransferases p300/CBP, which are recruited by the above-mentioned transcription factors¹⁵⁷. AP-1 helps recruit the SWI/SNF chromatin remodeler. However, this remodeler requires target specificity in BRD4^{60,158}. Therefore at least in myeloid cells, AP-1 acts as an amplifier of NF- κ B-driven IL8 gene expression¹⁶.

NF- κ B also recruits BRD4 to the genomic regulatory region of *Myc*²⁷. In leukemia cells, BRD4 and SWI/SNF maintain transcription factor occupancy on the *Myc* gene and facilitate promoter interactions with a lineage-specific super-enhancer located 1.7 megabases at the 3' direction from the *Myc* gene¹⁵⁹. However, the product c-Myc does not participate in *il8* gene regulation like the other NF- κ B targets¹⁶⁰. The genomic locus of *Myc* contains abundant STAT3 DNA binding sites. This observation is consistent with the expression of *Myc* in cells “licensed” to proliferate⁵. In cancer, c-Myc activates the expression of several metabolic enzymes that enable cell proliferation. c-Myc also requires NF- κ B activity for cell survival, because *Myc* induces the expression of apoptotic genes¹⁶¹.

Besides being a transcriptional cofactor, MUC1 is encoded by an NF- κ B target gene (**Figure 3**). The MUC1 protein regulates tissue metabolism, integrity, and gene expression¹⁶². MUC1-C/ β -catenin/TCF4 complexes promote p300 recruitment on the *Myc* promoter. This observation indicates that β -catenin-complexes can induce *Myc* expression in response to BRD4-dependent inflammatory signals¹⁶³. MUC1-C complexed with NF- κ B activates the expression of enzyme DNMT1, which methylates and inactivates tumor suppressor genes and then permits malignant cell growth over time¹⁶⁴.

