Revista de
Medicina e Investigación

ARTÍCULO DE REVISIÓN

Cancer as a defective network for NF-κB

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Support: None.

No part of the manuscript's information has been previously presented.

Word count. Main text 3570. Abstract 140.

Contribution: all authors contributed in writing of the article, critical review, and approval of the final version.

Recibido: 03 de mayo de 2016
Aceptado: 28 de septiembre de 2016

KEYWORDS

Chromatin, Hormones, Inflammation, Transcription Factors, NF-κB.

Abstract
In a recent review we addressed the role of the transcription factor NF-κB, in shaping the cancer microenvironment. NF-κB, which interacts with chromatin modulators by cell-specific dynamics, controls cell interactions during inflammation, and its abnormal feedback regulation is implicated in cancer. Inflammation normally reprograms cells through changes in key topological elements of chromosomal DNA. As a result, inflammation overrides cell phenotype: initially, reprogramming cell function halts processes that impede the response of a damaged tissue to the cause of the harm, and eventually, late reprogramming of cells will replenish tissue structure and restore function. Each cell type provides a distinct resource for restoration of tissue integrity, tissue function, and for replenishment of the responsiveness of the immune system. Modulators of NF-κB transcriptional activity alter key aspects of gene expression and tissue integrity. NF-κB network alterations confer transcriptional plasticity to cancer.

PALABRAS CLAVE

Cromatina, hormonas, inflamación, factor de transcripción, NF-κB.

Cáncer como una red defectuoso para NF-κB

Resumen
En una revisión reciente se abordó el papel del factor de transcripción NF-κB en la formación del microambiente del cáncer. NF-κB, que interactúa con los moduladores de la cromatina por la dinámica específica de células, controla las interacciones de células durante la inflamación, y su regulación por retroalimentación anormal está implicada en el cáncer. La inflamación normalmente reprograma células a través de cambios en los elementos topológicos clave de ADN cromosómico. Como resultado, la inflamación anula fenotipo celular: inicialmente, la reprogramación de la función celular detiene los procesos que impiden la respuesta de un tejido dañado de la causa del daño, y, finalmente, a finales de reprogramación de células va a reponer la estructura del tejido y restaurar la función. Cada tipo de célula proporciona un recurso distinto para la restauración de la integridad del tejido, la función del tejido, y para la reposición de la capacidad de respuesta del sistema inmunológico. Moduladores de la actividad transcripcional de NF-κB alteran los aspectos clave de la expresión génica y la integridad del tejido. Alteraciones de la red NF-κB confieren plasticidad transcripcional al cáncer.

http://hdl.handle.net/20.500.11799/62933

Tissue states and NF-κB: impact on regulatory chromatin regions

A healthy mammalian tissue is essentially found in three main states, or in their transitions: morphogenesis, fully functional condition, or inflammation[1-5]. At the end of inflammation the organism reactivates a part of the mechanisms involved in morphogenesis, to restore the tissue into a fully functional state. Cells in the tissue coordinate these transitions by secreting cytokines, chemokines, and adhesion molecules in discrete cohorts[6-11]. These molecules bind to their cognate receptors and elicit signal cascades that alter gene expression, which results in a change in the cellular protein contents and the molecules the cell secretes[12]. Inflammation overrides cellular phenotypes by activating transcription factor NF-κB[13-15]+ which rapidly recruits the transcriptional machinery also to inaccessible heterochromatic regions[16] and redistributes transcriptional cofactors such as the mediator subunit MED1[17]. Inflammation, therefore, is a process that tests the hormonal integrity of a tissue because the process requires coordination of gene expression between diverse cell types[1,18].

