



Review

Roles of NF- κ B Signaling in the Regulation of miRNAs Impacting on Inflammation in Cancer

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Abstract: The NF- κ B family of transcription factors regulate the expression of genes encoding proteins and microRNAs (miRNA, miR) precursors that may either positively or negatively regulate a variety of biological processes such as cell cycle progression, cell survival, and cell differentiation. The NF- κ B-miRNA transcriptional regulatory network has been implicated in the regulation of proinflammatory, immune, and stress-like responses. Gene regulation by miRNAs has emerged as an additional epigenetic mechanism at the post-transcriptional level. The expression of miRNAs can be regulated by specific transcription factors (TFs), including the NF- κ B TF family, and vice versa. The interplay between TFs and miRNAs creates positive or negative feedback loops and also regulatory networks, which can control cell fate. In the current review, we discuss the impact of NF- κ B-miRNA interplay and feedback loops and networks impacting on inflammation in cancer. We provide several paradigms of specific NF- κ B-miRNA networks that can regulate inflammation linked to cancer. For example, the NF- κ B-miR-146 and NF- κ B-miR-155 networks fine-tune the activity, intensity, and duration of inflammation, while the NF- κ B-miR-21 and NF- κ B-miR-181b-1 amplifying loops link inflammation to cancer; and p53- or NF- κ B-regulated miRNAs interconnect these pathways and may shift the balance to cancer development or tumor suppression. The availability of genomic data may be useful to verify and find novel interactions, and provide a catalogue of 162 miRNAs targeting and 40 miRNAs possibly regulated by NF- κ B. We propose that studying active TF-miRNA transcriptional regulatory networks such as NF- κ B-miRNA networks in specific cancer types can contribute to our further understanding of the regulatory interplay between inflammation and cancer, and also perhaps lead to the development of pharmacologically novel therapeutic approaches to combat cancer.

Keywords: miRNAs; NF- κ B; transcriptional regulatory networks; oncogenic and tumor suppressor pathways; cancer; inflammation

1. Introduction

Carcinogenesis involves the accumulation of mutations in conjunction with epigenetic changes resulting in dominant alterations in gene expression and cellular physiology. NF- κ B TFs and their signaling pathways play important roles in cellular growth and viability control and are often subject to deregulation in cancer. Oncogenic driver mutations and inactivating mutations in tumor suppressor genes along with epigenetic changes in normal cells, can lead to the growth of tumor containing cells with distinct phenotypic characteristics, known as the hallmarks of cancer [1]. Cancer cells are also characterized by extensive epigenetic alterations compared to their normal counterparts, as a result of deregulated tissue-specific gene regulatory mechanisms. Elucidating the interaction between genetic and epigenetic factors in cancer onset, development, and progression is considered as a main challenge in both our understanding of cancer biology and for the development of new therapeutic approaches [2,3].

Transcriptional control of gene expression involves binding of TFs to regulatory elements in gene promoters or enhancers. NF- κ Bs constitute a family of TFs that influence the expression of genes involved in many physiological processes, such as cell proliferation, cell survival, cell adhesion, inflammation, and immunity. The NF- κ B signaling components are aberrantly expressed and/or activated in cancer [4–8]. NF- κ Bs play a central role in the regulation of inflammatory responses at the cellular and systemic levels, and can have tumor promoting effects [9]. However, the NF- κ B biology is strikingly complex and NF- κ B TFs and their upstream activating signaling components can have either tumorigenic or tumor suppressor roles in cell context-dependent manner and under certain conditions [6,10].

Genes encoding ~22 bp long, small non-coding RNAs, known as microRNAs (or miRNAs or miRs) are emerging as major epigenetic regulators of cell physiology and/or pathology [11–13]. MiRNAs regulate gene expression at the posttranscriptional level by acting as negative regulators of mRNA translation and/or stability resulting in the suppression of translation [13,14], and play an important role in inflammatory and immune responses [15–18] and cancer [11].

In cancer, miRNAs can act as oncogenes, targeting tumor suppressor mRNAs or as tumor suppressors, targeting oncogenic mRNAs. MiRNA genes can also be mutated or epigenetically altered, and suppressed or activated by transcription factors leading to changes in their expression [11]. Importantly, the balance between oncogenic and tumor suppressor miRNAs expressed in a cell, can be a major epigenetic factor that influences cancer onset, development, and progression [11]. Hence, the specific expression of miRNAs and their interplay may tip that balance towards cell proliferation, leading to tumor expansion, or cell cycle arrest, senescence or apoptosis leading to the impairment of tumor growth [11].

