NF- κ B signaling and crosstalk during carcinogenesis

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Abstract – Transcription factors (TFs) are proteins that control the transcription of genetic information from DNA to mRNA by binding to specific DNA sequences either on their own or with other proteins as a complex. TFs thus support or suppress the recruitment of the corresponding RNA polymerase. In general, TFs are classified by structure or function. The TF, Nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), is expressed in all cell types and tissues. NF- κ B signaling and crosstalk are involved in several steps of carcinogenesis including in sequences involving pathogenic stimulus, chronic inflammation, fibrosis, establishment of its remodeling to the precancerous niche (PCN) and transition of a normal cell to a cancer cell. Triggered by various inflammatory cytokines, NF- κ B is activated along with other TFs with subsequent stimulation of cell proliferation and inhibition of apoptosis. The involvement of NF- κ B in carcinogenesis provides an opportunity to develop anti-NF- κ B therapies. The complexity of these interactions requires that we elucidate those aspects of NF- κ B interactions that play a role in carcinogenesis, the sequence of events leading to cancer.

Keywords: α -SMA, AFT3, AMPK, ANXA2, AP1, APO-1, BAG-1, Barrett, Bcl-2, BiP, Cancer, Carcinogenesis, CCC, CD54, CD95, CD106, cdk2, CDX2, Cell transition, Chronic inflammation, Cox-2, cRel, CXCL8, Cyclin B1, Cyclin D1, C/EBP β , EBV, ECM, EGFR, ELAM-1, Epstein-Barr virus, E-selectin, Fas, Fibrosis, GC-C, GERD, Ghrelin, GHS-R, GM-CSF, GTPase, HBV, HBx, HCC, HCV, Helicobacter, Hepatitis, HIAP, HPV, H-ras, hTERT, ICAM-1, I κ B α , I κ B β , I κ B γ , I κ B ϵ , I κ B kinase (IKK) complex, IKK1, IKK2, IKK γ , IL-6, IL-8, IL-13, IL-1 β , iNOS, Lysyl oxidase, LOX, LOXL2, MAP2K1, Metallo proteinase, Metaplasia, Microbiome, MIP1 α , MMP, MMP-1, MMP-9, Morbid obesity, Mycoplasma, *M. fermentans*, *M. hominis*, *M. penetrans*, NEMO, Nuclear factor kappa-light-chain-enhancer of activated B cells, NF- κ B, p50, p52, p53, p65, p100, Pathogenic stimulus, PLA2, PRDM1, RelA, RelB, Remodeling, RHD, Schistosomiasis, *S. japonicum*, *S. mansoni*, SOCS2, STAT3, TGF- β 1, TF, TLR, TNF α , TRAF1, TRAF2, TTF, UPR, VCAM-1, VEGF.

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B)

DNA transcription factors

Transcription factors (TFs) are proteins that control the transfer of genetic information from deoxyribonucleic acid (DNA) to messenger ribonucleic acid (mRNA) by binding to specific DNA sequences. TFs are effective by themselves or in conjunction with other proteins as a complex. TFs stimulate or suppress the recruitment of the corresponding ribonucleic acid (RNA) polymerase. In general, TFs are classified by structure or function [1]. The complexity of transcription is reflected by the fact that a tumor suppressor protein, such as protein 53 (p53), can act as an

intracellular ligand (autocrine)-dependent functional TF and can be activated by small intracellular molecules. Other TFs are inactive and become activated only after translocation into the nucleus e.g., nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B).

NF- κ B discovery and structure

NF- κ B is a TF which occurs in all cell types and tissues [2]. NF- κ B was discovered at the Salk Institute by Ranjan and Harinder Singh in David Baltimore's lab in 1986 [3]. The hidden form of NF- κ B within the cytoplasm of unstimulated cells was discovered by Patrick Baeuerle in 1988 [4] who also reported the purification of an inhibitor [5] as previously reviewed [6, 7].

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The NF- κ B protein superfamily family [8] has a DNA-binding/dimerization termed the Rel homology domain (RHD) [9] and consists of NF- κ B1 protein 50 (p50) and its progenitor protein 105 (p105), NF- κ B2, protein 52 (p52) and its progenitor protein 100 (p100)), transcription factor p65 encoded by RELA gene (RelA, protein 65, p65), transcription factor encoded by the RELB gene (RelB), and proto-oncogene, c-Rel, encoded by REL gene (cRel, Rel) and *Drosophila* Dorsal and Dif. NF- κ B inhibiting proteins are I κ B proteins (nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor protein) such as I κ B α , I κ B β , I κ B γ , I κ B ϵ , and *Drosophila* Cactus.

The NF- κ B-I κ B complex is located in the cytoplasm in its inactive latent form. The I κ B kinase complex (IKK) with its regulating subunits nuclear factor kappa-B kinase 1 (IKK1, inhibitor of nuclear factor kappa-B kinase subunit alpha, IKK- α), inhibitor of nuclear factor kappa-B kinase 2 (IKK2, inhibitor of nuclear factor kappa-B kinase subunit beta, IKK- β) and the framework protein NF- κ B essential modulator (NEMO, inhibitor of nuclear factor kappa-B kinase subunit gamma, IKK- γ) phosphorylates and degrades I κ B resulting in NF- κ B dimers with their translocation into the nucleus. The major dimer in cells is the specific p50-RelA heterodimer.

NF- κ B controls many genes involved in inflammation and in cancer and directly influences cell proliferation, cell survival, and can decrease apoptosis via tumor necrosis factor alpha (TNF α) receptor-associated factor 1 and 2 (TRAF1, TRAF2).

NF- κ B inhibiting I κ B proteins

NF- κ B is present in the cytoplasm as “a heterotrimer consisting of p50, p65, and inhibitory subunit of NF- κ B (I κ B) α subunits” (reviewed in [10]). NF- κ B builds a complex with inhibitory I κ B proteins such as I κ B α , I κ B β , I κ B ϵ , I κ B ζ , p100, p105, B-cell lymphoma 3 (Bcl-3), or the Toll-like receptor (TLR)-inducible nuclear I κ B protein I κ BNS, and this complex is maintained within the cytoplasm in its inactive form [11, 12]. Activating signaling pathways promote the degradation of I κ B, mediated by the IKK complex consisting of the kinases IKK α (IKK1) and IKK β (IKK2) and a regulatory scaffolding protein, NEMO (IKK γ). In this manner, I κ B is phosphorylated resulting in its degradation with translocation of NF- κ B dimers into the nucleus to affect the target gene expression. After phosphorylation of the subunit of I κ B α and its degradation on the p50-p65 heterodimer, phosphorylation of the p65 molecule occurs with binding to a specific DNA-sequence, resulting in gene transcription. I κ Bn can regulate inflammation by inhibiting the induction of TLRs-dependent genes through modulation of NF- κ B [13].

Canonical and non-canonical NF- κ B signaling

Canonical pathways are “idealized or generalized pathways that represent common properties of a particular signaling module or pathway, and accordingly categorizes the genes in specific canonical pathways and networks” [14].

The canonical (Fig. 1) and non-canonical NF- κ B (Fig. 3) pathways have been extensively reviewed [11, 12]. Both, canonical (classical) and non-canonical (alternative) pathways in IKK/NF- κ B signaling influence whether a cell lives or dies [11].

In the canonical pathway, various cytokines such as TNF α , interleukin 1 beta (IL-1 β), and viruses or TLRs are involved in inflammatory and immune-mediated responses. These include increases in TNF α , IL-1 β , interleukin 6 (IL-6), granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin 8 (IL-8, chemokine (C-X-C motif) ligand 8, CXCL8), macrophage inflammatory protein 1 alpha (MIP1 α , chemokine (C-C motif) ligand 3, CCL3), vascular cell adhesion molecule 1 (VCAM-1, cluster of differentiation 106, CD106), intercellular adhesion molecule 1 (ICAM-1, cluster of differentiation 54, CD54), E-selectin (endothelial-leukocyte adhesion molecule 1, ELAM-1, CD62 antigen-like family member E, CD62E, leukocyte-endothelial cell adhesion molecule 2, LECAM2), or nitric oxidase synthase (iNOS), cyclooxygenase 2 (Cox-2) and phospholipase A2 (PLA2).

The *non-canonical* NF- κ B signaling is dependent on IKK α homodimers. It is activated by lymphotoxin beta receptor (LT β R), B cell-activating factor belonging to the TNF family (BAFF), cluster of differentiation 40 (CD40) ligand (CD40L), and cluster of differentiation 154 (CD154)-induced expression of interferon regulatory factor 3 (Irf3) or retinoid X receptor alpha (Rxra, nuclear receptor subfamily 2, group B, member 1, NR2B1) [11]. LT β R can induce apoptosis in both the canonical and non-canonical pathways [15]. Knocking down Irf3 or the stimulator of interferon genes (STING) results in reduced inflammation and apoptosis modulated by NF- κ B [16], and Irf3 inhibition results in decreases of the transforming growth factor beta 1 (TGF- β 1)-induced proliferation of hepatic stellate cells (HSC) [17].

Recently, a novel mechanism of NF- κ B activation B-cell receptor (BCR) was reported which could be relevant in B-lymphoproliferative disorders: NF- κ B p50/p65 was rapidly activated (within 30 s) by anti-IgM stimulation of BCR through a Bruton's tyrosine kinase (Btk)-dependent and IKK-independent mechanism [18]. Btk expression is increased and required for EGFR-induced NF- κ B activation with poor prognosis in glioma [19]. Furthermore, Btk membrane translocation is observed in multiple myeloma [20] as it regulates Toll-like receptor 7 and 8 (TLR7/8) induced TNF transcription through NF- κ B [21]. Inhibiting Btk by the small molecule and inhibitor of tubulin polymerization, KS99, results in the inhibition of tumor growth in multiple myeloma and osteoclastogenesis in vivo [22].

NF- κ B polymorphism

Blood samples from 565 healthy volunteers in a Turkish cohort were tested to determine the frequency of polymorphisms. Polymerase chain reaction (PCR) amplification was performed followed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). This revealed that NF- κ B1-94ins/delATTG and NF- κ BIA

3' UTR polymorphisms were, in general, quite similar to other populations in Germany, Sweden, Czechoslovakia, and Australia [23]. Wang et al. tested 564 gastric cancer patients and 566 healthy controls to see if the polymorphism rs2233408 T/C genotype in the promoter region of *IκBα* was associated with increased risk for gastric cancer [24], and found that “*IκBα* rs2233408 T heterozygotes were associated with reduced gastric cancer risk”. Stable expressions of Runt-related transcription factor 3 (RUNX3)/protein 33 (p33) were associated with a 1.9-fold elevation in NF-κB transcriptional activity [25]. In 1010 gastric cancer patients compared to 1500 healthy controls in Guangdong, China, *IκBα* rs17103265 deletion homozygote was identified as a novel risk factor for gastric cancer [26]. This was followed by the association of homozygous rs4648068 GG with an increased risk of gastric cancer in the Han Chinese population [27]. Lo et al. correlated polymorphisms of NFKB1 promoter with susceptibility to gastric cancer in aged patients [28].

Ubiquitination and degradation

The process of adding ubiquitin known as “ubiquitination” is used to mark proteins or protein complexes for degradation through covalent binding by monoubiquitin or polyubiquitin chains with different enzymes such as ubiquitin-activating enzyme (E1), ubiquitin-conjugating enzyme (E2), and ubiquitin ligase (E3). Adding a monoubiquitin is a regulatory modification compared to adding polychains by a polyubiquitin which is involved in distinct cellular functions, e.g., signaling a molecule for degradation by the proteasome [29–35].

Because of their discovery of protein-regulating systems, the 2004 Nobel Prize for chemistry was awarded to Aaron Ciechanover, Avram Herskko, and Irwin Rose [36–39].

Ubiquitin-mediated proteolysis of *IκBs* is irreversible, and ubiquitination and degradation of the inhibitors of NF-κB is an important component of transcriptional activation (reviewed in [40]).

NF-κB and cancer

NF-κB association with precancerous lesions and cancer

Increased constitutive NF-κB activity has been reported in precancerous lesions of the skin [41, 42], breast [43], head and neck [44, 45], Barrett’s esophagus [46], colon adenoma [47], chronic pancreatitis [48], colitis [49, 50], in premalignant lung [51] and in the stroma of precancerous lesions of colon adenoma [52].

Furthermore, NF-κB has been reported in a number of adenocarcinoma cell lines [53] and NF-κB activity was associated with cancers of the breast [54–60], ovaries [61, 62], endometrium [63], prostate [64–66], thyroid [67–70], pancreas [71–74], squamous cell carcinoma (SCC) [75, 76], esophagus [77–79], stomach [80], colorectum [61, 81–83], liver [84–86], kidneys [87–89], bladder [90], lymphoma [91–95], leukemia [96–98], multiple myeloma [99–102], brain [103–105], melanoma [106–109], and sarcoma [110–112].