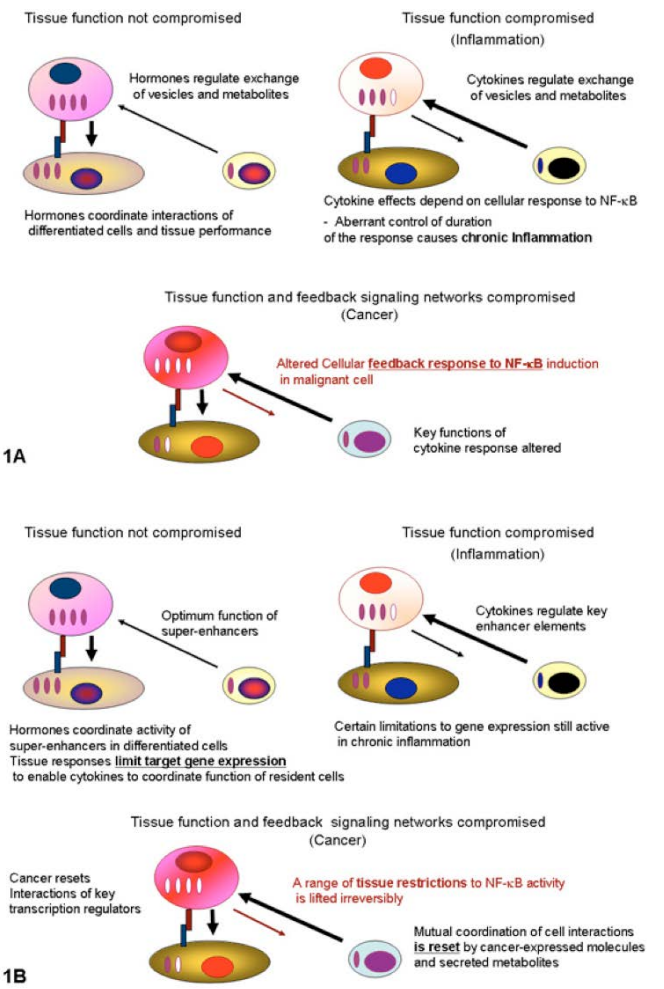
Chromosomal DNA folds into topological elements that control gene expression[19]. One such type of elements is termed super-enhancers; they contain a high abundance of binding sites for sequence-specific transcription factors[13]. Even though a cell typically contains a few hundred super-enhancers, they control expression of genes that determine the differentiated state[20]. Cell feedback signaling through exchange of mediators is mutual, but asymmetric[7,8]. This asymmetry ensures that each cell type incorporates information from the tissue, and in turn provides a distinct resource for restoration of tissue integrity, tissue function, and for replenishment of the responsiveness of the immune system[7,8,21,22].

A stimulus that changes the cell phenotype induces binding of sequence-specific transcription factors on the portion of cellular super-enhancers that control genes that are essential for the phenotypic change[23]. It is very important to note that a main aspect of induced transcription factors is a mutual titration that results in synergy or antagonism in the cytoplasm[4], as well as on the regulatory sequences these factors bind on the chromatin[24,25].

Inflammation normally reprograms cells through changes in key topological elements of chromosomal DNA[17,26]. Specifically, through secretion of discrete cytokine cohorts, inflammation overrides cell phenotype: initially, reprogramming cell function halts processes that impede the response of a damaged tissue to the cause of the harm, and eventually, late reprogramming of cells will replenish tissue structure and restore function once the cause of damage has been removed[1,3]. Cytokines typically induce NF-κB activity, as well as other transcription factors that modulate gene expression[17,27,28]. NF-κB, which recruits the transcriptional machinery to chromatin with cell-specific kinetics and dynamics, regulates cell communication during inflammation[13,17, 29].

A number of feedback mechanisms serve to fine tune and ultimately shut down NF-κB activity according to the phenotypic state of the cell *(Figure 1)*[21]. The duration of gene expression depends on sequential binding of transcription factors that recruit histone acetyltransferases to maintain open chromatin configuration at the DNA sequences encompassing the locus of a given gene and cell-specific regulatory regions[23]. The combination of activated transcription factors determines the permissiveness of the cell to hormonal or metabolic signals, the interaction of the cell with the immune system, and the contribution to cell fate[30-32].

Figure 1. NF-κB network integrates hormonal signaling to determine cellular function.