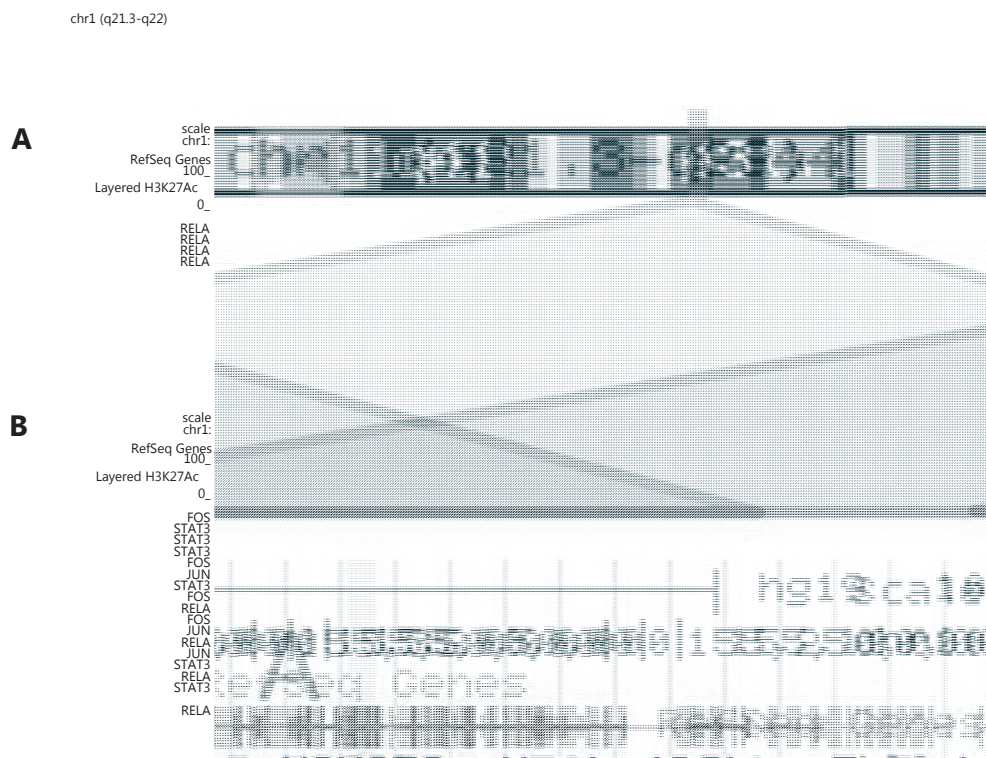


Figure 3 Genomic locus of the MUC1 gene on human chromosome 1. (A) The locus contains DNA binding sites for the RelA subunit of NF- κ B. (B) NF- κ B binding sites increase in abundance when transcription factors that interact with NF- κ B bind to their cognate DNA target sites, and thereby recruit NF- κ B to the locus. These transcription factors change in activity during inflammation. The product of the MUC1 gene is the protein MUC1, which participates in cytokine gene regulation and tissue homeostasis.

The full-length product of the MUC1 gene, MUC1, is a transmembrane protein normally expressed on the luminal surfaces of ductal epithelia. MUC1 regulates apical-basal polarity and fine tunes macrophage phenotypes, whereas the MUC1 protein-derived cytoplasmic domain provides feedback regulation to NF- κ B transcriptional activity^{165,166}. MUC1 can interact with β -catenin and p120 catenin to modulate WNT signaling. That is, in pancreatic cancer cells, MUC1 augments the activity of cyclin D1 gene (CCND1) promoter through β -catenin and TCF-Lef, and by stabilizing p120 catenin isoforms that displace the repressor protein KAISO¹⁶⁷. The cytoplasmic domain of MUC1 (MUC1-C) spurs cell growth by recruiting β -catenin and acetylase p300 on the genes CCND1 and *Myc*¹⁶⁸. In breast cancer cells, the complexes of MUC1-C/STAT3 can be also detected on the promoters of CCND1 and MUC1, which are STAT3 target genes¹⁶⁹. T helper (Th) 17 cells produce the effector cytokine IL-17 along with IL-22, which stimulates colonic epithelial cells to produce MUC1. MUC1 normally switches off Th17-driven inflammation¹⁷⁰. However, in neoplasia, MUC1-C and STAT3 link cytokine-induced inflammatory response to

cancer cell survival.

MUC1-C interacts directly with RelA at the Rel homology domain (RHD). MUC1 blocks binding of RelA to I κ B α , and thereby releases NF- κ B¹⁶⁹. In carcinoma cells, MUC1-C generally provides positive feedback to the STAT1/3 and NF- κ B RelA complex that activates the MUC1 gene¹⁷¹. Experiments on pancreatic cancer cells showed that MUC1 stabilizes lysosomes, which are an important turnover system and an auxiliary system for NF- κ B induction after cell stress, sparked by inhibition of proteasome activity^{24,172,173}. Through NF- κ B, β -catenin and MUC1, lung cancer cells interact with M2-polarized macrophages and gain stemness properties¹⁷⁴. Therefore, *muc1* is a characteristic target gene of NF- κ B that could provide cancer cell populations with vital transcriptional regulation and concurrently affect the microenvironment of a tumor nest.

NF- κ B target gene regulation is tissue dependent

Chromatin remodeling complexes act in a highly locus-

specific and cell-specific manner. Notably, the SWI/SNF subunit Brg-1 activates tumor-suppressing mechanisms in solid tumors, as well as potent oncogenes in leukemias^{159,175,176}. This contrast can be explained by the parallel role of some molecules involved in extracellular activity in regulating gene expression. NF- κ B activity modulators drive changes in cellular programming, while modulating tissue interactions and the immune response⁵. These changes are evident in the altered abundance of chromatin-modifying molecules on key regulatory regions of the chromosomal DNA that controls cell activity⁷. These alterations manifest in the cells that steer the immune response and result in measurable changes in cytokine abundance. In cancer, a part of this regulatory link between the intracellular control of cell proliferation and extracellular activity fails to function accurately¹⁷⁷. At the cellular level, interaction with the rest of the organism involves diverse molecular types. However, the changes detectable by basic methodology typically involve cytokines¹⁰¹. Cytokine abundance changes in pathological conditions that involve inflammation.