However, NF-κB signaling in carcinogenesis is complex and depends on which subunits are involved: NF-κB2/p52 seems to be required for colitis-associated adenoma while c-Rel-induced signaling is involved in colonic epithelial cell turnover [113]. Furthermore, there is a difference between acute versus chronic inflammation. NF-κB can have anti-inflammatory effects in an acute, chemically induced colitis model with IL-β1 suppression and IKKβ inhibitors could potentially serve as a therapeutic option in such cases [49], but IKKβ is needed for healing after colitis [114] and “*NF-κB2/p52 is necessary for the development of colitis, whilst c-Rel-mediated signalling regulates colonic epithelial cell turnover*” [113].

In vitro NF-κB cancer model

For about 25 years, increased NF-κB activity has been recognized to be associated with cancer development in transgenic mice [115]. For example, the chemotherapeutic efficacy of cisplatin can be enhanced by inhibiting NF-κB in vitro and in vivo [116]. In 2014, an in vitro model of NF-κB driven carcinogenesis was published [117]. The authors used a cell-based phenotypic readout and isolated 12 genetic elements that induced NF-κB activity (NF-κB-activating genetic elements, NASPs) of lentiviral libraries encoding 20 or 50 amino acid-long polypeptides “*none of which was previously associated with NF-κB activation, were isolated from libraries of 200 000 peptides derived from 500 human extracellular proteins*”. By selective knockdown experiments, it was shown that isolated NASPs “*act either via or upstream of TNF receptor-associated factor 6*” (TRAF6). Growth in mice or rat embryo fibroblasts was unaffected after NASP transduction but co-expression with Ras (protein superfamily of small guanosine triphosphate hydrolase enzymes (GTPases) by GTP hydrolase enzyme, transforming protein p21 (H-ras, H-Ras^{V12}) resulted in cell transformation. Constitutive activation of NF-κB attenuated p53 and promoted carcinogenesis. In contrast, activated K-Ras, but not H-Ras or N-Ras was assumed to imitate tumors of endodermal origin via stem cell expansion [118] though this could be related to the model used. Buchanan et al. showed that phospholipase D1 (PLD1) activity in H-Ras^{V12} is required for transformation [119].

NF-κB and cancer aggressiveness

Tumor aggressiveness in gastric cancer was shown by investigating 90 human cancer tissues versus 50 nonmalignant specimens. A higher NF-κB expression in cancer tissue versus normal mucosa (31% vs. 4%, $p < 0.0001$) was found along with activation of metalloproteinase 9 (MMP-9), IL-β1, and IL-8 in AGS cells [120]. Another example of NF-κB signaling and chronic inflammation was provided by Kwon et al. [121] who demonstrated that the Vitamin D(3) upregulated protein 1 (VDUP1) with its tumor suppressive effect was shown in VDUP1 knockout (KO) revealing that VDUP1 negatively regulates *Helicobacter pylori* (*H. pylori*)-associated gastric cancer by inhibiting the

induction of $\text{TNF}\alpha$, $\text{NF-}\kappa\text{B}$, and Cox-2, and by disrupting cell growth.

Combining non-steroidal anti-inflammatory drugs (NSAIDs) with $\text{NF-}\kappa\text{B}$ inhibitors increased apoptosis in different ovarian cancer cell lines SKOV-3, CAOV-3, SW626 and 36M2 [122].

NF- κB signaling and crosstalk in carcinogenesis and pathogenic stimulus

The importance of $\text{NF-}\kappa\text{B}$ signaling in carcinogenesis was emphasized in the proposed new paradigm for the origin of the majority of cancers [123, 124].

Viruses

Increased $\text{NF-}\kappa\text{B}$ activity has been associated with pathogenic stimuli such as Epstein-Barr virus (EBV) [125], Hepatitis B virus (HBV) [126], and Hepatitis C Virus (HCV) [127].

Hepatitis B viral protein (HBx) is a small transcriptional transactivator essential for infectivity and which activates $\text{NF-}\kappa\text{B}$ signaling in the cytoplasm [128] via deactivation of two $\text{NF-}\kappa\text{B}$ inhibitors [129], phosphorylation of $\text{I}\kappa\text{B}\alpha$ inhibitor and $\text{NF-}\kappa\text{B1}$ (p50) precursor inhibitor protein p105 (Fig. 2) with reduction of $\text{I}\kappa\text{B}\alpha$ stability, and decreased $\text{NF-}\kappa\text{B1}$ (p50), resulting in the accumulation of $\text{NF-}\kappa\text{B}$ within the nucleus.

HBV and HCV trigger chronic inflammation with $\text{NF-}\kappa\text{B}$ activation, which in turn, is associated with hepatocellular carcinoma (HCC) [130–132]. Despite HBV suppression, HCC development is still observed in patients with residual hepatitis B surface antigen (HBsAg) titers ([133, 134] reviewed in [135]). Patients with spontaneous HBV DNA clearance and residual high HBsAg titers also show increased HCC risk ([136] reviewed in [135]).

HBV induces an unfolded protein response (UPR), $\text{NF-}\kappa\text{B}$ activation [136], signal transducer and activator of transcription 3 (STAT3) [137], and IL-8 [138]. HBsAg, together with inhibition of $\text{NF-}\kappa\text{B}$, decreases UPR, binding immunoglobulin protein (BiP, 78 kDa glucose-regulated protein, GRP-78, heat shock 70 kDa protein 5, HSPA5), Cyclin E, cyclin-dependent kinase 2 (cdk2), and increases cytosine-cytosine-adenosine-adenosine-thymidine (CCAAT)/enhancer binding protein homologous protein (CHOP), activating transcription factor 3 (ATF3), Cyclin D1 which results in a 100% incidence of HCC [135].

Human papilloma virus (HPV) infection with HPV Type 16 (HPV16) appears to be responsible for some 18% of oral cancers [139] and has been shown to modulate $\text{NF-}\kappa\text{B}$ signaling [140]. This is associated with the p65 $\text{NF-}\kappa\text{B}$ complex formation and consequent heterodimerization of p50/p65 which is thought to be one reason why disease outcome is better in patients with HPV-positive oral cancers than in patients with HPV-negative oral cancers [141]. HPV16 E6 protein activates $\text{NF-}\kappa\text{B}$ signaling via p50, $\text{NF-}\kappa\text{B}$ -inducing kinase (NIK), and TRAF-inter-

acting protein [142] while human fibroblasts expressing E7 protein decreases pro-caspase 8 activation, and can partially protect from apoptosis by activating the TNF receptor 1-related cytokine receptor, first apoptosis signal receptor (Fas, FasR, apoptosis antigen 1, APT, cluster of differentiation 95, CD95) [143].

HPV-negative tumors are associated with STAT3/pSTAT3 together with $\text{NF-}\kappa\text{B}$ “irrespective of the presence or absence of activator protein 1 (AP1)” while “AP1 and $\text{NF-}\kappa\text{B}$ lacking involvement of STAT3” are associated in HPV-positive tumors [144].

Inhibition of $\text{NF-}\kappa\text{B}$ and AP1 transcription factors by the T-cell-specific inhibitor, 2-chloro-4-(trifluoromethyl)-pyrimidine-5-N-(39,59-bis(trifluoromethyl)phenyl)-carboxamide (SP100030), suppressed fibrosis in the lung by decreasing coagulation, and decreasing collagen deposition in the lung [145].

Another important example is the first apoptosis signal receptor (Fas, FasR, apoptosis antigen, APO-1, APT, cluster of differentiation 95 CD95), TNF receptor superfamily member 6 (TNFRSF6). Fas is a cell surface receptor whose activation results in apoptosis [146]. $\text{NF-}\kappa\text{B}$ can directly regulate Fas-mediated apoptosis by acting as a Fas transcriptional activator in human colon carcinoma cells and in mouse embryonic cells (MEFs). Thus, an anti- $\text{NF-}\kappa\text{B}$ therapy might suppress Fas-mediated apoptosis and impair natural immune anti-cancer cell suppression [147] or act via the regulation of caspase-4 [148].

Stromal fibroblasts in HPV infection acts via IL6/CCAAT/enhancer-binding protein β (C/EBP β) signaling to recruit T helper 17 cells (Th17) with consequent chronic inflammation during carcinogenesis [149]. C/EBP β signaling together with adenovirus early region 1A (E1A) binding protein (p300, EP300) induces IL-8/CXCL8 expression in lung cancer [150] and promotes $\text{NF-}\kappa\text{B}$ triggered invasion and cell migration in renal cancer [151]. Metastasis by migration via C/EBP β also occurs by $\text{TNF}\alpha$ -induced matrix metalloproteinase 1 (MMP-1)/matrix metalloproteinase 3 (MMP-3) expressions in a p38 MAPK-dependent manner [152]. Interestingly, knockdown of C/EBP β inhibits p65- $\text{NF-}\kappa\text{B}$ signaling resulting in protection against fibrosis in cardiac myocytes [153] and in adipocyte-mediated chronic inflammation via mitogen-activated protein kinase kinase (MEK, MAPK2, MAPKK), C/EBP β with $\text{NF-}\kappa\text{B}$ /RelA inducing 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1) [154].

Human papilloma virus type 8 (HPV8) induces matrix metalloproteinase 14 (MMP-14, MT1-MMP) in the stroma and cells of cutaneous tumors [155], but the exact role of HPV-induced fibrosis in HPV-triggered cancers remains to be elucidated. Human ovarian carcinoma cell line, SK-OV-3, transfected with adenovirus early region E1A protein revealed increased sensitivity to radiation-induced cell death for which $\text{NF-}\kappa\text{B}$ modulation and/or inactivation is required [156].

$\text{NF-}\kappa\text{B}$ signaling is associated with G2/mitotic-specific cyclin-B1 (Cyclin B1), Cyclin D1, human inhibitor of apoptosis protein (HIAP), BAG family molecular chaperone regulator 1 (BAG-1), transcription termination factor (TTF),

and fibronectin in radioresistance of p53-inactive human keratinocytes [157].

Bacteria

Enteroinvasive bacteria induce chronic inflammation [158–160] through the activation of cytokines such as IL-8, iNOS, and Cox-2 [161]. Enteroinvasive bacteria can also suppress NF- κ B activation and expression of IL-6 and IL-8 [162, 163].

NF- κ B activation via DNA and RNA from bacteria and viruses likely occurs through the promotion of inflammatory cytokines such as TNF, IL-6, inactive IL- β 1 precursor (pro-IL-1 β), intracellular NOD-like receptor pyrin domain containing 3 (Nlrp3), IFN, TLRs [164–167], lipopolysaccharide (LPS) [168] mediated by cluster of differentiation 14 (CD14) [169].

Helicobacter pylori was shown to be actively involved in stimulating IL-8 in gastric cancer [170]. Increased NF- κ B binding activity is observed with elevated IL-8 levels from the more virulent *H. pylori* strains [171, 172]. In a series of 289 biopsies, an association between increased NF- κ B activity was reported in *H. pylori* virulence factor (cagA) positive metaplasia, dysplasia, and in gastric carcinoma [173]. *H. pylori* infected human gastric epithelial cells induce matrix metalloproteinase 7 (MMP-7) through activation of the Ras homolog gene family (Rho) and the subfamily of the Rho family of GTPases (Rac). Here Ras homolog gene family member A (RhoA) activates NF- κ B and AP1, while Rac activates NF- κ B, but not AP1 [174] so the effects are selective.

The *H. pylori* virulence factor CagA promotes chronic inflammation and proliferation through phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) signaling with consequent activation of beta-catenin and NF- κ B [175]. The *Helicobacter* species, *H. bilis*, in the human bile duct cancer cell line, HuCCT-1, activated NF- κ B activity independent of the tumor stage. This was associated with production of vascular endothelial growth factor (VEGF) [176] and was later shown in extrahepatic cholangiocellular carcinoma (CCC) specimens to occur especially within the common bile duct [177].

Mycoplasma

Mycoplasma infection was shown to induce NF- κ B activation, p53 suppression, and promotion of Ras-induced cell transformation [178, 179]. Infecting the gastric mucosa of immunodeficient mice with the prokaryotic intracellular parasite, *Mycoplasma sp.*, induced chronic inflammation and facilitated malignant cell transformation with increased expression of p53, p21, B-cell lymphoma 2 (Bcl-2)-associated X protein (Bax), transforming protein p21 (GTPase HRas, H-ras), B-cell lymphoma 2 (Bcl-2), transcription factor p65 (p65, nuclear factor NF-kappa-B p65 subunit) and TNF α together with upregulated NF- κ B signaling, which by itself elicits resistance to apoptosis [180].

Mycoplasma hyorhinis (*M. hyorhinis*) expresses the *M. hyorhinis* membrane protein p37 and binds to gastric

cancer cells, MGC803 and AGS, in a time- and dose-dependent manner as shown in the cell ELISA, which is p37-dependent mediating the p37/annexin II (ANXA2) interaction and important for the host-receptor mediating *M. hyorhinis* infection.