(A) Regular tissue function is controlled by hormones. Inflammation elicits cytokines, which take control of cells by activating NF-κB and other transcription factors. NF-κB activates genes that control its own network. In cancer, the products of certain NF-κB target genes fail to limit its activity. Specifically genes that respond to changes in tissue composition lose key operating modules for control of NF-κB, due to mutations and metabolic changes that are characteristic for the cancer cell.
(B) The changes in cell phenotypes correspond to changes in super-enhancer activity.
Normal cell interactions converge in control of gene expression that coordinates tissue function and organelle activity with cell survival.
Source: author's original figures.

Canonical NF-κB is composed by a Rel protein dimer which is held in a latent form in the cytoplasm by IκBα[21]. IκBα is phosphorylated in response to activation of the IKK complex or other kinases, leading to its degradation by the proteasome; the freed Rel dimer then enters the nucleus and binds to cognate DNA response elements. The Rel dimer then reprograms the expression of target genes by recruiting the basal transcription factors and enzymes to the site[13,33]. In malignant cells a number of proteolytic systems can initiate degradation of IκBα, especially in response to cell stress caused by cytotoxic drugs[15,34]. While these systems may also interfere with effects of drugs through alterations in metabolism, their effect on NF-κB provides a

pathway to activate cell survival signals, and recruit diverse cell types in the tissue microenvironment to protect the cancer cell from the immune system and from metabolic challenge[35,36].

A healthy tissue eliminates cells that cannot support organ needs. This elimination occurs through a tight coupling of cell survival mechanisms to hormonal signals and to a wide interdependence of survival mechanisms to the expression and activity of specific adhesion molecules. Essentially, restrictions on NF-κB activity tie cell survival with tissue integrity[15,37]. Controlled NF-κB helps a cell survive only if it contributes to protection of the tissue, or to restoration of tissue function[15]. Abolishing basic elements of NF-κB control counteracts cellular tumor suppressors, allowing activated oncogenes to transform a cell[15,38,39]. We recently described the essential aspects of the NF-κB role in the tissue microenvironment to illustrate how failure of a key feedback node can enable a cell to initiate metastatic cancer[15].

Different assortments of inducible enzymes can activate noncanonical NF-κB signalling to regulate developmental genes, which can also have overlapping effects with canonical signalling[40]. However under certain conditions, especially in cancer cells, noncanonical can substitute for canonical NF-κB activity[15]. Importantly, however, cell stress by metabolic imbalance, activates the potent NF-κB subunit p65 RelA, by a variety of mechanisms[35]. Through NF-κB diverse mechanisms of cell stress activate innate immunity[21]. It is remarkable that hybrid periportal hepatocytes with high proliferative potential can repopulate niches without giving rise to tumors: their lineage does not operate detoxifying enzymes, or innate immunity responses [41]. In line with this note, in mouse lung, oncogenic gene expression clusters increase after induction of the base excision OGG1/ NF-κB pathway, and not by reactive oxygen species (ROS) alone[42]. Cell stress and innate immunity therefore determine oncogene impact.

Modulators of NF-κB: effect of combinations

Every developmental signal that can interface with inflammation is a direct or indirect modulator of NF-κB activity. Many target genes of NF-κB can themselves shut down NF-κB transcriptional activity. Two characteristic products of target genes include the protein IκBα and the microRNA miR146, which protect the organism from excessive activation of the immune system[15]. Tissue function can change in response to inflammation; the extent of this change depends on the expression of cytokines that coordinate diverse cell types. Every cell expresses a specific pattern of cytokine receptors, and their interacting molecules, which determine to which cytokines it responds to, and by what type of result[43-47].

A potent inducer of canonical NF-κB activity is cytokine Tumor Necrosis Factor-α (TNFα), encoded by the tnf gene[27,36]. The transcription start site for the tnf gene remains in a closed chromatin configuration in primary T helper (Th) cells, but acquires an open state after activation or polarization under Th1 and Th17 conditions, where it is maintained by c-Jun[45]. Furthermore, the distinct position and movement capacity of different cell types has as result that the secreting cell type determines overall impact of a specific cytokine on tissue physiology[48-50].