The epigenetic mechanisms of TF or miRNA regulation, act at different stages of gene expression, and have some unique features but also share some similarities [19]. TFs can target and regulate the expression of specific miRNAs and, vice versa, miRNAs can target TF mRNAs. This property of TF and miRNA regulation, offers the cells an opportunity to create genomic-scale regulatory networks in which positive or negative feedback loops can act in concert to influence the epigenomic landscape of cells [20]. In the current review, we discuss the specific roles of the regulatory networks between NF- κ B TFs and miRNAs and their impact on the conditions of inflammation and cancer development, as well as their interactions.

2. NF- κ B Signaling Pathway Activation and Its Multifaceted Functional Role in Cancer and Inflammation

The NF- κ B TF family members are critical regulators of pro-inflammatory/stress-like responses. There are three protein subfamilies involved in NF- κ B signaling: The NF- κ B TF subunit subfamily (c-Rel, p65/RelA, RelB, p105/NF- κ B1, and p100/NF- κ B2), the regulatory family of NF- κ B inhibitors, inhibitors of κ B (I κ Bs), and the catalytic IKK (Inhibitor of NF- κ B (I κ B) kinase (IKK) complex) subfamily comprising the NF- κ B upstream activating Ser/Thr kinases IKK α and IKK β and a regulatory protein NEMO (NF- κ B essential modulator)/IKK γ that together form a high molecular weight IKK

signalosome complex, that activates NF- κ B signaling in response to specific stimuli. Members of the NF- κ B TF subfamily bind to DNA as hetero- or homodimers and can either activate or repress target gene transcription in different physiological contexts. Three of these NF- κ B subunits (c-Rel, p65/RelA, and RelB) contain a transactivation domain (TAD), while the other two (p50 and p52) lack a TAD domain and are derived by proteolytic processing of the larger precursor proteins, p105/NF- κ B1 and p100/NF- κ B2, respectively. Activation of NF- κ B signaling occurs by two major pathways: the canonical NF- κ B pathway and the noncanonical or alternative NF- κ B pathway. In unstimulated cells, heterodimers of p65/p50 subunits, involved in canonical NF- κ B signaling, are retained in the cytoplasm by I κ Bs. Pro-inflammatory and stress stimuli lead to NEMO-dependent activation of IKK β by phosphorylation of Ser177/181. Activated IKK β then phosphorylates I κ B α at Ser32/36 resulting in its proteasomal degradation and the release of p65/50 heterodimer that translocates to the nucleus where it binds and regulates target gene expression. In contrast, IKK α activation, through phosphorylation of Ser176/180, by adaptive immune response stimuli, is mediated by the NF- κ B inducing kinase (NIK). IKK α kinase phosphorylates NF- κ B2, inducing its proteasomal processing yielding the mature p52 subunit. Active p52/RelB heterodimers translocate to the nucleus and regulate distinct NF- κ B target genes [4,6,7,21,22].

NF- κ B target genes encode proteins and miRNAs that regulate a wide range of biological effects that together can be categorized as stress-like, pro-inflammatory reaction programming. The NF- κ B signaling pathways have pleiotropic biological effects which may be context dependent. In cancer, NF- κ B can exhibit tumor promoting and tumor suppressor activities in a cell context- and tissue-dependent manner [6]. Several mouse cancer models have shown a requirement for canonical NF- κ B signaling in tumor onset, development and progression [6,23–37].

The tumor promoting effects of NF- κ B are mediated by the activities of NF- κ B-regulated genes that promote cancer cell survival, proliferation, metastasis, and angiogenesis, and modify the tumor microenvironment by inducing the secretion of proinflammatory cytokines. NF- κ B also promotes a cancer cell metabolic switch from oxidative phosphorylation to glycolysis (Warburg effect) by inducing the expression of glycolytic enzymes while also directly repressing mitochondrial gene expression [38–41]. Thus, NF- κ Bs function as tumor promoters within transformed cells, but also influence the host's innate immune response to cancer cells by regulating functions of infiltrating lymphocytes and macrophages [22,42]. Although under physiological conditions NF- κ B responses are self-limiting via the induction of negative feedback loops, such auto-regulatory loops often become deregulated in cancer cells. However, the regulatory circuitry that leads to dominant IKK/NF- κ B-dependent effects in cancer is impressively complex [6,7,9,23].