EGFR increases ANXA2 phosphorylation and facilitates *M. hyorhinis* infection. This increases expression of NF- κ B target genes I κ B α , Cox-2, MMP-1, PR domain zinc finger protein 1 (PRDM1), suppressor of cytokine signaling 2 (SOCS2), dual specificity mitogen-activated protein kinase kinase 1 (MAP2K1) contributing to cell invasiveness [181]. Furthermore, the direct induction of the LT β R and non-canonical NF- κ B signaling has recently been demonstrated [182].

Tsai et al. found unusually high frequencies of *Mycoplasma fermentans* (*M. fermentans*) and *Mycoplasma penetrans* (*M. penetrans*) in acquired immune deficiency syndrome (AIDS) patients that could not be associated with immediate (acute) transformation of cells into cancer cells [183]. Investigating the mouse fibroblast cell line, C₃H cells, a persistent infection with *M. fermentans* resulted in cell phenotypes with malignant characteristics, which were more pronounced with prolonged infection. Furthermore, the authors reported that this phenomenon was dependent on the number of passages: mycoplasma needed one week per passage, at least six passages were necessary and until the 11th passage the malignant transformation was reversible if anti-mycoplasma therapy was implemented. In contrast, the malignant state was irreversible if mycoplasma infection persisted until the 18th passage. *Importantly, no chromosomal loss or translocations were observed during the reversibility window.* In regards to our knowledge today, the authors drew the incorrect conclusions when they assumed that genetic instability was most likely caused by somatic mutations. The important take away from this investigation was that despite the long latency, a mycoplasma infection triggered development of malignant cells, that there was a reversible stage which could be eradicated, and which speaks against hypothesizing the need for mutations or other genetic changes at least within a window of time. Nonetheless, after another long period of persistent infection, signs of genetic instability were reported.

This also explains why locally advanced cancers reveal mutations or other genetic changes and why recurrent cancers show chromosomal aberrations [184] and even why reports of mycoplasma-infected cancer cells were correctly observed to show chromosomal aberrations [185, 186] but incorrectly interpreted in assigning genetic changes as being causal to the cancer.

Tsai et al. showed almost 50 years ago that latency, as well as multiple cell passages, were mandatory events in carcinogenesis [183].

In 194 Nigerian women tested for *high-risk human papillomavirus* (hrHPV), a significant association with *Mycoplasma hominis* (*M. hominis*) was observed with an OR of 8.78 (95% Confidence Interval, 1.49–51.6, $P = 0.01$) and human immunodeficiency virus (HIV) positive females had a three-fold increase in OR in the presence of persistent hrHPV infection [187].

As multiple biological stimuli may be involved during carcinogenesis, it seems that we are at the beginning of creating a focus in cancer research by exploring the role played by physiological and chemical stimuli [123, 124, 188–191].

Schistosomiasis

Schistosomula are the parasitic stage of *Schistosomiasis* residing in the lungs and retained in capillaries responsible for initiating inflammatory response and leukocyte recruitment [192]. Endothelial cells (ECs) are activated by *Schistosoma mansoni* (*S. mansoni*) with schistosomula gaining an anti-inflammatory phenotype with reduction of VCAM-1 and E-selectin in TNF α stimulated ECs mediated by cyclic 5' adenosine monophosphate (cAMP)/protein kinase A (PKA) signaling [193] which, in turn, is affected in reducing NF- κ B transcriptional activity (and not by blocking NF- κ B) [194] through PKA-induced cAMP response element-binding protein (CREB) phosphorylation. This results in the removal of the transcriptional co-activator CREB binding protein (CBP) from the NF- κ B complex ([195] reviewed in [194]).

RNAse resistant double-stranded RNAs (dsRNAs) from *Schistosoma mansoni* activates toll like receptor 3 (TLR3) with consequent phosphorylation of signaling transducer activator of transcription 1 (STAT1) together with interferon (IFN) stimulated gene expression [196].

The association of *Schistosomiasis*-induced cancers and fibrosis has long been reported in liver cancers such as HCC and CCC [197, 198] but under-appreciated in the literature. Anti-*Schistosomiasis* therapy improves and ameliorates fibrosis via NF- κ B signaling [199, 200]. The application of Boswellic acid (BA)-containing extracts attenuated *Schistosoma japonicum* (*S. japonicum*)-induced fibrosis via decreases in NF- κ B signaling and subsequent decreases in VEGF, TNF α , and monocyte chemoattractant protein 1 (MCP-1, chemokine (C-C motif) ligand 2, CCL2) [201]. Other anti-helminthic drugs, such as niclosamide, target NF- κ B, Wnt/ β -catenin, Notch, reactive oxygen species (ROS), mammalian target of rapamycin complex 1 (mTORC1), and STAT3 [202]. Paeoniflorin (PAE) decreases interleukin 13 (IL-13), NF- κ B, TGF- β 1 and α -smooth muscle actin (α -SMA, α -actin 2) expression resulting in a decrease of fibrosis [199].

Although increases of lysyl oxidase (LOX) were shown in murine *Schistosomiasis* some 25 years ago [203], an anti-LOX approach was not investigated. LOX is expressed in *Escherichia coli* (*E. coli*) [204]. Lysyl oxidase homolog 2 (LOXL2) [205] was found in human lung fibrosis, bronchiolo-alveolar carcinomas, and *in situ* ductal breast tumors [206]. In *S. mansoni*-infected mice and early stages of liver granuloma, the LOX gene and LOX-like gene (LOXL) were upregulated. LOXL2 promotes zinc finger protein SNAI1 (Snail) and decreases E-cadherin, both important for metastasis. Investigations of the extracellular matrix (ECM) by atomic force microscopy showed that LOXL2 does not affect ECM properties [207]. Incubating oral epithelial cells with the natural di-thiol α -Lipoic acid was

shown “to modulate periodontal bacterial induced NF- κ B activation, pro-inflammatory gene expression and cytokine production” [208].

Barrett's, reflux and bile acid

The development of Barrett's intestinal metaplasia is multifactorial in etiology [209]. The incidence rates vary between 0.19 and 0.33% ([210, 211] reviewed in [212]) while in 1997 the prevalence was reported as being 19.8% in patients with heartburn [213]. Although it was previously assumed that Barrett's originates from intestinal metaplasia, Takubo et al. showed that small lesions of Barrett's are surrounded by non-intestinalised epithelium and not by intestinal metaplasia [214], a finding that was subsequently reproduced [215, 216]. On the one hand, intestinal metaplasia shows higher rates of molecular aberrations compared to non-intestinal metaplasia [217] while on the other, even *The Cancer Genome Atlas* (TCGA) which consists of approximately 10 000 specimens representing 33 types of cancer [218] and the most recent Mutational Assessment of iClusters [219] failed to provide evidence of one unique genetic signature for the majority of Barrett's cancers. Despite this, the contributors to Barrett's are assumed to be gastro-esophageal reflux disease (GERD), hiatal hernia, and alcohol [212], all of which have just one condition in common: chronic inflammation.

Babar et al. investigated Barrett's patients who underwent anti-reflux surgery versus proton pump inhibitor (PPI) treatment and investigated endoscopic biopsy specimens from 2 cm below the squamo-columnar junction for NF- κ B, cytokines, and growth factors [220]. “Mean activated NF-kappaB p50 and p65 subunits, interleukin (IL)-1alpha, IL-1beta, and interleukin-8 levels, were significantly ($P < 0.05$) lower in the surgically treated group” and led the authors to conclude that anti-reflux surgery may create a less inflammatory environment.

Bile acids activate farnesoid X receptor (FXR)/nerve growth factor (NGF)/transient receptor potential vanilloid 1 (TRPV1) axis through mucosal mast cell-to-nociceptor signaling inducing visceral hypersensitivity in a rat model investigating diarrhea-predominant irritable bowel syndrome (IBS-D) [221].

In obesity, FXR additionally promotes inflammation in diet-induced obese mice through a dysregulation of homeostasis of pro- and anti-inflammatory signaling [222]. Otherwise, FXR activation occurred in high-fat diet (HFD) fed mice with increased proinflammatory leukotrienes B4 (LTB4) and lower (~ 3 -fold) anti-inflammatory epoxyeicosatrienoic acids (EETs) [223]. FXR induced inflammation can be suppressed by the novel FXR-agonist, dioscin, with consequent suppression of NF- κ B and High mobility group box 1 protein (HMGB-1), and subsequently decreased the mRNA levels of IL- β 1, IL-6, and TNF α [224].

NGF attenuates apoptosis and inflammation in diabetic keratinopathy decreasing ROS activation and levels of cleaved caspase-3, BAX, IL- β 1, and TNF α [225]. These contradictory findings are explained as the NGF effect is

Figure 1. Canonical NF-κB signaling pathway. Simplified scheme of the canonical NF-κB pathway. *Nomenclature:* **TNFα**: tumor necrosis factor α; **TNFR1**: tumor necrosis factor receptor 1; **IL-1**: interleukin 1; **ILR1**: interleukin 1 receptor; **LPS**: lipopolysaccharide; **TLR4**: toll-like receptor 4; **IKK complex**: IκB kinase enzyme complex to upregulate the NF-κB signaling; **IκBα**: IκB kinase 1 (IKK1); **IκBβ**: IκB kinase 2 (IKK2); **IκBγ**: IκB kinase gamma; **NEMO**: NF-kappa-B essential modulator, regulatory scaffolding protein; **P**: phosphorylated; **Akt**: protein kinase B (PBK); **p65**: NF-κB3 (**RelA**); **c-Rel**: proto-oncogene NF-κB transcription factor; **p50**: NF-κB1 (*progenitor is p105*). Canonical NF-κB-IKK-complex is the inactive cytoplasmic form, consisting out of IκBα, p65 and p50. The canonical NF-κB heterodimer is the active form entering into the nucleus consisting out of p65 and p50.

dose-dependent in that it appears to be dependent on how strongly the homeostasis is disrupted [226, 227] as it was shown, that NGF stimulates T-lymphocyte-dependent basophilic cell differentiation in vivo at sites of allergic tissue inflammation [228] as NGF is also often a secondary upregulated endogenous factor [229].

The induction of NF-κB through NGF works through the p75 receptor with an anti-apoptotic effect in Schwannoma cells [230] contributing to survival of NGF-dependent sympathetic neurons [231]. Here, NGF is contrary to TNFα, as the Bcl-x survival gene expression requires tyrosine phosphorylation of IκappaBalpha [232] explaining the disruption of homeostasis of the NGF-TNFα axis is of importance. TNFα regulates the response to NGF in neuroblastoma cells [233].

Upregulation of TRPV1 is mediated by the p38 mitogen-activated protein kinase (MAPK) and NF-κB signaling pathways by urban particulate matter (UPM) resulting into chronic inflammation [234]. Local acidotic microenvironment incudes TRPV1 activation with consequent NF-κB activation with observed lymphangiogenesis in lymphatic endothelial cells (LECs) [235].

Bile acid is associated with homeobox protein CDX-2 (Cdx2) expression, a transcription factor for the intestine-specific tumor suppressor guanyl cyclase (GC-C), and mediated by NF-κB. The increase in Cdx2 by deoxycholate is associated with NF-κB nuclear translocation. This was interpreted as bile acid-induced intestinal metaplasia involving Cdx2 and NF-κB [236]. Deoxycholic acid shows a non-linear dose response relationship for DNA damage only above doses of 100 mM and even higher in esophageal OE33 cells with a similar dose-response association to NF-κB activation but it was not possible to replicate the applied deoxycholic acid doses in the gene expression part of the study [237]. However, the close association of IL-8 and IκB gene expression levels, together with NF-κB activity was shown earlier (Figure 2 in [237] – not shown here).

The bile acid-induced chronic inflammation involves the suppression of EGFR and Akt, resulting in activation of the NF-κB- and the Cdx2 axis [238]. Human telomerase reverse transcriptase (hTERT) which upregulates Cdx2 through NF-κB signaling promoting intestinal metaplasia [239]. Wang et al. found increased activity of NF-κB and hTERT

Figure 2. Atypical (p105) NF- κ B signaling pathway. Simplified scheme of the atypical (p105) NF- κ B signaling pathway. *Nomenclature:* **TNF α** : tumor necrosis factor α ; **TNFR1**: tumor necrosis factor receptor 1; **IL-1**: interleukin 1; **ILR1**: interleukin 1 receptor; **LPS**: lipopolysaccharide; **TLR4**: toll-like receptor 4; **MAPK3**: mitogen-activated protein kinase 3 (ERK1); **IKK complex**: I κ B kinase enzyme complex to upregulate the NF- κ B signaling; **I κ B α** : I κ B kinase 1 (IKK1); **I κ B β** : I κ B kinase 2 (IKK2); **I κ B γ** : I κ B kinase gamma, **NEMO**: NF-kappa-B essential modulator, regulatory scaffolding protein; **P**: phosphorylated; **p105**: p50 (NF- κ B1) progenitor. Atypical (p105) NF- κ B-complex is the inactive cytoplasmic form, consisting out of p105 and two p50. The NF- κ B (p50-p50) homodimer is the active form entering into the nucleus; it can act as a transcriptional repressor and as an activator together with B-cell lymphoma 3-encoded protein (BCL3).

when comparing normal gastric mucosa with dysplasia, intestinal metaplasia, and gastric cancer [240].