Metabolism can modify NF-κB activity by multiple mechanisms[35]. Under homeostatic conditions, histone deacetylase SIRT1 stimulates oxidative energy production, and in parallel binds to nuclear RelA and deactivates it by deacetylating lysine 310, while, inducing RelB; thereby SIRT1 generates heterochromatin on inflammatory genes, and activates euchromatin on genes that trigger successive changes in cellular function, and metabolic activity[40].

Enzymes like the protein kinase S6, and stress-activated protein kinase JNK have the capacity to mediate induction of TNF –stimulated transcriptional activity, via phosphorylation of RelA, and c-Jun correspondingly[21,51] It can be noted that c-Jun may activate TNFα gene expression[45] itself, which probably allows tumor promotion by amplification of TNF-induced signal cascades[52]. Genotoxic conditions and radiation, trigger c-Abl, p53, ATM (Ataxia telangiestasia mutated), and other proteins to initiate JNK signal pathways[51,53] and in parallel ATM offers a scaffold that accommodates induction of RelA transcription-coupled synthesis of type I and type III interferons and CC and CXC chemokines[21].

TNFα induces MMP-9 protein expression and mRNA level in U937 cells, via kinase AKT-mediated-NFκB/p65 activation and JNK-mediated c-Jun activation; thereby, cooperative recruitment of histone acetyltransferase p300 to *mmp9* promoter regions surrounding NF-κB and AP-1 binding sites modifies the level of DNA looping[54]. By overexpressing mmp2 and *mmp9* leukemic cells can degrade tight junction proteins ZO-1, claudin-5 and occludin, resulting in increased permeability of the Blood-Brain-Barrier[55]. It is therefore not surprising that bioinformatic analysis of the gene expression signatures for clinically significant presence of leukemic blast cells in the cerebrospinal fluid in childhood acute lymphoblastic leukemia, implicated alterations in the NF-κB network, including AKT, among the main factors involved[56].

One characteristic example of an NF-κB target gene that encodes a protein regulating tissue metabolism, integrity, and gene expression, is *muc1*[57]. The full-length product of the *muc1* gene, Muc1, is a transmembrane protein that is normally expressed on the luminal surfaces of ductal epithelia, regulates apical-basal polarity, and fine-tunes macrophage phenotypes[58], while the Muc1 protein-derived cytoplasmic domain provides feedback regulation to NF-κB transcriptional activity[59].

Many types of virus regulate NF-κB transcriptional activity to tie cell fate with viral propagation[60,61]. Regulation can promote viral replication, prevent virus-induced apoptosis, and even mediate the immune response to the invading pathogen[60]. Inflammatory signals are a key part in pathology of infections, including virus- induced cancer, with the important distinction that viruses use their own mechanisms for control of the NF-κB network, to change the kinetics of expression for specific gene clusters in the cell[60].

Epstein-Barr virus (EBV) is an example of virus that transforms cells via NF-κB dependent tumor modulators[62]. EBV oncoprotein, latent protein 1 (LMP1), induces MUC1 expression through binding of STAT1 and STAT3 to the *muc1* promoter[63]. LMP1-induced cell invasiveness is suppressed by silencing *muc1*, indicating that the increases in MUC1 expression contribute to the metastasis of EBV-infected tumor cells. The cytoplasmic domain of protein MUC1 (MUC1-C) affects cell growth, by recruitment of β-catenin and p300 on the genes encoding cyclin D1 (*ccnd1*) and c-Myc (*myc*)[64]. In breast cancer cells, complexes of MUC1-C/STAT3 are also detectable on the promoters of STAT3 target genes, such as ccnd1 and muc1[63]. MUC1-C and STAT3 can link cytokine-induced inflammatory response to cancer cell survival. MUC1-C interacts directly with RelA at the Rel homology domain (RHD) and, notably, blocks binding of RelA to IκBα[63]. MUC1-C provides positive feedback to the STAT1/3 and NF-κB RelA transcription factors that activate the muc1 gene[65].