2.1. Oncogenic Functions of NF- κ B: A Link between Inflammation and Cancer

Epidemiological, clinical, genetic, and biochemical evidence obtained from cells, tissues, and mouse models indicate that NF- κ B-dependent induction of pro-inflammatory cytokines are pivotal links between chronic inflammation and cancer development and progression [43–48].

Inflammation can either promote tumor growth, or it may be induced as a consequence of the tumor microenvironment leading to cancer progression [44]. Inflammation promotes cancer onset, development, and progression, and it also affects the immune surveillance and chemotherapy resistance of tumors. In addition, inflammation affects the crosstalk between infiltrating immune effector cells and tumor cells thereby linking immunity to tumor development [9,22,24,49–52].

NF- κ B TFs have a central role in innate immunity, inflammation, and cancer [6–8,22,42,48–55]. NF- κ Bs induce inflammation and the secretion of inflammatory mediators enhances canonical NF- κ B signaling [9], a feedback mechanism acting as tumor promoter [8,25,26,48,56], and a hallmark of cancer [1]. In chronic inflammation, canonical NF- κ B that controls production of inflammatory mediators might prevent the elimination of genetically altered cells present in precancerous lesions by inhibiting their apoptosis [57]. Tumor-associated macrophages (TAMs) were shown to promote tumor growth in part by suppressing immune response to cancer cells but also by producing specific cytokines,

most of which are dependent on IKK β -mediated canonical NF- κ B signaling (e.g., IL-6) that enhance tumor cell growth in vivo [9,56,58]. Canonical NF- κ B also modifies the tumor microenvironment by inducing the secretion of proinflammatory cytokines such as IL-6, resulting in the activation of its responsive transcription factor STAT3 in *K-Ras*-mutant lung tumors [58]. IL-6 modifies the tumor microenvironment and promotes breast and lung cancer development and progression [58,59]. NF- κ B functions in *K-Ras* oncogene transformation by suppressing immune surveillance of both innate and adaptive immune cells [60]. Moreover, canonical NF- κ B pathway activation and the interplay with other signaling pathways such as those of STAT3 and p53, may affect tumor onset, development, and progression [44]. One of the critical contributing factors to the oncogenic functions of canonical NF- κ B signaling is the induction of inflammation making NF- κ B as the critical link between inflammation and cancer [27,28,44–46,48].

While the contribution of canonical NF- κ B-activating IKK β as a tumor promoter in oncogene and carcinogen-induced inflammation and non-small cell lung cancer (NSCLC) has been documented [25,30,31,34] functional studies on noncanonical NF- κ B [61–64] and IKK α [65–67] suggest that they can act as tumor promoters or tumor suppressors and are involved in the resolution of inflammation [68–72], but an evolutionary conserved mechanism of action remains largely unknown. These different outcomes of canonical versus non-canonical NF- κ B signaling pathways may be related to the preference of NF- κ B dimers for binding to κ B sites contained within the promoters or enhancers of target genes. Sensing the differences within κ B sites, NF- κ B dimers modulate physiological programs by activating, repressing, and altering the expression of effector genes [73–75].

A crosstalk between canonical and noncanonical NF- κ B signaling pathways has also been shown. It was shown that NF- κ B2 [76,77] and RelB [78] gene expression is induced by canonical NF- κ B signaling. RelA/p65 suppresses RelB activity in response to TNF α and induces selective NF- κ B target gene expression [79]. It was also shown that TNF α -induced canonical NF- κ B signaling upregulates RelB expression that inhibits both basal and non-canonical NF- κ B-dependent CXCL12 expression [80]. NIK which activates noncanonical NF- κ B signaling may also contribute to the activation of canonical NF- κ B [81]. While IKK α activates noncanonical NF- κ B signaling, evidence show that it also inhibits the canonical NF- κ B pathway [82–84]. It was also shown that nuclear IKK α is required for p65 DNA binding in a gene-specific manner [85].

NF- κ B TFs are often deregulated and constitutively activated in many different types of cancer [4,6,53], leading to the development of different hallmarks of cancer [1]. NF- κ B's function as a tumor promoter is also due to its role in driving cell proliferation and protecting cells from cell death under stress conditions by regulating the expression and activity of target genes involved in cell cycle progression and apoptosis [5–7,9,49,86–88]. Canonical NF- κ B was shown to activate genes involved in cell cycle progression such as CcnD1 [5,86,89,90], E2F1 [5,86], and several E2F target genes [5] and the mitotic checkpoint Ser/Thr-protein kinase BUB1 [34]. It was also shown to suppress genes involved in apoptosis such as FOXO3a, leading to increased cell survival [4,21,91,92]. In keeping with this, miR-155, a canonical NF- κ B regulated miRNA, was identified as a negative regulator of FOXO3a leading to increased gefitinib resistance and lung cancer stemness in vitro and in vivo [92]. NF- κ B also suppresses the expression of c-Jun N-terminal kinase (JNK) via Gadd45 β and blocks apoptosis [93,94]. Canonical NF- κ B also contributes to chemoresistance of tumor cells such as leukemic cells, in part through its ability to induce p21^{waf1/cip1} [95,96] and p27^{Kip1} [97].