Morbid obesity

The association of morbid obesity and the role played by its different signaling pathways during carcinogenesis have recently been published [191] and the disruption of NF- κ B signaling could present a therapeutic approach in the future [241].

The gastric peptide, Ghrelin, associated with food intake and energy balance was shown to be able to induce cell migration via its receptor growth hormone secretagogue receptor (GHS-R), Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII), 5' adenosine monophosphate-activated protein kinase (AMP)-activated protein kinase (AMPK), and the NF- κ B signaling pathway in rat C6 and human U251 glioma cells [242].

NF- κ B signaling and crosstalk in carcinogenesis and chronic inflammation

Chronic inflammation is extensively reviewed within this Special Issue (Fig. 4) [189, 190]. In summary, the inclusion of chronic inflammation within a multistep sequence to explain carcinogenesis revealed that continuously induced inflammatory cells such as monocytes, lymphocytes, plasma cells, fibroblasts, and mast cells (MCs), together with cell-communication and the crosstalk of two major components, TGF- β and LOX play important roles in the overall process [123, 124].

TGF- β 1 activates Akt through PI3K followed by phosphorylation of glycogen synthase kinase-3 β (GSK3 β) promoting stability and activity of Snail. Furthermore, TGF- β 1 activates the mechanistic targets of mTORc1 and mTORc2. Together with various inflammatory cytokines, such as TNF α , NF- κ B is activated along with other transcriptional factors, such as hypoxia-inducible factor

Figure 3. Non-canonical NF-κB signaling pathway. Simplified scheme of the non-canonical NF-κB signaling pathway. *Nomenclature:* **RANKL**: receptor activator of nuclear factor kappa-B ligand; **RANK**: receptor activator of nuclear factor kappa-B; **TNFβ**: tumor necrosis factor-beta, lymphotoxin; **LTβR**: lymphotoxin β-receptor; **CD40L**: cluster of differentiation 40 ligand, CD154, protein expressed on T-cells; **CD40**: cluster of differentiation 40, costimulatory protein on T-cells; **BAFF**: B-cell activating factor, tumor necrosis factor ligand superfamily member 13B; **BAFFR**: B-cell activating factor receptor; **NIK**: NF-κB inducing kinase; **IKK complex**: IκB kinase enzyme complex to upregulate the NF-κB signaling; **IκBα**: IκB kinase 1 (IKK1); **IκBβ**: IκB kinase 2 (IKK2); **IκBγ**: IκB kinase gamma; **NEMO**: NF-kappa-B essential modulator, regulatory scaffolding protein; **P**: phosphorylated; **p100**: NF-κB2 (p52) precursor protein; **p52**: NF-κB2; **RelB**: transcription factor RelB. Non-canonical NF-κB-IKK-complex is the inactive cytoplasmic form, consisting out of **IκBα**, **p52** and **RelB**. The non-canonical NF-κB heterodimer is the active form entering into the nucleus consisting out of **p52** and **RelB**.

alpha (HIF1α) and STAT3, resulting in decreases of E-cadherin and apoptosis. Nuclear protein 120 (p120) accumulation stimulated by TGF-β and LOX promotes cell division control protein 42 homolog (cdc42) activating Ras-related C3 botulinum toxin substrate 1 (Rac1), further decreasing E-cadherin and increasing matrix metalloproteinases (MMPs), fibronectin, vimentin, and twist-related protein 1 (TWIST), zinc finger E-box-binding homeobox 1 (ZEB1), and ZEB2 [123].

The proinflammatory cytokine, interleukin 32 (IL-32), induces NF-κB. Gastric cancer patients were more often IL-32 positive than negative for IL-32 expression ($p < 0.01$) and the five-year survival rate of the IL-32 positive group was 56%, significantly higher than the IL-32

negative group ($p < 0.01$). Multivariate analysis showed that IL-32 expression was an independent prognostic marker for gastric cancer ($p < 0.05$) after lymph node stage and metastasis [243].

NF-κB is constitutively found within the nucleus in B-lymphocytes and dendritic cells and inactive NF-κB is usually found in the cytoplasm where it can be triggered by inhibitory proteins, such as nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (IκBα). Activation can also occur by cytokines, bacteria, viruses, or chemical agents, which result in phosphorylation (pNF-κB). Activation of NF-κB was also shown to be triggered by Cox-2 or IL-6 with increases in TNFα, IL-β1 as well as production of prostaglandin-E2 (PGE2,

Figure 4. NF- κ B signaling and crosstalk during carcinogenesis – Special Issue: Disruption of homeostasis-induced signaling and crosstalk in the carcinogenesis paradigm “*Epistemology of the origin of cancer*”. Simplified scheme of NF- κ B signaling and crosstalk during carcinogenesis in the Disruption of signaling homeostasis induced crosstalk in the carcinogenesis paradigm “*Epistemology of the origin of cancer*” consisting of a six-step sequence: (1) a pathogenic stimulus followed by (2) chronic inflammation from which develops (3) fibrosis with associated remodeling of the cellular microenvironment; and from these changes a (4) precancerous niche (PCN), a product of fibrosis, with remodeling by persistent inflammation, develops which triggers the deployment of (5) a chronic stress escape strategy and when this fails resolve it by (6) normal cell to cancerous cell transition (NCCCT) by PCN-induced cell matrix stress occurs. This figure was published in paper 2 of this Special Issue [189] and modified in accordance to NF- κ B signaling and crosstalk. *Nomenclature:* Common abbreviations are bold, followed by the common trivial names (if available) and (if available) by the name in accordance to the International Union of Pure and Applied Chemistry (IUPAC): **PCN**: precancerous niche; **CSES**: chronic stress escape strategy; **NCCCT**: normal cell to cancerous cell transition; **SphK**: sphingosine kinase isoform; **S1P**: sphingosine-1-phosphate; **IL-6**: interleukin 6; **IL-8**: interleukin 8; **TNF α** : tumor necrosis factor alpha; **IFN γ** : interferon gamma; **ALOX**: lipoxygenase, arachidonate lipoxygenase; **ALOX12**: 12-lipoxygenase, 12-LOX, 12S-LOX, arachidonate 12-lipoxygenase 12S type; **ALOX5**: 5-lipoxygenase, 5-LOX, arachidonate 5-lipoxygenase; **12-HETE**: 12-hydroxyeicosatetraenoic acid; **LTA4**: leukotriene A4, 4-[(2S, 3S)-3-[(1E,3E,5Z,8Z)-tetradeca-1,3,5,8-tetraenyl]oxiran-2-yl]butanoic acid; **LTB4**: leukotriene B4, (5S,6Z,8E,10E,12R,14Z)-5,12-dihydroxyocta-6,8,10,14-tetraenoic acid; **LTC4**: leukotriene C4, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-[(4S)-4-amino-4-carboxybutanoyl]amino]-3-(carboxymethylamino)-3-oxopropyl]sulfanyl-5-hydroxyocta-7,9,11,14-tetraenoic acid; **LTD4**: leukotriene D4, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-amino-3-(carboxymethylamino)-3-oxopropyl]sulfanyl-5-hydroxyocta-7,9,11,14-tetraenoic acid; **LTE4**: leukotriene E4, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-amino-2-carboxyethyl]sulfanyl-5-hydroxyocta-7,9,11,14-tetraenoic acid; **5-oxo-EETE**: (6E,8Z,11Z,14Z)-5-oxoocta-6,8,11,14-tetraenoic acid; **Cox**: cyclooxygenase; **Cox-1**: cyclooxygenase 1; **Cox-2**: cyclooxygenase 2; **Cox-3**: isoform of Cox-2 (therefore in brackets); **PGG2**: prostaglandin G2, (Z)-7-[(1S,4R,5R,6R)-5-[(E, 3S)-3-hydroperoxyoct-1-enyl]-2,3-dioxabicyclo[2.2.1]heptan-6-yl]hept-5-enoic acid; **PGH2**: prostaglandin H2, (Z)-7-[(1S,4R,5R, 6R)-5-[(E,3S)-3-hydroxyoct-1-enyl]-2,3-dioxabicyclo[2.2.1]heptan-6-yl]hept-5-enoic acid; **PGFF2 α** : prostaglandine F2 alpha, (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]cyclopentyl]hept-5-enoic acid; **PGD2**: prostaglandin D2, (Z)-7-[(1R,2R,5S)-5-hydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]-3-oxocyclopentyl]hept-5-enoic acid; **PGE2**: prostaglandin E2, (Z)-7-[(1R,2R,3R)-3-hydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]-3-oxocyclopentyl]hept-5-enoic acid; **MDA**: malondialdehyde, propanedial; **TXA2**: thromboxane A2, (Z)-7-[(1S,2S,3R,5S)-3-[(E,3S)-3-hydroxyoct-1-enyl]-4,6-dioxabicyclo[3.1.1]heptan-2-yl]hept-5-enoic acid; **CYP***: cytochrome P450 isoforms; **20-OH-PGE2**: 20-hydroxy prostaglandin E2; **20-HETE**: 20-hydroxyeicosatetraenoic acid, (5Z,8Z,11Z,14Z)-20-hydroxyocta-5,8,11,14-tetraenoic acid; **SOX**: [sex-determining region Y (Sry) box-containing] transcription factor family; **IL- β 1**: interleukin beta 1; **IL-33**: interleukin 33; **ROS**: reactive oxygen species; **CXC CC**: chemokine receptors; **α SMAD**: alpha-smooth muscle actin; **miR21**: micro RNA-21; **p300**: protein 300 (p300-CBP coactivator family); **SP1**: specificity protein 1; **AP1**: activator protein 1; **E2F4/5**: cytoplasmic complex of Smad3, retinoblastoma-like protein 1 (P107, RBL1), E2F4/5 and D-prostanoid (DP1); **p107**: retinoblastoma-like protein 1, RBL1; **TGF β** : transforming growth factor beta; **Pro-MMP-9**: pro-matrix metalloproteinase 9; **Pro-MMP-1**: pro-matrix metalloproteinase 1; **Pro-MMP-7**: pro matrix metalloproteinase 7; **SNAIL**:

(Z)-7-[(1R,2R,3R)-3-hydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl]hept-5-enoic acid) [97, 244–247].

Caspase-associated recruitment domain 6 (CARD6)

CARDs are important in virus infections and in interactions with mitochondria and innate immunity [248]. CARDs exist as inactive zymogens and are activated with adaptor molecules containing CARD and involved in apoptosis and inflammation through NF- κ B signaling [249]. The microtubule-associated protein, CARD6, increases receptor-interacting protein1 and 2 (RIP1 and 2) triggering mitogen-activated protein kinase kinase kinase 3 (MEKK3) which induces NF- κ B. CARD6 acts as a NF- κ B modulator [250].

Kim et al. analyzed 100 gastric carcinoma (GC) and 58 esophageal squamous cell carcinoma (ESCC) tissues and 103 colorectal cancer (CRC) specimens and found increased CARD6 expression in ESCC (70.7%), GC (45%) and CRC (78.6%) compared to adjacent normal epithelium used as controls [251]. The GC expression was higher in intestinal type GC (77.8%) according to the Lauren classification compared to diffuse GC (20%).

Chronic inflammation by *H. pylori* increases Cox-2 [252] resulting in an increase of NF- κ B, which also can be activated by Akt. This results in an increase of Snail and a decrease of E-cadherin resulting in compromised tissue integrity, increased cell detachment, and greater invasive potential, which serves as a precursor to metastasis [253].

Activation of NF- κ B occurs by cysteine-rich 61 (Cyr61, CCN family member 1, CCN1) which promotes the expression of Cox-2 mRNA as suppression of Cyr61-mediated NF- κ B activation, Cox-2 gene expression, and invasiveness can be achieved by applying function-neutralizing antibodies to alphavbeta3 (but not to alphavbeta5) [254, 255]. NF- κ B activation signaling also occurs through the ubiquitin-proteasome pathway [256].

Lipopolysaccharide (LPS) of bacteria was previously shown to induce NF- κ B in pre-B cells ([3, 168] reviewed in [257]).

There is extensive cytokine involvement in inflammation. An example is the sequential events in interleukin 1 (IL-1) binding to its receptor, thereby demonstrating that tyrosine kinase signaling is essential [258]: IL-1 triggers tyrosine kinase activity and NF- κ B protein activation followed by NF- κ B protein binding to NF- κ B1 site in gro-promoter regions and simulating the growth-related oncogenes (*gro*).