Yet in cancer, aberrant activity of the genes involved in cytokine feedback regulation in tissues provides malignant cells with amplifying signals for cell proliferation and metastasis. This occurrence is expected to critically influence the disease course¹⁷⁷. In solid tumors NF- κ B overexpression is generally linked to worsened overall survival at 3, 5, or 10 years after diagnosis¹⁷⁸. However, the molecular aberrations are not uniform, even within a given cancer type. These variations thereby complicate the epidemiological analysis of systemic cytokine levels. Higher serum IL-6 levels correlate with poor prognosis, but the degree of epidemiological association with prognosis varies across studies¹⁰⁸. In NSCLC, high IL-6 concentration is associated with poor prognosis in patients treated with chemotherapy but not in those who underwent surgery¹⁷⁹. When considering transcription factors, high STAT3 expression marks poor prognosis in NSCLC¹⁸⁰. STAT3-activating cytokines IL-6, IL-10, and IL-17 do not show a uniform prognostic profile in lung cancer¹⁸¹. This complexity can be attributed to the distinct homeostatic roles of each cytokine in a given tissue context. Cancer cells deviate in their response to cytokine stimulation depending on the composition of their internal regulatory network, and this deviation is linked to the developmental cell fate.

A different example of a network's context dependence between cell genomic integrity and the immune system is triple-negative breast cancer. BRCA1 is a DNA repair protein functioning as a cofactor for the expression of the RelA-target

DNMT1 (involved in the long-term regulation of gene expression). BRCA1 apparently determines the immune response switching from oncosuppressive Th1 to oncogenic Th2^{182,183}. BRCA1 loss allows NF- κ B-driven immune signals to maintain the M1 macrophage, which supports the sustained presence of cytotoxic CD8+ T-cells. In this case, deficiency of the DNA repair protein BRCA1 switches the tumor microenvironment to an oncosuppressive mode associated with a favorable disease prognosis. Evidently the cooperation between resident macrophages and infiltrating T-cells is critical in the cells' individual functions within the tumor niche.

Conclusions

Inflammation is a process that challenges the developmental integrity of a tissue. This process activates mechanisms that disrupt optimum hormonal function and interfere with the coordination of gene expression between different cellular components. Apoptotic mechanisms tie normal cell survival with functional fidelity within the organism. The transcription factor NF- κ B is regulated by key modules of protein turnover. The transcription factor acts as a mediator for apoptotic and survival signals. NF- κ B integrates the input from signaling cascades that alter post-translational modifications of NF- κ B subunits, as well as the input from the feedback regulation exerted by the protein products of its own gene targets. Malignant cells acquire defects in the coordination of intracellular turnover with the extracellular cell communication, with the harboring tissue, and the response of the cell to circulating hormonal mediators. Some of these defects interfere with the regulation of the cellular response to NF- κ B activity induction, reflected in the coordination of genomic function. As a result, the disrupting of NF- κ B feedback control by its target genes changes the intensity and duration of inflammatory gene expression in the cells of the tumor nest, and their microenvironment. This change enables cancer cells to escape immune surveillance and grow in metastatic niches. Dissecting the gene regulation dynamics in the tumor nest and tumor stroma would yield insights in the capacity of cells to migrate and interact within the metastatic niche.

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Starting with the hg19 assembly, the human genome sequence was obtained from the Genome Reference Consortium (GRC). The credits for the GRC are listed in <http://www.ncbi.nlm.nih.gov/projects/genome/assembly/grc/credits.shtml>.

Conflict of interest statement

S. Vlahopoulos is listed as co-inventor in patent applications that describe the subcellular targeting of substances potentially interfering with autophagy and transcription factor activity in a tissue-selective mode.

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