NF- κ B targets that play an important role in cancer progression are those involved in epithelial-to-mesenchymal cell transition (EMT), such as Snail, Twist, matrix metalloproteinases (MMPs) and cell adhesion molecules that promote metastasis, and pro-angiogenic genes such as Vascular Endothelial Growth Factor (VEGF), stimulating tumour neovascularization [8,48,98–100]. Canonical NF- κ B also regulates the expression of matrix metalloproteinases involved in tissue remodeling, inflammatory diseases and cancer [101–105]. In addition, Timp1 (tissue inhibitor of metalloproteinase 1), was identified as a NF- κ B target gene that contributes to mouse lung tumor growth [34], and it is highly expressed, and correlates with NF- κ B activation in advanced lung-cancer

patients with poor prognosis [106,107]. NF- κ B is also a critical transcriptional regulator of HIF1 α , and IKK β -mediated canonical NF- κ B activation is required for the hypoxia-induced accumulation of HIF1 α and the expression of HIF1 α target genes [108,109]. Several lines of evidence suggest a bi-directional crosstalk between NF- κ B and HIF pathways, with the latter also contributing to inflammatory responses and cancer [109–113].

In physiological conditions, NF- κ B activity is tightly regulated and inhibited after a short period of time through negative feedback loops [4]. Based on this concept, aberrant NF- κ B signaling activation leading to chronic inflammation and increased cell proliferation and survival are additional factors contributing to the oncogenic function of NF- κ B [6,23,47,48].

2.2. Tumor Suppressor Function of NF- κ B

NF- κ Bs can also suppress tumor growth under certain conditions, a functional role dependent on the presence and crosstalk with tumor-suppressor-proteins, such as p53, which modulate NF- κ B activity in cancer. These tumor suppressive functions of NF- κ B are due to NF- κ B-dependent activation of gene expression that can lead to the inhibition of cancer cell cycle progression and proliferation, apoptosis, suppression of cell invasion, and metastasis [6,55,114,115].

The tumor suppressive functions of canonical NF- κ B may be due to the modulation of NF- κ B activity by tumor suppressors such as p53 [6,61,116–118] or due to alterations in the phosphorylation status of NF- κ B subunits [6,119–121] suppressing NF- κ B's ability to induce the expression of genes that are associated with tumor growth and survival. Canonical NF- κ B can also inhibit tumor growth by inducing the expression of tumor suppressors such as Bach2 induced in B-cells by c-Rel or RelA suggesting a tumor suppressive function of c-Rel in B-cell lymphoma [114]. *c-Myc* overexpression was shown to sensitize cells to NF- κ B-induced apoptosis, and persistent inactivity of NF- κ B signaling was shown to be a prerequisite for *c-myc*-mediated lymphomagenesis [122].

The tumor suppressive functions of canonical NF- κ B may also be attributed to an attenuated inflammatory response. NF- κ B p50 subunit functions as a transcriptional regulator either as a heterodimer with NF- κ B subunits RelA, c-Rel, and RelB, or as a p50 homodimer. p50 heterodimers induce gene expression and are critical in inflammatory responses, while p50 homodimers generally act as transcriptional repressors [7,55,123]. The p50 homodimer has an important function as suppressor of inflammation through repressing proinflammatory gene expression while enhancing the expression of anti-inflammatory genes [55,124,125]. *Nfkb1*(p105/p50)^{-/-} mice display increased inflammation and susceptibility to DNA damaging agents, leading to cancer including lymphomas and liver cancer, and an ageing phenotype [55,126,127]. Reduced levels of p50 were observed in human tumor tissues from head and neck and glioblastoma cancers; and these results were further supported by xenograft models of human glioblastoma and breast cancer cell lines in mice [128].