Viral oncogenic proteins can have combinatorial effects, too: simultaneous expression of the EBV LMP1, with the human papillomavirus-16 (HPV16) protein E6, transforms primary mouse embryonic fibroblasts through NF-κB[66]. This co-expression of LMP-1 and E6, increases NF-κB activity, suppresses DNA damage response, leading the fibroblasts to transformation. In vitro, LMP-1 and E6 co-expression leads to anchorage-independent growth,

and in nude mice, co-expression induces tumor formation[66].

Inflammatory signals and NF-κB synergies in gene expression

Inflammatory signals are transduced by many families of inducible transcription regulatory proteins in the nucleus. Transcription factors of the NF-κB family are in a latent form in the cytoplasm and upon stimuli that induce either phosphorylation or proteolysis of their inhibitor they enter the nucleus[27], c-Jun factor of the AP-1 family is transcribed and translated rapidly[67] upon phosphorylation of factors that activate its own promoter, making the c-Jun protein available to take over regulation of transcription. STAT proteins can then be activated by JAK family kinases to fine tune the time course of inflammation in a tissue[68].

NF-κB activity normally fluctuates rapidly according to tissue needs, and regulation of its target genes such as nfkbia (IκBα) and *stat3* serves to allow a restricted window of activity by cell-specific negative feedback; in cancer this network is disrupted, enabling simultaneous decrease and increase of target gene cohorts that do not follow identical kinetics in normal tissue[15,69,70]. In childhood acute lymphoblastic leukemia, reduced levels of both transcripts for the *stat1* and *stat3* genes were associated with a good prognosis, and there was a strong correlation between these two transcripts in the patient samples, as opposed to samples negative for neoplasia[70].

Inflammatory signals and signals for cell proliferation have been known to intersect and overlap, by interactions between NF-κB and hormone receptors, or by competition for accessory proteins4. Cross-talk between hormonal and inflammatory signals determines disease, and becomes apparent in puberty[4,71].

In particular, recent research data converge to suggest that NF-κB changes the chromatin landscape and enables access of AP-1 and then STAT3, where the ratio between the protein partners composing the AP-1 dimer contributes to altering chromatin accessibility in subsequent rounds of transcription[72,73]. Furthermore, the posttranslational phosphorylation of the RelA on serine 276 enables on the one hand inducibility of inflammatory genes by ROS, and synergy with AP-1, and on the other hand repression by glucocorticoids via GR[74]. AP-1 can bring the ATP-dependent chromatin remodeler SWI/SNF to increase histone acetylation75. STAT3, on the other hand, recruits acetyltransferase p300 to increase acetylation and transcriptional activity of RelA under certain conditions[76,77]. Furthermore, STAT3 induces expression of fos[73].

The protein products of the human fos and jun genes are the proteins c-Fos and c-Jun, which form one of the most thermodynamically stable versions of the dimeric transcription factor AP-1[78,79]. Their protein families have a distinct capacity to form heterodimers, while some of them, notably c-Fos cannot form homodimers (with itself), a feature that dictates the priority of discrete signal combinations to regulate gene expression from chromatin loci that allow access to the AP-1 binding site ATGACTCAT[80,81]. c-Fos enables mTOR to regulate the TLR-induced T-cell response in vivo by controlling the balance between IL-12 and IL-10[49], while c-Jun activity mainly characterizes T-helper cell subsets Th1 and Th17[45].

Tumor progression, especially invasion and migration are in many types of cancer experimentally repeated by stimulation of neoplasia with TNFα and tumor promoter, Phorbol 12-myristate 13-acetate (PMA) that activates protein kinase C [82]. PKC may also activate p65 RelA Ser-536 phosphorylation to enhance selectively DNA binding affinity without affecting IκB degradation or p65 nuclear translocation[83].