The previous term “*gro-oncogenes*” is synonymous with *gro1* oncogene, *gro α* , KC, neutrophil-activating protein 3

(NAP-3), and melanoma growth stimulating activity alpha (MSG α - α) all of which are now summarized by the chemokine (C-X-C motif) ligand 1-3: CXCL1 (*gro α*), CXCL2 (*gro β*), and CXCL3 (*gro γ*). The isolation and characterizing of the CXCL/*gro*-oncogenes occurred within the last three decades (reviewed in [259]): *gro α* [260], *gro β* and *gro γ* [261, 262].

Increased *gro α* expression in melanoma enhances “*colony-forming activity and tumorigenicity*” in nude mice ([263] reviewed in [28]). The inhibition of NF- κ B by sodium salicylate or nuclear factor NF-kappa-B protein 65 (p65) subunit (p65) RNA results in decreases of *gro α* and *gro β* expression [28].

The constitutive expression of *gro α* and its receptor CXCR2 (*gro α* receptor) was shown to be associated with metastatic potential, modulation of cancer cell proliferation, and with an invasive phenotype [264].

The chemokine family members “*are divided into four main classes based on their cysteine (C) residue sequence: the CXC chemokines, the CC chemokines, the C chemokines, and the CX3C chemokines, in which X represents any amino acid*” ([265] reviewed in [266]). Their roles are complex with the immunology in different cell compartments versus when carcinogenesis is completed and cancer cells result. Chemokines are therapeutically promising in inhibiting angiogenic CXC chemokine ligands and/or receptors as options to decrease cancer cell development or to decrease metastasis [267, 268].

Another ubiquitous protein is valosin-containing protein (VCP, CDC48) which can be stimulated by IL-6 and results in the progression of prostate cancer LNCaP cells through proto-oncogene serine/threonine-protein kinase (Pim-1) via signal transducer and STAT3 signaling [269]. Transfecting LNCaP cells for VCP overexpression resulted in an increase in cell proliferation, migration, and invasive behavior. VCP expression is also involved in the regulation of NF- κ B activation [270, 271]. Yamamoto et al. found VCP to be an independent factor in multivariate analysis in GC patients for disease-free progression and overall survival, for lymph node metastasis ($P < 0.01$), and depth of invasion ($P < 0.01$) [272, 273].

A member of the IL-1 family, interleukin 33 (IL-33), is involved in carcinogenesis and high doses result in inflammation, mucosal atrophy and metaplasia in the gastric fundus in mice, with concurrent increases in IL-6 and interleukin 9 (IL-9) expression. IL-33 also binds to interleukin 1 receptor-like 1 (IL1RL1, ST2) and IL-1 receptor protein IL1-RAP activating NF- κ B and MAPK signaling ([274] reviewed in [275]).

Figure 4. (Continued) zinc finger protein SNAI1; **MMP-1:** matrix metalloproteinase 1; **MMP-7:** matrix metalloproteinase 7; **MMP-2:** matrix metalloproteinase 2; **E-Cadherin:** CAM 120/80 or epithelial cadherin, cadherin-1, epithelial cadherin; **CXCL1:** chemokine (C-X-C motif) ligand 1; **Osm:** oncostatin-M; **PI3K:** phosphatidylinositol 3-kinase; **FOXO3a:** forkhead box protein O3a; **p120:** catenin delta-1, protein 120; **Rho:** Ras homolog gene family, member A; **Rac1:** Ras-related C3 botulinum toxin substrate 1; **cdc42:** cell division control protein 42 homolog; **BIM:** Bcl-2 interacting mediator of cell death; **PUMA:** BH3-only protein; **CXCR4:** C-X-C motif of chemokine receptor 4; **cdk2:** cyclin-dependent kinase 2; **LOXL3:** lysyl oxidase homolog 3; **mTORc1:** rapamycin complex 1; **PAI1:** Plasminogen activator inhibitor-1; **NF- κ B:** nuclear factor kappa-light-chain-enhancer of activated B cells.

Exosomes derived from GC cells have the ability to sustain chronic inflammation by activating macrophages through phosphorylation of NF- κ B in macrophages [276].

Knockdown of the cytoskeleton protein, Radixin, together with the NF- κ B/Snail signaling resulted in an increase of E-cadherin with suppression of metastasis in human gastric carcinoma SGC-7901 cells [277]. Radixin is also involved in the transition of a normal cell to a cancer cell: Akt phosphorylates Ezrin (pEzrin), which is a member of the ERM (Ezrin/Radixin/Moesin) proteins. High levels of pEzrin together with increased vimentin, and decreased E-Cadherin levels, were seen in tongue squamous cell carcinoma patients with poor prognosis and metastasis [278]. Vimentin is induced by NF- κ B and TGF- β 1 and is an independent predictor of recurrence after radical prostatectomy [279].

NF- κ B signaling and crosstalk during carcinogenesis in fibrosis and remodeling

The association of NF- κ B signaling and fibrosis due to various pathogenic stimuli have been previously reviewed. The involvement of NF- κ B and fibrosis in carcinogenesis has been recognized for some 20 years [280, 281]. IL-1 induces NF- κ B with consequent c-myc expression in fibroblasts [282]. Yokoo et al. showed that NF- κ B together with c-Jun/AP1 activation is needed to induce MMP-9 in glomerular mesangial cells and IL- β 1 [283]. In human gingival fibroblasts, NF- κ B is induced by IL-1 [284].

MMP-9 induction in malignant glioma cells needs actin polymerization with consequent MMP-9 modulation [285]. LOX, and especially LOXL2, are major players in remodeling the tumor microenvironment to create the PCN for the transition of a normal cell to a cancer cell [123, 286]. LOXL2 promotes cell proliferation and inhibits apoptosis via a regulator of cellular homeostasis: myristoylated alanine-rich C kinase substrate-like 1 (MARCKSL1) [287].

Keratin 8 (K8) is involved in the development of papillomas to malignant tumors in transgenic mice [288] and has a regulatory signaling effect on target of methylation-mediated silencing (TMS1), MARCKSL1, Ran-specific binding protein 1 (RanBP1), tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein gamma (14-3-3 γ), Rho GDP-dissociation inhibitor 2 (Rho-GDI2) and K8 loss results into alteration of TMS1 NF- κ B signaling [289].

NF- κ B signaling is increased in the precancerous lesion, oral submucosal fibrosis (OSF) compared to human buccal mucosal fibroblasts (BMFs) [44]. Another regulator of transcription interacting with NF- κ B is the DNA repair protein, Ku [290]. The double-strand repair of DNA with its DNA repair protein, Ku activity, can be mediated by NF- κ B activity affecting cell growth and proliferation [291, 292].

Inflammatory signaling induces chronic stress with consequent fibrosis and a remodeled tumor microenvironment which leads to the PCN [293]. Even for stress-induced lymphatic remodeling, chronic inflammatory signaling is necessary [294]. Such chronic stress results in the disruption of

homeostasis, which uncorrected, leads to carcinogenesis [286]. With regard to NF- κ B, protein kinase RNA-like endoplasmic reticulum kinase (PERK) appears to be important since it functions as a sensor of UPR [295] – next to inositol-requiring enzyme 1 (Ire1) and activating transcription factor 6 (ATF6) [296].

The transcription factor STAT3 induces IL-6 and modulates PERK “*independently of the classic canonical I κ B α signaling pathway*” [295]. Fan et al. showed that inhibition of PERK interfered with “*DNA binding of both STAT3 and NF- κ B, thereby preventing induction of NF- κ B-dependent genes and E2-induced apoptosis*” in breast cancer cells.

The PCN consists of an altered tumor microenvironment that also induces chemoresistance by fibroblast-derived IL-6 upregulating the cell membrane receptor C-X-C motif of chemokine receptor 7 (CXCR7, G-protein coupled receptor 159, GPR159, atypical chemokine receptor 3) via NF- κ B [297].

Thelen M and Thelen S investigated 45 ESCC tissues, normal esophageal cell line Het-1a and human ESCC lines TE1, TE7, EC109, KYSE70 and KYSE450 for chemoresistance mechanism and CXCR7 knockdown decreased gene expression associated with cell transition. Until recently it was assumed that CXCR7 “*does not mediate typical chemokine receptor responses*” [298] but Peng et al. demonstrated that inhibiting CXCR7 decreases chemotaxis of adipose tissue macrophages [299].

C-C chemokine receptor type 7 (CCR7) promotes invasion via activation of PI3K/Akt/mTOR signaling [300]. The PI3K/Akt/mTOR axis is associated with cell proliferation, migration and invasion in cancer [301] and activation through TGF- β 1 resulting in EMT [302].

HIF-1 α activation by inflammation induces cell transition via PI3K/Akt/mTOR [303] and inhibition results in apoptosis and autophagy [304]. The crosstalk between NF- κ B and PI3K/Akt/mTOR has been shown in lymphoma [305] and there is hope that targeting this pathway might be effective in anticancer therapy [306].

NF- κ B activation by CCR7 via PI3K/Akt/mTOR signaling is relevant as both NF- κ B and CCR7 are upregulated in head and neck cancers and promote cell invasion [300]. C-C chemokine receptor (CCR) together with chemokine (C-C motif) ligand 19 (CCL19) results in phosphorylation of I κ B α , the inhibitor of NF- κ B promoting NF- κ B translocation to the nucleus while inhibiting NF- κ B and CCR7/PI3K signaling increases apoptosis, cell arrest, and attenuated survival of SCCHN cells.

The novel PEST-containing nuclear protein (PCNP) along with the ubiquitin ligase ubiquitin-like, containing PHD and RING finger domains 1 (UHRF1, Np95)/ICBP90-like RING finger protein (NIRF), both located in the nucleus, were recently associated with increased NIRF expression in a human fibrosarcoma and hepatocellular carcinoma cell line (HT-1080, HepG2 cells) [307, 308]. PCNP mediates cell proliferation, migration and invasion in neuroblastoma through activating PI3K/Akt/mTOR together with MAPK [309].

NF- κ B regulates C-X-C chemokine receptor 4 (CXCR4) while the O-GlcNAc modification of p65-NF- κ B stimulates

its activity [310]. Prostate cancer cells showed dysregulation of NF- κ B and STAT1 signaling, a property dependent upon the cell line under investigation and the production of angiostatic CXC chemokines [311]: PZ-HPV-7 cells produce a high amount of CXC chemokines whereas a lower amount were observed in CA-HPV-10 and PC-3 cell lines.

NF- κ B signaling and crosstalk during carcinogenesis in cell transition

Transformation of a normal cell to a cancer cell is dependent on the microenvironment, the cell matrix, and transcription factors ([312] reviewed in [188]). NF- κ B is important for cell transition [313, 314].

Chronic application of TGF- β 1 to HeLa cells resulted in chronic inflammation with increased TNF α , with TGF- β 1 induced increase of epithelial-to-mesenchymal cell transition, and self-renewal [315]. This effect was dependent on NF- κ B and Twist1 and “*Overexpression of NF- κ Bp65 upregulated Twist and promoted EMT and cancer stem cell-like (CSCL) properties in HeLa cells exposed to inflammatory cytokines*”. The inhibition of TGF- β 1 by Disulfiram resulted in the inhibition of cell transition and stem cell features via extracellular signal-regulated kinase (ERK)/NF- κ B/Snail signaling [316].

Using an in vivo breast cancer model it was shown that the IKK-2/IkappaB α /NF- κ B pathway is required for introduction, maintenance, and cell transition, and that NF- κ B inhibition in mesenchymal cells reversed cell transition [317].

Inhibiting NF- κ B or TGF- β 1 signaling in prostate cancer PC-3 cell line decreased Vimentin expression as well as invasive cell capability. Cell transition was shown to be TGF- β 1 induced and mediated by NF- κ B. Investigating a large number of prostatectomy specimen revealed that high expressions of TGF- β 1, NF- κ B and vimentin together with low levels of cytokeratin 18 resulted in recurrence [279].

TGF- β 1 induces IL-6 through mothers against decapentaplegic homolog 2 (Smad2), p38-NF- κ B, c-Jun N-terminal kinase (JNK), and the protein superfamily of small guanosine triphosphate hydrolase enzymes (Ras, GTPases) in prostate cancer cell lines [318]. However, it seemed to matter as to which NF- κ B pathway and/or subunit was activated [319]. The inhibition of Akt and NF- κ B suppressed epidermal growth factor (EGF)-induced cell transition in a squamous cell carcinoma cell line of the tongue and facilitated both cell migration and invasion [278].