The tumor suppressive functions of noncanonical NF- κ B may be attributed to a reduced inflammatory response and oxidative stress [29,52,65,67,70,129,130]. For example, enforced expression of a kinase-dead IKK α mutant protein in mice led to spontaneous lung squamous cell cancer (SCC) development and the recruitment of TAMs, suggesting a tumor suppressor role for IKK α in lung SCC [65,130]. IKK α loss has also been reported to promote *K-Ras*-initiated NSCLC development through a redox regulatory pathway involving ROS accumulation [67].

Emerging evidence suggests that the tumor promoting or suppressive functions of NF- κ B, in a cell- and tissue-dependent context may also be determined by miRNAs and their targets. Thus the IKK/NF- κ B-miRNA transcriptional regulatory network may play a critical role in inflammation impacting on cancer [11].

3. MiRNAs: Epigenetic Regulators in Inflammation and Cancer

MiRNAs regulate gene expression at the post-transcriptional level acting as negative regulators of mRNA translation and/or stability by binding to complementary sequences in the 3' untranslated region (3' UTR) of their target mRNAs. Individual miRNAs may target several different mRNAs to

inhibit their translation into polypeptides, partly because target sites on an mRNA require only partial base complementarity with their corresponding miRNAs. In cases of perfect complementarity, cleavage of the target mRNA is induced. Moreover, individual mRNAs may contain multiple binding sites for different miRNAs, resulting in complex regulatory networks. Conversely, binding sites for a specific miRNA may be limited to few mRNAs, while others may target a larger number of mRNAs. Hence, some miRNAs may regulate specific individual targets, while others can positively or negatively regulate a variety of cellular processes [11,131]. For example, the balance between oncogenic miRNAs (that target tumor suppressor genes) and tumor suppressive miRNAs (that target oncogenes) may influence tumor development. Sometimes, miRNAs act in concert with transcription factors, creating TF-miRNA transcriptional regulatory networks, such as the p53-miRNA and the NF- κ B-miRNA networks that may also interconnect and influence each other [11].

4. General Concept: NF- κ B Meets miRNAs

NF- κ B TFs influence the expression of miRNAs, and importantly NF- κ B signaling is also affected by miRNAs which target either the upstream NF- κ B activating kinases or other NF- κ B signaling components, in positive or negative feedback loops in several different cell types and under different conditions [6,16,52].

4.1. MiRNAs Regulated by NF- κ B

Several miRNAs, including miR-9, miR-21, miR-30b, miR-143/miR-145, miR-146a, miR-155, miR-221/222, miR-224, miR-301a, and the miR-17-92 cluster have been validated as targets of the NF- κ B transcription factors [11,16,52].

Most of these NF- κ B-targeted miRNAs have been identified by low throughput methods or unbiased screens. Importantly, the availability of whole-genome data such as transcription factor binding sites based on Chip-Seq experiments, or whole-genome histone modification profiles and also RNA-Seq analyses makes it possible to objectively analyze and efficiently find transcription factors that regulate gene expression. By employing a bioinformatics tool that is used to characterize promoter regions of miRNAs (DIANA miRGen v3.0) [132], we additionally identified 40 miRNAs that contain experimentally verified NF- κ B binding sites in their promoter regions (Table 1). Most of these miRNAs are novel potential targets and need further verification. Nevertheless, these data provide an additional, unbiased approach to verify known targets, and also to screen for possible novel targets of specific transcription factors under certain conditions.

Oncogenic miR-21 is an established NF- κ B target [42]. NF- κ B-dependent induction of miR-21 expression has been detected under different conditions, such as inflammation [16] or DNA damage responses [133] and can target multiple genes, such as *BCL2*, *MASPIN*, *PDCD4*, and *PTEN* [11]. For example, in breast cancer the NF- κ B-dependent induction of miR-21 confers chemoresistance and induces cell invasion by repressing *PDCD4* expression which regulates apoptosis, and *PTEN* phosphatase, an inhibitor of Akt pathway that leads to cell survival [133].

In tumor-associated inflammation, the pro-inflammatory cytokine IL-1 leads to NF- κ B activation and subsequent upregulation of miR-425 in gastric cancer cells. MiR-425 in turn acts as a tumor promoter by targeting *PTEN* to enhance cell survival [134].

In addition to oncogenic miRNAs, NF- κ B can also upregulate tumor suppressive miRNAs, such as miR-143 and miR-145. The expression of these two miRNAs can lead to inhibition of cancer cell proliferation, and also metastasis and invasion by targeting oncogenes such as *MYC*, *ERK5*, and *KRAS*. Non-tumorigenic prostate cells secrete miR-143 to inhibit the growth exclusively of prostate cancer cells that bear activated oncogenes some of which have been mentioned above [11,18].