This capacity to bypass IκBα provides an additional mechanism for tumor promotion by PMA, and possibly also explains lack of glucocorticoid –induced cytostasis for some cell types[84,85]. In prostate and ovarian adenocarcinoma IKKβ phosphorylates p65 Ser536 and thereby can decrease sensitivity of cancer cells to proteasome inhibitors[15,86,87]. At least in ovarian cancer cells both *in vitro* and *in vivo*, this type of p65 RelA activation was induced after proteasome inhibition with bortezomib, allowing recruitment of S536P-p65 to the promoter of chemokine IL-8 in tumor tissue[88]. p65 can recruit different combinations of other transcription factors on the IL-8 gene promoter, such as and transcription factor EGR1[87].

The example of NF-κB synergy with AP-1

NF-κB on the IL-8 gene promoter has the capacity to integrate regulation by different types of transcription factors including AP-1, EGR1, helicase WRN[89], and MUC1[90]. AP-1 has overlapping sets of gene targets with NF-κB, and in some gene promoters, such as IL-8, or TANK, AP-1 can amplify NF-κB-dependent early gene expression that is induced up to 1 hour after cell stimulation with TNF[27,91], and possibly expel NF-κB later, as is suggested by jun-quencing siRNA for TNF-induced invasion genes for triple negative breast cancer[81]. This way, the expression of inflammatory genes could be followed by the expression of genes that restore tissue function[92].

Abnormal coordination between the transcription factors involved in the inflammation and regeneration sequence could cause chronic inflammation, or cancer, depending on the type of gene targets affected by the disrupted feedback response[15]. In airway smooth muscle cells in asthma, the il8 promoter chromatin is enriched in the acetyltransferase p300, and histone H3 lysine 18 acetylation; in contrast, the histone acetylation reader proteins, Brd3 and Brd4, are present in both cells from patients, as well as healthy cells, on this promoter, and Brd4 appears an essential limiting factor for il8 expression93. Use of Bromodomain and extraterminal (BET) inhibitors reduces il8 expression without cytotoxic effect on those cells[93].

Monocytic cells stimulated by TNFα express IL-8[27,94]. This expression is mainly driven by transcription factor NF-κB which is induced by TNFα, in synergy with AP-1. AP-1 amplifies activity of the NF-κB dependent il8 gene promoter; AP-1 activity can be separately induced by activators of protein kinase C, such as phorbol esters[80]. Recent studies have suggested a role of NF-κB as a pioneer factor that promotes an open chromatin in response to inflammatory signaling on the chromosomal sites of at least certain cohorts of the TNF- regulated genes[81].

AP-1 in turn, can amplify inflammatory cascades enhancing expression of diverse genes, including tnf[45], Ifnb1, and metalloproteases that degrade the basal lamina to enable matrix invasion[54,95]. As TNF can increase further AP-1 activity also via NF-κB-induced genes, restriction of AP-1 activity, is an essential limit on disease pathology.

The HPV virus restricts AP-1 activity, and can thereby limit aggressiveness of HPV-related cancer by protein E2: Epidemiologically, HPV-related and HPV-unrelated sites have similar tumor growth dynamics once initiated[96]. However, survival rates for HPV-positive and HPV-negative tumors are drastically different[96]. AP-1 activity could explain that difference in prognosis, as selective participation of c-Jun in AP-1 dimers appears to promote poor differentiation and aggressive tumorigenesis only in HPV negative cases, while HPV infection leads to better differentiation and prognosis[97]. HPV protein E2 inhibits AP-1-dependent HPV chromatin transcription through bromodomain protein Brd4 that binds to acetylated histones. Knockdown of Brd4 in human cells alleviates E2-mediated repression of HPV transcription[98]. These results highlight the importance of AP-1

contribution to transcriptional activity of cancer-promoting genes.