In a tetracycline model, activation of proto-oncogene c-Rel (cRel, transcription factor containing Rel homolog domain, RHD) activation with consequent nuclear expression, arrested cell proliferation in the G1/S-phase together with accumulation of hypophosphorylated retinoblastoma protein (Rb), increase of the cyclin-dependent kinase (CDK) inhibitor 1 (p21, CIP1/WAF1/CAP20/SDI1, p21^{WAF1}), reduced cdk2 activity, increased p53 protein stability [318]. cRel knockdown abolished these effects. This is concordant to cRel expression found in all hematopoietic tissues, but cRel is abundant in mature lymphocytes [320]

and induces cell proliferation and survival in mature B-Cells [321]. Furthermore, cRel induces apoptosis in avian fibroblasts [322] but this apoptosis can be inhibited by cRel activating the Bcl-2 homolog Bfl-1/A1 [323, 324]. However, it is not just the transcription factor itself, but that NF- κ B activation is dependent on which way NF- κ B acetylation/deacetylation occurs with its effect on other pathways such as HIF-1 [325].

TNF-like weak inducer of apoptosis (TWEAK), together with its fibroblast growth factor-inducible 14 (Fn14), has pro-inflammatory and tissue remodeling effects ([326] reviewed in [327]) and increases TGF- β 1 induced epithelial-mesenchymal transition in human bronchial epithelial cells and downregulates E-cadherin which requires p38 MAPK and NF- κ B [327]. The fibroblast growth factor-inducible 14 (Fn14) gene was located and isolated in 1999 and shown to modulate fibroblast adhesion [328]. The member of the TWEAK superfamily is a ligand to Fn14 meaning Fn14 serves as a receptor at the cell surface and TWEAK increases during cancer progression [329]. The absence of Fn14 is associated with carcinogenesis in colitis-associated cancer but Fn14 can be protective in an acute inflammatory situation [330]. Thus, Fn14 action is necessary in homeostasis and acts aberrantly when homeostasis is disrupted.

The Fn14 protein mediates NF- κ B activation [331] and contains NF- κ B binding sites [332]. TWEAK/Fn14 activation is also involved in the development of another chronic inflammatory disease, atherosclerosis, where it results in increases of MMP-9 through NF- κ B and involved in modulation of the ECM [333]. Fn14 is increased in various cancers such as glioblastoma [332], breast cancer [334], ovarian cancer [335], melanoma [336], non-small lung cancer [337], hepatocellular cancer (HCC) [338], pancreatic cancer [339], colon cancer [340], as well as in esophageal [341] and gastric cancer [342].

Fn14 knockdown showed that Fn14 affects cell growth through NF- κ B and B-cell lymphoma-extra large (Bcl-xL) in gastric cancer [342] and in small-cell lung cancer (SCLC) [343]. Microarray analysis comparing Barrett’s biopsies to surgically resected esophageal adenocarcinoma showed only Fn14 over expression when the biopsied Barrett’s epithelium was directly adjacent to esophageal adenocarcinoma [341] which was in contrast to a prior investigation [344]. We contend that this is related to the difference in the degree of development of the PCN.

The TWEAK/Fn14 axis is reported in biological pathogenic stimulus, such as HPV infection, triggering the switch of keratinocytes from apoptosis into proliferation [345]. TWEAK also regulates mesenchymal cells [346] and the switch to proliferation was also observed in endothelial cells [347]. Intraabdominal TWEAK application induced peritoneal inflammation with “*increased Fn14, MCP-1 and chemokine (C-C motif) ligand 21 (CCL21) expression and submesothelial tissue macrophage recruitment*” [348]. This might be relevant to a future understanding how peritoneal carcinomatosis develops and progresses. TWEAK induces next to changes of phenotype a decrease of cell-cell interaction and anchoring junctions such as E-cadherin,

Cadherin-16, β -catenin and adherens, and the tight junction protein Zonula occludens-1 (ZO-1) resulting in weaker epithelial integrity as well as epithelial-mesenchymal transition (EMT) which occur through Fn14 together with NF- κ B ERK activation and the vitamin D receptor modulation independent of TGF- β 1 [349].

TRADDs, TRAFs, RIPs, FADD, RANK signaling with NF- κ B

The TNF superfamily contains multiple transmembrane proteins that interact with the TNF receptor superfamily (TNFRSF) and various cytokines, named TNF-related activation-induced cytokines (TRANCE), which are expressed on cell surfaces, such as activated T-cells and osteoblasts [350]. TNF receptors need an adaptor protein such as TNF receptor type 1-associated DEATH domain proteins (TRADDs), TNF receptor associated factors (TRAFs), receptor-interacting protein kinases (RIPs) and/or Fas-associated protein with death domain (FADD) [351]. TNFs, TNFRSFs as well as TRANCE, TRADDs, TRAFs and RIPs and FADDs are of importance in the signaling and crosstalk with NF- κ B [352, 353].

The disruption of bone homeostasis affecting osteoclastogenesis and osteoblastogenesis is important in the elderly who may be osteoporotic, and apparently with cancers connected by multiple signaling pathways of cytokines, hormones, and growth factors [354–356]. Bone remodeling is of importance in prostate cancers. In a routine autopsy study among 19,316 individuals from 1967 to 1995, 8.2% (1589) had prostate cancers and, of these, hematogeneous metastasis were most frequently observed (90%) in the bone of men older than 40 years [357]. The NF- κ B signaling pathway is involved here as well.

The receptor of nuclear factor kappaB (RANK) was discovered in 1997 [358] and is of importance together with its receptor activator of NF- κ B ligand (RANKL), and decoy receptor osteo NF- κ B protegerin (OPG), as expression analysis of the RANKL/RANK/OPG axis correlates with aggressive advanced and metastatic prostate cancers [359].

Esophageal high-grade dysplasia tissue revealed a weaker RANK immunoreactivity compared to 23 esophagectomy cancer specimens [360], and investigating 309 ESCC showed that RANK over expression was associated with a poor prognosis [361]. Increased RANK expression was found in breast cancer [358, 362–364]. As reviewed recently, RANK signaling targets various pathways, such as the PI3K/Akt axis, MAPK signaling (JNK, ERK and p38), and NF- κ B [365]. RANK promotes IL-1, IL-6 and interleukin 12 (IL-12) and the RANK signaling pathway is mediated by the adaptor protein TRAF6 to induce osteoclast differentiation [366].

TGF- β 1 mediated NF- κ B activation induces expression of metalloproteinase 12 (ADAM-12) in a dose-dependent manner in MDA-MB-231 breast cancer cells [367]. The gene expression signature studied by Ooi et al. identified proliferation/stem cell- and Wnt/ β -catenin- signaling as well as deregulation of the NF- κ B pathway in more than 70% of gastric cancers [368].

NF- κ B influences transcription-dependent genes by binding to specific sections of DNA (κ B-motif) [369] and thus has numerous target genes which mediate its varied effects [370]. The κ B-motif, by itself, has a certain degree of variability which suggests that it has the ability to fine tune its effects [371]. NF- κ B counteracts senescence induced by oncogenes and thus drives pro-carcinogenic inflammation [117, 179]. KO experiments of the NF- κ B-pathway revealed that NASPs occur upstream of TNF receptor-associated factor 6. After transduction of NASPs into the fibroblasts of mice and rats resulted in the co-expression of Ras (H-Ras V12) and revealed that rodent fibroblasts mastered the p53-dependent senescence which is mediated by H-Ras V12 and this in turn resulted in a transformed carcinogenic phenotype [117]. These observations underly the different functions of NF- κ B and its cooperation with Ras as an oncogene by the attenuation of p53 as well its effects on the inflammatory cascade.

NF- κ B Inhibition

In 1992, p65 antisense oligonucleotide treatment in mice gave hope that anti-NF- κ B therapy could be useful against cancer [115]. 7,12-dimethylbenz-(a)anthracene (DMBA) treatment in rats showed NF- κ B activation with the development of mammary gland cancer [54]. NF- κ B activation in fibroblasts in hormone-independent ER negative cancers occurs through IL-6 and urokinase plasminogen activator (uPA) dependent on interleukin 1 alpha (IL-1 α) [56].

There is potential to using anti-NF- κ B therapy in gastric cancer patients because Cyclosporin A increased docetaxel (Taxotere)-induced apoptosis through the activation of NF- κ B in human gastric cancer cells and thereby prevented the anti-apoptotic NF- κ B effect [372]. This may explain why NF- κ B data were generated in upper GI cancers. However, the reality of immunosuppressed patients who have undergone organ transplants is different as such patients have an increased risk of developing cancer later [373]. Furthermore, this might serve as an example that inhibition of a single signaling pathway is not enough in diseases such as cancer as *cancer occurs from the broader disruption of homeostasis* [189–191, 286, 293]. It has been reported that targeting NF- κ B might have a therapeutic effect in cancer treatment [374–376].

Preventing NF- κ B activation does not alter deoxycholate-induced apoptosis, suggesting that NF- κ B may not be essential for apoptosis and likely represents just one of many signaling pathways. However, aspirin prevents the deoxycholate-induced apoptosis although it has not been shown to have a direct anti- NF- κ B effect [377]. This illustrates the complexity of the various pathways involved.

Urokinase-type plasminogen activator receptor (uPAR) together with uPA forms a complex that is associated with tumor cell invasion and that affects cell motility and integrin function ([378, 379] reviewed in [380]). The uPAR expression through NF- κ B suppression was demonstrated by investigating the diterpenoid triepoxide, triptolide from the Chinese herb *Tripterygium wilfordii* Hook F.

NF- κ B was also implicated in cancer with regard to 5-fluorouracil (5-FU). Scientists showed an induction of NF- κ B by 5-FU application within human gastric adenocarcinoma cell line, NUGC3 cells (5-fluorouracil sensitive), but not within NUGC3/5FU/L cells, which are 5-fluorouracil resistant. The inhibition of NF- κ B reduced chemoresistance and increased apoptosis again lends credence to the likelihood of addressing a huge problem in chemotherapy, namely the development of chemoresistance [381]. Inhibition of NF- κ B-dependant signaling might overcome bromodomain and extra terminal protein inhibitors (BETi) resistance in uveal melanoma [382]. Additionally, paeoniflorin from *Paeonia lactiflora*, can inhibit NF- κ B activity in gastric SGC-7901 cancer cells with consequent increases of 5-FU induced apoptosis [383].

Non-steroidal anti-inflammatory drugs (NSAID)

The NSAID drug aspirin and sodium salicylate suppresses NF- κ B [384] and prostaglandin production by inhibiting cyclooxygenase 1 (Cox-1, prostaglandin G/H synthase 1) and Cox-2 and is effective in suppressing colon cancer growth but only at high concentrations [385]. The investigation of the mechanism of ibuprofen showed that it activates IkappaB kinase alpha with consequent inhibition of the activation of NF- κ B and IKK α in human prostate cell lines (hormone-independent cell lines, PC-3 and DU-145) and it may be noted that ionizing PC-3 cells did not result in NF- κ B modulated DNA-binding activity [386].

Metformin

Metformin inhibits inflammatory response and malignant cell transformation [387]. It also inhibits NF- κ B in a dose-dependent manner [388]. Metformin decreases both pro-inflammatory cytokines and NF- κ B and improves the immune response to cancer cells in colorectal, prostate, pancreatic, renal, cervical, endometrial, gastric, lung, breast, and ovarian cancer (reviewed in [389]). These findings, and the fact that NF- κ B signaling triggers E-cadherin downregulation, and enhanced by connective tissue growth factor (CTGF, CCN2): it is upregulated in gastric cancer tissues promoting cell proliferation and metastasis [390] which explain recent signaling pathways identified during carcinogenesis as affecting the disruption of homeostasis [189–192, 286, 293, 388, 391]. Furthermore, Metformin decreases NF- κ B in the soleus muscle of diabetic rats and increases its inhibitor, I κ B [392]. The transcriptional factors NF- κ B and STAT3 are ubiquitously expressed and operate in concert to promote cancer development and progression of colon, gastric and liver cancers [393].

Silibinin

The polyphenolic flavonoid, Silibinin, is an extract from milk thistle (*Silybum marianum*) and was earlier reported to have an anticancer effect [394–397]. Silibinin is a direct STAT3 inhibitor [398] with no direct effect on apoptosis or changes in p53 and bcl2 [395]. Silibinin inhibits NF- κ B p50 translocation via the upregulation of I κ B and

downregulates ZEB1 and Zinc finger protein SNAI2 (SLUG) transcription factors, and can reverse cell transition [399]. In colon carcinoma, protein levels of Bcl-2, Cox-2, iNOS, VEGF and MMPs, which are also NF- κ B-regulated molecules, can be decreased in cell culture and xenograft analyses by the application of Silibinin due to inhibition of nuclear p50 (NF- κ B1) and 65 translocation [400].

NF- κ B signaling balances between apoptosis versus necrosis both at host and tumor interfaces through various pathways, which reveal that the weight of disruption of homeostasis in this regard determine which effect will prevail.

Caffeic acid phenethyl ester (CAPE)

Another inhibitor of NF- κ B activity and chronic inflammation with reduced expression of mediators such as TNF α , interferon gamma (IFN γ), IL-2, IL-6, KC (IL-8 homologue), and inducible iNOS is the anti-inflammatory caffeic acid phenethyl ester (CAPE) in *H. pylori*-induced gastritis in *Mongolian gerbils* [401]. NF- κ B activity was also shown to be suppressed by the novel oligosaccharide, JG3, derived from marine oligomannuric acid which results in tumor growth in xenograft models [402].

Furthermore, more detailed information of inhibitory effects of potential anti NF- κ B compounds were confirmed in TNF α induced NF- κ B *bla* assay investigating 2800 clinically approved drugs and bioactive compounds from the NIH Chemical Genomics Center Pharmaceutical Collection (NPC) [403]. Nineteen drugs inhibiting NF- κ B with potencies as low as 20 nM were identified: bithionol, bortezomib, cantharidin, chromomycin A3, daunorubicin, digitoxin, ectinascidin 743, emetine, flurosalan, manidipine hydrochloride, narasin, lestaurtinib, ouabain, sorafenib tosylate, su-11274, tioconazole, tribromsalan, trichlorfon and zafirlukast. Some induce NF- κ B inhibition through inhibition of IkappaB α phosphorylation (emetine, flurosalan, sunitinib malate, bithionol, narasin, tribromsalan, and lestaurtinib).

However, as a disruption of homeostasis in NF- κ B signaling also results in the consequent various activation/deactivation of pathways, the expectations may have to be toned down, especially as it has been shown that some classical drugs may act as NF- κ B modulators or IKK β inhibitors [404]. For example, the compound salvianolic acid C (SalC) isolated from the plant, *Salvia miltiorrhiza* Bunge, can inhibit “LPS-induced inflammatory response and NF- κ B activation through the activation of AMPK/Nrf2 signaling both *in vivo* and *in vitro*” [405].

Otherwise, having an anti-NF- κ B therapeutic modality might result into unwanted effects. Nrf2 is responsible for migration and invasion in cancers of the cervix [406], and aggressiveness in various cancers, such as breast cancer [407, 408], gastric cancer [409] and colorectal cancer [410], or responsible for drug resistance in glioma and melanoma [411].

This reveals how carefully any anti-NF- κ B approach needs to be investigated prior to drawing conclusions about its role in a specific anticancer regimen.

Summary

The available information on NF- κ B expression in tissues provides a perspective on understanding signaling and crosstalk during pathogenic stimuli and carcinogenesis. This provides a rational basis to investigate NF- κ B and to implement an anti-NF- κ B therapy into existing anti-cancer treatment regimens, when appropriate. For this, the NF- κ B interplay in sequences that contribute to carcinogenesis such as chronic inflammation, remodeled fibrosis with the precancerous niche (PCN), and the transition of a normal cell to a cancer cell is essential. However, inhibition of a single signaling pathway is not enough in diseases such as cancer as *cancer occurs from the broader disruption of homeostasis*.

Nomenclature of abbreviations

5-FU	5-fluorouracil
5-oxo-EETE	(6E,8Z,11Z,14Z)-5-oxoicosa-6,8,11,14-tetraenoic acid
12-HETE	12-hydroxyeicosatetraenoic acid
14-3-3 γ	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein gamma
20-HETE	20-hydroxyeicosatetraenoic acid, (5Z,8Z,11Z,14Z)-20-hydroxyicosa-5,8,11,14-tetraenoic acid
20-OH-PGE2	20-hydroxy prostaglandin E2; 20-HETE 20-hydroxyeicosatetraenoic acid, (5Z,8Z,11Z,14Z)-20-hydroxyicosa-5,8,11,14-tetraenoic acid
α -SMA	Alpha smooth muscle actin, alpha-actin-2
11 β -HSD1	11 β -hydroxysteroid dehydrogenase type 1
ADAM-12	Matrix metalloproteinase 12 (MMP-12)
AFT3	Activating transcription factor 3
AIDS	Acquired immune deficiency syndrome
Akt	Protein kinase B
ALOX	Lipoxygenase, arachidonate lipoxygenase
ALOX5	5-lipoxygenase, 5-LOX, arachidonate 5-lipoxygenase
ALOX12	12-lipoxygenase, 12-LOX, 12S-LOX, arachidonate 12-lipoxygenase 12S type
AMPK	5' adenosine monophosphate-activated protein kinase (AMP)-activated protein kinase
ANXA2	Annexin II
AP1	Activator protein 1
APO-1	Apoptosis antigen 1 (APT), cluster of differentiation 95, CD95, first apoptosis signal receptor (Fas, FasR)
APT	Apoptosis antigen 1 (APO-1), cluster of differentiation 95, CD95, first apoptosis signal receptor (Fas, FasR)
ATF6	Activating transcription factor 6
BAFF	B cell-activating factor belonging to the tumor necrosis factor (TNF) family
BAFFR	B-cell activating factor receptor

BAG-1	BAG family molecular chaperone regulator 1
Bax	B-cell lymphoma 2 (Bcl-2)-associated X protein
Bcl-2	B-cell lymphoma 2
Bcl-3	B-cell lymphoma 3
BCR	B-cell receptor
BETi	Bromodomain and extra terminal protein inhibitor
BIM	Bcl-2 interacting mediator of cell death
BiP	Binding immunoglobulin protein, 78 kDa glucose-regulated protein (GRP-78), heat shock 70 kDa protein 5 (HSPA5)
BMF	Buccal mucosal fibrosis
Btk	Bruton's tyrosine kinase
C	Cysteine
CaMKII	Ca ²⁺ /calmodulin-dependent protein kinase II
cAMP	Cyclic 5' adenosine monophosphate (AMP)
CAPE	Caffeic acid phenethyl ester
CARD6	Caspase-associated recruitment domain 6
CBP	Co-activator CREB binding protein
CCAAT	Cytosine-cytosine-adenosine-adenosine-thymidine
CCC	Cholangiocellular carcinoma
CCL2	Chemokine (C-C motif) ligand 2, monocyte chemoattractant protein 1, MCP-1
CCL3	Chemokine (C-C motif) ligand 3, macrophage inflammatory protein 1 alpha (MIP1 α)
CD14	Cluster of differentiation 14
CD40	Cluster of differentiation 40, costimulatory protein on T-cells
CD40L	Cluster of differentiation 40 (CD40) ligand, CD154, protein expressed on T-cells
CD54	Cluster of differentiation 54, intercellular adhesion molecule 1 (ICAM-1)
CD62	Cluster of differentiation 62
CD62E	Cluster of differentiation (CD62, endothelial-leukocyte adhesion molecule 1, E-selectin) antigen-like family member E (leukocyte-endothelial cell adhesion, molecule 2, LECAM2)
CD95	Cluster of differentiation 95, first apoptosis signal receptor (Fas, FasR), apoptosis antigen 1 (APO-1, APT)
CD106	Cluster of differentiation 106, vascular cell adhesion protein 1, vascular cell adhesion molecule 1 (VCAM-1)
CD154	Cluster of differentiation 154
cdc42	Cell division control protein 42 homolog
CDK	Cyclin-dependent kinase
cdk2	Cyclin-dependent kinase 2
CDX2	Homeobox protein CDX-2
C/EBP β	CCAAT/enhancer-binding protein β

cagA	<i>Helicobacter pylori</i> virulence factor CagA, cytotoxin-associated gene A	EGFR	Epidermal growth factor receptor (ErbB-1, HER1)
CCL19	Chemokine (C-C motif) ligand 19	ELAM-1	Endothelial-leukocyte adhesion molecule 1
CCL21	Chemokine (C-C motif) ligand 21	E-selectin	Endothelial-leukocyte adhesion molecule 1, cluster of differentiation (CD62) antigen-like family member E (CD62E), leukocyte-endothelial cell adhesion molecule 2 (LECAM2)
CCN1	CCN family member 1, cysteine-rich 61 (Cyr61)		
CCN2	Connective tissue growth factor (CTGF)		
CCR	C-C chemokine receptor		
CCR7	C-C chemokine receptor type 7	ERK	Extracellular signal-regulated kinase
CHOP	Cytosine-cytosine-adenosine-adenosine-thymidine (CCAAT)/enhancer binding protein homologous protein	ESCC	Esophageal squamous cell carcinoma
Cox	Cyclooxygenase	FADD	Fas-associated protein with death domain
Cox-1	Cyclooxygenase 1, prostaglandin G/H synthase 1	Fas	First apoptosis signal receptor (FasR), apoptosis antigen 1 (APT, APO-1), cluster of differentiation 95 (CD95)
Cox-2	Cyclooxygenase 2	Fn14	Fibroblast growth factor-inducible 14
Cox-3	Isoform of Cox-2 (therefore in brakes)	FOXO3a	Forkhead box protein O3a
CRC	Colorectal carcinoma	FXR	Farnesoid X receptor
CREB	cAMP response element-binding protein	GC	Gastric carcinoma
cRel	Proto-oncogene c-Rel, transcription factor containing Rel homolog domain (RHD)	GC-C	Guanyl cyclase 2
CSES	Chronic stress escape strategy	GERD	Gastro-esophageal reflux disease
CTGF	Connective tissue growth factor (CCN2)	GHS-R	Growth hormone secretagogue receptor
Cyclin B1	G2/mitotic-specific cyclin-B1	GM-CSF	Granulocyte-macrophage colony-stimulating factor
Cyclin D1	G1/S phase transition specific cyclin-D1	gro	Growth-related oncogene
Cyclin E	G1-to-S phase transition specific cyclin-E	gro- α	Growth-related oncogene alpha, CXCL1
CXC CC	Chemokine receptors	gro- β	Growth-related oncogene beta, CXCL2
CXCL1	Chemokine (C-X-C motif) ligand 1	gro- γ	Growth-related oncogene gamma, CXCL3
CXCL8	Chemokine (C-X-C motif) ligand 8, interleukin 8 (IL-8)	GSK3 β	Glycogen synthase kinase-3 β
CXCR2	Gro- α receptor	GTP	Guanosine triphosphate hydrolase enzyme
CXCR4	C-X-C chemokine receptor 4	GTPase	Guanosine triphosphate (GTP) hydrolase enzyme, transforming protein p21, HRas, H-ras
CXCR7	C-X-C motif of chemokine receptor 7 (G-protein coupled receptor 159, GPR159, atypical chemokine receptor 3)	<i>H. pylori</i>	<i>Helicobacter pylori</i>
CYP*	Cytochrome P450 isoforms	<i>H. bilis</i>	<i>Helicobacter bilis</i>
Cyr61	Cysteine-rich 61, CCN family member 1 (CCN1)	HBsAg	Hepatitis B surface antigen
DMBA	7,12-dimethylbenz-(a)anthracene	HBV	Hepatitis B virus
DNA	Deoxyribonucleic acid	HBx	Hepatitis B viral protein
dsRNAs	Double-stranded RNAs	HCC	Hepatocellular carcinoma
E2F4/5	Cytoplasmic complex of Smad3, retinoblastoma-like protein 1 (P107, RBL1), E2F4/5 and D-prostanoid (DP1)	HCV	Hepatitis C virus
<i>E. coli</i>	<i>Escherichia coli</i>	HIAP	Human inhibitor of apoptosis protein
E-Cadherin	CAM 120/80 or epithelial cadherin, cadherin-1, epithelial cadherin	HIF1 α	Hypoxia-inducible factor alpha
ECM	Extracellular matrix	HIV	Human immunodeficiency virus
EMT	Epithelial-mesenchymal transition	HMGB-1	High mobility group box 1 protein
E1	Ubiquitin-activating enzyme	HPV	Human papilloma virus
E1A	Adenovirus early region E1A protein	HPV8	Human papilloma virus type 8
E2	Ubiquitin-conjugating enzyme	HPV16	Human papilloma virus type 16
E3	Ubiquitin ligase	H-ras	Guanosine triphosphate (GTP) hydrolase enzyme, transforming protein p21, H-ras
EBV	Epstein-Barr virus	HFD	High-fat diet
ECs	Endothelial cells	hrHPV	High-risk human papillomavirus
EET	Epoxyeicosatrienoic acid	HSC	Hepatic stellate cells
		hTERT	Human telomerase reverse transcriptase
		IBS-D	Diarrhea-predominant irritable bowel syndrome
		ICAM-1	Intercellular adhesion molecule 1, cluster of differentiation 54, CD54