Therapeutic implications of cancer plasticity

One effect of cancer drugs that can result to drug resistance, is the induction of cell stress[99,35]. A key example is the induction of NF-κB activity by its FDA-approved blocker, Bortezomib. Bortezomib blocks proteasome, activity, triggering auxiliary proteolytic mechanisms such as the lysosome to degrade IκBα[35,100]. Even a last generation drug that targets NF-κB-dependent gene expression, the BET inhibitor JQ1, can be rendered ineffective by abnormal activity of the wnt/β-catenin signaling cascade, driving myc gene expression through an alternative enhancer[101]. In particular, JQ1-resistant cancer may activate myc expression from the pvt promoter without a detectable contribution to JQ1 resistance by the pvt gene product.

In respect to the wnt pathway, diverse mechanisms can be expected to modulate JQ1 resistance:

a) The proteasome and lysosome systems interact in β-catenin storage and degradation[102,103].

b) The downstream signalling of β-catenin can be activated by synergy of wnt pathway protein LEF1 with ATF2 even in the absence of β-catenin stabilization[104]. ATF2 is a c-Jun partner protein and an activator for the jun gene[105]. (Figure 2) ATF2 is used by EBV to induce myc and thereby force expression of the EBV-encoded RNAs[106]. It is interesting that lef1 is an NF-κB target gene[107,108]. LEF1 induces myc expression in subsets of breast cancer, and of acute leukemia cells[109,110]. LEF1 also gives feedback to the NF-κB transcriptional activity: IL-1β stimulation induces chromatin DNA looping in cyclooxygenase 2 (cox2) and matrix metalloproteinase 13 (mmp13) genomic loci, through interaction of LEF1 with β-catenin, AP-1, and NF-κB that augments expression of COX2 and MMP13[111]. Specifically, chromosome conformation capture (3C) assay shows the 5' and 3' genomic regions of these genes juxtaposed after stimulation of cells with IL-1β[111].

c) It must be noted here that increased levels of type I collagen can also induce IκBα phosphorylation without degradation, and p65 translocation followed by lef1 expression, resulting in EMT, in human pancreatic carcinoma (PANC-1), colon carcinoma (DLD1), and normal kidney proximal tubule epithelial (HK-2) cells[107]. p65 nuclear translocation and LEF1 activation was also involved in HGF-induced EMT of triple negative breast cancer cells[108]. If these events occur in the presence of intact IκBα this could allow IκBα to neutralize tumor suppressor p53[112], enabling growth of cancer cells with wildtype p53.

d) Inactivation of apoptotic BH3 domain proteins, which renders many upstream-targeted drugs ineffective[85,113].

e) MUC1 protein overexpression[114]. MUC1 can recruit β-catenin and p300, and thereby activate the myc promoter independently from Brd4; MUC1 inhibitor, therefore, kills human lung adenocarcinoma cells in synergy with JQ1[114].

f) The MEK/ERK pathway can sustain cancer cell viability in synergy with wnt and Brd4[115].

g) mTOR activity. Against osteosarcoma cells, rapamycin and JQ1 can have synergistic cytotoxicity[116]. However, temsirolimus induces canine mammary carcinoma cells with high HER2/3 and Src activity to overexpress MUC1 and β-catenin[117], making c-Src an important variable here.

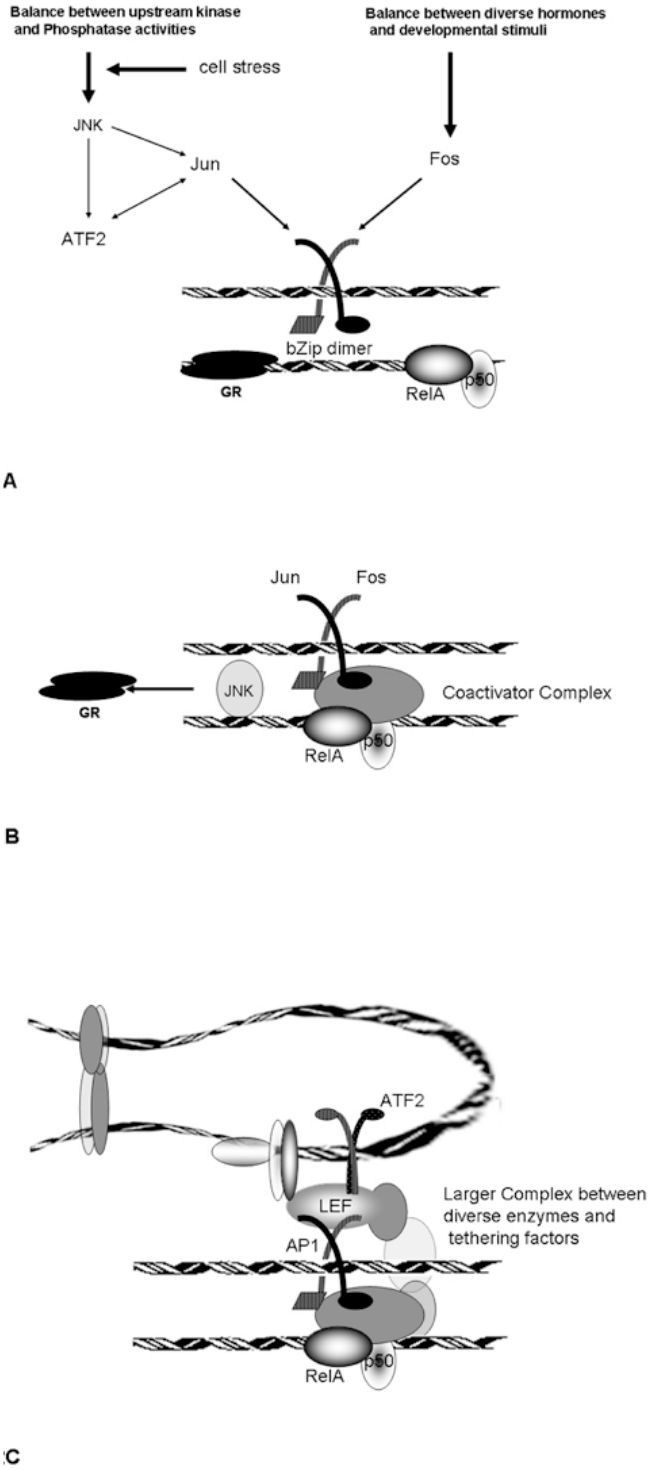


Figure 2. Transcriptional regulation by NF-κB integrates signaling pathways through hormones and cytokines.

(A) Several genes that encode for proteins regulating cell growth, are themselves controlled by AP-1, GR, and NF-κB. The interactions between these transcription factors integrate signals from cell stress and hormones to change gene expression.

(B) Steroid receptors interact with signal pathways of inflammation and cell stress at multiple levels. These levels include both chemical (covalent modifications) as well as physical (steric hindrance).

(C) DNA looping in chromatin allows larger complexes to form between diverse proteins. The presence of ATF2 for example, allows recruitment of protein LEF1, which integrates noncanonical wnt signaling on an enhancer. The enhancer can then continue to operate when redundant cofactors are blocked. Wnt signaling was recently proposed to compensate for Brd4 in enhancing

myc expression of JQ1-resistant cell lines through an alternative enhancer of myc.
Source: author's original figures.

Importantly, wnt signaling is also known to act systemically as a potent metastasis suppressor[118]. Therefore the activity of interacting pathways that regulate metastasis directly is crucial in evaluation of cancer gene expression. In addition, comparative analysis of transcripts for factors, such as c-Myc that steer cell metabolism, with the turnover of apoptotic proteins, can yield a useful lead to translational approaches in defining therapeutic targets, and in decreasing the potential for side-effects[85,119].

Future translational work will assess the resulting synergies of rationally designed anti-inflammatory agents[120] and match anti-inflammatory intervention to classical interventions on growth-factor-receptors, or hormone receptors[32,121]. Analysis of secreted cytokines or miRNA signatures can help to evaluate and develop new therapeutic approaches[36,122]. Translational research is thereby expected to help refine application of established drugs, and augment innovative strategies.

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