IFN	Interferon	LPS	Lipopolysaccharide
IFN γ	Inteferon gamma	LT β R	Lymphotoxin beta receptor
I κ B	Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor protein	LTA4	Leukotriene A4, 4-[(2S,3S)-3-[(1E,3E,5Z,8Z)-tetradeca-1,3,5,8-tetraenyl]oxiran-2-yl]butanoic acid
I κ B α	Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha	LTB4	Leukotriene B4, (5S,6Z,8E,10E,12R,14Z)-5,12-dihydroxyicosa-6,8,10,14-tetraenoic acid
I κ B β	Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, beta, I κ B kinase 1 (IKK1)	LTC4	Leukotriene C4, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-[(4S)-4-amino-4-carboxybutanoyl]amino]-3-(carboxymethylamino)-3-oxopropyl]sulfanyl-5-hydroxyicosa-7,9,11,14-tetraenoic acid
I κ B γ	Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, gamma, I κ B kinase gamma	LTD4	Leukotriene D4, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-amino-3-(carboxymethylamino)-3-oxopropyl]sulfanyl-5-hydroxyicosa-7,9,11,14-tetraenoic acid
I κ B ϵ	Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, epsilon	LTE4	Leukotriene E4, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-amino-2-carboxyethyl]sulfanyl-5-hydroxyicosa-7,9,11,14-tetraenoic acid
IKK	I κ B kinase enzyme complex	mTORc1	Rapamycin complex 1
IKK- α	Inhibitor of nuclear factor kappa-B kinase subunit alpha, inhibitor of nuclear factor kappa-B kinase 1 (IKK1)	<i>M. fermentans</i>	<i>Mycoplasma fermentans</i>
IKK- β	Inhibitor of nuclear factor kappa-B kinase subunit beta, inhibitor of nuclear factor kappa-B kinase 2 (IKK2)	<i>M. hominis</i>	<i>Mycoplasma hominis</i>
IKK- γ	Inhibitor of nuclear factor kappa-B kinase subunit gamma, NF-kappa-B essential modulator (NEMO)	<i>M. hyorhina</i>	<i>Mycoplasma hyorhina</i>
IKK1	Inhibitor of nuclear factor kappa-B kinase 1, inhibitor of nuclear factor kappa-B kinase subunit alpha (IKK- α)	<i>M. penetrans</i>	<i>Mycoplasma penetrans</i>
IKK2	Inhibitor of nuclear factor kappa-B kinase 2, inhibitor of nuclear factor kappa-B kinase subunit beta (IKK- β)	MAPK	p38 mitogen-activated protein kinase
IL-1 α	Interleukin 1 alpha	MAPK2	Mitogen-activated protein kinase kinase, MEK, MAPKK
IL- β 1	Interleukin beta 1	MAPK3	Mitogen-activated protein kinase 3 (ERK1)
IL-1	Interleukin 1	MAP2K1	Dual specificity mitogen-activated protein kinase kinase 1
IL-6	Interleukin 6	MAPKK	Mitogen-activated protein kinase kinase, MEK, MAPK2
IL-8	Interleukin 8, chemokine (C-X-C motif) ligand 8 (CXCL8)	MARCKSL1	Myristoylated alanine-rich C kinase substrate-like 1
IL-9	Interleukin 9	MC	Mast cell
IL-12	Interleukin 12	MCP-1	Monocyte chemoattractant protein 1, chemokine (C-C motif) ligand 2, CCL2
IL-13	Interleukin 13	MDA	Malondialdehyde, propanedial
IL-32	Interleukin 32	MEFs	Mouse embryonic cells
IL-33	Interleukin 33	MEK	Mitogen-activated protein kinase kinase, MAPK2, MAPKK
ILR1	Interleukin 1 receptor	MEKK3	Mitogen-activated protein kinase kinase kinase 3
IL1RL1	Interleukin 1 receptor-like 1 (ST2)	MIP1 α	Macrophage inflammatory protein 1-alpha, chemokine (C-C motif) ligand 3 (CCL3)
iNOS	Nitric oxide synthetase	miR21	Micro RNA-21
Ire1	Inositol-requiring enzyme 1	MMP	Matrix metalloproteinase
Irf3	Interferon regulatory factor 3	MMP-1	Matrix metalloproteinase 1
JNK	c-Jun N-terminal kinase	MMP-2	Matrix metalloproteinase 2
K8	Keratin 8	MMP-3	Matrix metalloproteinase 3
KC	IL-8 homologue	MMP-7	Matrix metalloproteinase 7
KO	Knockout	MMP-9	Matrix metalloproteinase 9
LEC	Lymphatic endothelial cell	MMP-12	Matrix metalloproteinase 12 (ADAM-12)
LOX	Lysyl oxidase		
LOXL	LO-like gene		
LOXL2	Lysyl oxidase homolog 2		
LOXL3	Lysyl oxidase homolog 3		

MMP-14	Matrix metalloproteinase 14, MT1-MMP	PAE	Paeoniflorin
mRNA	Messenger ribonucleic acid	PAI1	Plasminogen activator inhibitor-1
MSGA- α	Melanoma growth stimulating activity al-pha	PCN	Precancerous niche
NAP3	Neutrophil-activating protein 3, gro-onco-gene	PCNP	PEST-containing nuclear protein
NASPs	NF- κ B-activating genetic elements	PCR	Polymerase chain reaction
NCCCT	Normal cell to cancerous cell transition	PCR-RFLP	Polymerase chain reaction-restriction frag-ment length polymorphism
NEMO	NF-kappa-B essential modulator, inhibitor of nuclear factor kappa-B kinase subunit gamma, IKK- γ	PERK	Protein kinase RNA-like endoplasmic reticulum kinase
NF- κ B	Nuclear factor kappa-light-chain-enhancer of activated B cells	PGD2	Prostaglandin D2, (Z)-7-[(1R,2R,5S)-5-hydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]-3-oxocyclopentyl]hept-5-enoic acid
NF- κ B1	Nuclear factor kappa-light-chain-enhancer of activated B cells 1, protein 50 (p50) its progenitor protein 105 (p105)	PGE2	Prostaglandin E2, (Z)-7-[(1R,2R,3R)-3-hydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl]hept-5-enoic acid
NF- κ B2	Nuclear factor kappa-light-chain-enhancer of activated B cells 2, protein 52 (p52) and its progenitor protein 100 (p100)	PGFF2 α	Prostaglandine F2 alpha, (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]cyclopentyl]hept-5-enoic acid
NGF	Nerve growth factor	PGG2	Prostaglandin G2, (Z)-7-[(1S,4R,5R,6R)-5-[(E,3S)-3-hydroperoxyoct-1-enyl]-2,3-di-oxabicyclo[2.2.1]heptan-6-yl]hept-5-enoic acid
NIRF	ICBP90-like RING finger protein	PGH2	Prostaglandin H2, (Z)-7-[(1S,4R,5R,6R)-5-[(E,3S)-3-hydroxyoct-1-enyl]-2,3-dioxabicyclo[2.2.1]heptan-6-yl]hept-5-enoic acid
NIK	Nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) -inducing ki-nase	PI3K	Phosphatidylinositol 3-kinase
Nlrp3	Intracellular NOD-like receptor pyrin do-main containing 3	Pim-1	Proto-oncogene serine/threonine-protein kinase
NPC	NIH Chemical Genomics Center Pharma-ceutical Collection	PKA	Protein kinase A
NR2B1	Nuclear receptor subfamily 2, group B, member 1, retinoid X receptor alpha (Rxra)	PLA2	Phospholipase A2
NSAID	Non-steroidal anti-inflammatory drugs	PLD1	Phospholipase D1
OPG	Decoy receptor osteo NF- κ B protegerin	PPI	Proton pump inhibitor
OSF	Oral submucousal fibrosis	PRDM1	PR domain zinc finger protein 1
Osm	Oncostatin-M	pro-IL-1 β	Inactive interleukin 1 beta precursor
p21	Protein p21, guanosine triphosphate (GTP) hydrolase enzyme, transforming H-ras	Pro-MMP-1	Pro-matrix metalloproteinase 1
p33	Protein 33	Pro-MMP-7	Pro matrix metalloproteinase 7
p37	<i>Mycoplasma hyorhinis</i> membrane protein p37	Pro-MMP-9	Pro-matrix metalloproteinase 9
p50	Protein 50, nuclear factor kappa-light-chain-enhancer of activated B cells 1 (NF- κ B1)	PUMA	BH3-only protein
p52	Protein 52	Rac	Subfamily of the Rho family of GTPases
p53	Protein 53	Rac1	Ras-related C3 botulinum toxin substrate 1
p65	Nuclear factor NF-kappa-B protein 65 (p65) subunit	RanBP1	Ran-specific binding protein 1
p100	Protein 100	RANK	Receptor of nuclear factor kappaB
p105	Protein 105, p50 (NF- κ B1) progenitor	RANKL	Receptor activator of NF- κ B ligand
p107	Retinoblastoma-like protein 1, RBL1	Ras	Protein superfamily of small guanosine triphosphate hydrolase enzymes (GTPases)
p120	Protein 120, catenin delta-1	Rb	Retinoblastoma protein
p300	Adenovirus early region 1A (E1A) binding protein p300, EP300, p300-CBP coactiva-tor family	Rel	Proto-oncogene c-Rel encoded by REL gene (cRel)
		RelA	Transcription factor p65 encoded by RELA gene,
		RelB	Transcription factor encoded by the RELB gene interacting with NF- κ B

RHD	Rel homology domain	TRANCE	TNF receptor superfamily
Rho	Ras homolog gene family	TRPV1	Transient receptor potential vanilloid 1
RhoA	Ras homolog gene family, member A	TTF	Transcription termination factor
Rho-GDI2	Rho GDP-dissociation inhibitor 2	TWEAK	TNF-like weak inducer of apoptosis
RIP	Receptor-interacting protein kinase	TWIST	Twist-related protein 1
RIP1	Receptor-interacting protein1	TXA2	Thromboxane A2, (Z)-7-[(1S,2S,3R,5S)-3-[(E,3S)-3-hydroxyoct-1-enyl]-4,6-dioxabicyclo[3.1.1]heptan-2-yl]hept-5-enoic acid
RNA	Ribonucleic acid		
ROS	Reactive oxygen species	UHRF1	Ubiquitin ligase ubiquitin-like, containing PHD and RING finger domains 1
RUNX3	Runt-related transcription factor 3	uPA	Urokinase plasminogen activator
Rxra	Retinoid X receptor alpha, nuclear receptor subfamily 2, group B, member 1, NR2B1	UPM	Urban particulate matter
		UPR	Unfolded protein response
S1P	Sphingosine-1-phosphate	VCAM-1	Vascular cell adhesion molecule 1, vascular cell adhesion protein 1, cluster of differentiation 106 (CD106)
<i>S. japonicum</i>	<i>Schistosoma japonicum</i>	VCP	Valosin-containing protein (CDC48)
<i>S. mansoni</i>	<i>Schistosoma mansoni</i>	VEGF	Vascular endothelial growth factor
SalC	Salvianolic acid C	VDUP1	Vitamin D(3) upregulated protein 1
SLUG	Zinc finger protein SNAI2	ZEB1	Zinc finger E-box-binding homeobox 1
Snail	Zinc finger protein SNAI1	ZO-1	Zonula occludens-1
SOCS2	Suppressor of cytokine signaling 2		
SOX	[Sex-determining region Y (Sry) box-containing] transcription factor family		
SP1	Specificity protein 1		
SP10030	T-cell-specific inhibitor 2-chloro-4-(trifluoromethyl)pyrimidine-5-N-(39,59-bis[trifluoromethyl]phenyl)-carboxamide		
SphK	Sphingosine kinase isoform		
STAT1	Signal transducer and activator of transcription 1		
STAT3	Signal transducer and activator of transcription 3		
STING	Stimulator of interferon genes		
TF	Transcription factor		
TCGA	The Cancer Genome Atlas		
TGF β	Transforming growth factor beta		
TGF- β 1	Transforming growth factor beta 1		
Th17	T helper 17 cells		
TLR	Toll-like receptor		
TLR3	Toll like receptor 3		
TLR4	Toll like receptor 4		
TLR7	Toll like receptor 7		
TLR8	Toll like receptor 8		
TMS1	Target of methylation-mediated silencing		
TNF α	Tumor necrosis factor alpha		
TNFR1	Tumor necrosis factor receptor 1		
TNFRSF6	Tumor necrosis factor receptor superfamily member 6		
TRADD	TNF receptor type 1-associated DEATH domain protein		
TRAF1	Tumor necrosis factor (TNF α) receptor-associated factor 1		
TRAF2	Tumor necrosis factor (TNF α) receptor-associated factor 2		
TRAF6	Tumor necrosis factor (TNF α) receptor-associated factor 6		

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Conflict of interest

The author reports the following conflict of interest: Björn LDM Brücher is Editor-in-Chief in Life Sciences-Medicine of 4open by EDP Sciences. Florian Lang is Editor-in-Chief of Cellular Physiology and Biochemistry. Ijaz S. Jamall is Senior Editorial Board member in Life Sciences-Medicine of 4open by EDP Sciences. The authors, of their own initiative, suggested to the Managing Editorial to perform a transparent peer-review of their submittals. Neither author took any action to influence the standard submission and peer-review process, and report no conflict of interest. The authors alone are responsible for the content and writing of the manuscript of this Special Issue. This manuscript contains original material that has not previously been published. All authors contributed on its contents and approved the different manuscript.

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