Table 1. MiRNAs containing experimentally verified NF- κ B binding sites in their promoter (miRGen v3.0 tool).

miRNA Name	Chromosomal Location of Promoter (hg19)	Strand
hsa-let-7a-1	chr9:96929483–96929484	[+]
hsa-let-7d	chr9:96929483–96929484	[+]
hsa-let-7f-1	chr9:96929483–96929484	[+]
hsa-let-7i	chr12:62997400–62997401	[+]
hsa-mir-101-1	chr1:65532138–65532139	[−]
hsa-mir-1204	chr8:128806768–128806769	[+]
hsa-mir-1205	chr8:128806768–128806769	[+]
hsa-mir-1206	chr8:128806768–128806769	[+]
hsa-mir-1207	chr8:128806759–128806760	[+]
hsa-mir-1208	chr8:128806759–128806760	[+]
hsa-mir-124-1	chr8:9763203–9763204	[−]
hsa-mir-125b-1	chr11:121971206–121971207	[−]
hsa-mir-1289-1	chr20:34042503–34042504	[−]
hsa-mir-135b	chr1:205426509–205426510	[−]
hsa-mir-137	chr1:98520169–98520170	[−]
hsa-mir-146a	chr5:159894835–159894836	[+]
hsa-mir-148a	chr7:25990290–25990291	[−]
hsa-mir-193a	chr17:29886484–29886485	[+]
hsa-mir-22	chr17:1618561–1618562	[−]
hsa-mir-223	chrX:65219544–65219545	[+]
hsa-mir-23a	chr19:13953455–13953456	[−]
hsa-mir-24-2	chr19:13953455–13953456	[−]
hsa-mir-2682	chr1:98520169–98520170	[−]
hsa-mir-27a	chr19:13953455–13953456	[−]
hsa-mir-2861	chr9:130548069–130548070	[+]
hsa-mir-29a	chr7:130794752–130794753	[−]
hsa-mir-29b-1	chr7:130794752–130794753	[−]
hsa-mir-30a	chr6:72130555–72130556	[−]
hsa-mir-30c-2	chr6:72130555–72130556	[−]
hsa-mir-3142	chr5:159894835–159894836	[+]
hsa-mir-3199-2	chr22:28315414–28315415	[+]
hsa-mir-365b	chr17:29886484–29886485	[+]
hsa-mir-3667	chr22:50051180–50051181	[−]
hsa-mir-3672	chrX:120325891–120325892	[+]
hsa-mir-3679	chr2:134877461–134877462	[+]
hsa-mir-3960	chr9:130548069–130548070	[+]
hsa-mir-4725	chr17:29886484–29886485	[+]
hsa-mir-505	chrX:139015225–139015226	[−]
hsa-mir-5194	chr8:131028942–131028943	[−]
hsa-mir-612	chr11:65190256–65190257	[+]

NF- κ B-miR-140 is another regulatory loop. MiR-140 acts as a liver tumor suppressor by negatively regulating NF- κ B activity by directly targeting DNA methyltransferase 1 (*Dnmt1*) expression. In this cellular context, NF- κ B suppresses miR-140 expression, resulting in the upregulation of *DNMT1* and increased NF- κ B activity, forming a positive feedback loop that promotes liver cancer [135,136]. Aberrant miRNAs have been detected during inflammation and hepatocellular cancer (HCC). Many of these dysregulated miRNAs modulate the initiation and progression of inflammation-induced HCC, the majority of which are NF- κ B-regulated miRNAs [137].

Finally, an interesting example of NF- κ B-regulated miRNAs is that of miR-221/222, a miRNA family with a dual functional role, acting, in different cellular contexts, either as oncomiRs promoting cancer progression, or as tumor suppressors, promoting cellular senescence [11,12,138–140].

4.2. NF- κ B-Regulating miRNAs

Multiple miRNAs have been shown to alter NF- κ B activity. The current version of Tarbase v8 (http://carolina.imis.athena-innovation.gr/diana_tools/web/index.php?r=tarbasev8%2Findex, access date 20 January 2018), a database comprised of experimentally validated miRNA-gene interactions [141], contains a total of 163 miRNAs that target at least one of the main gene components of NF- κ B signaling, either the NF- κ B transcription subunits or the upstream NF- κ B activating serine/threonine kinases, IKK α and IKK β (Figure 1 and Supplementary Table S1).

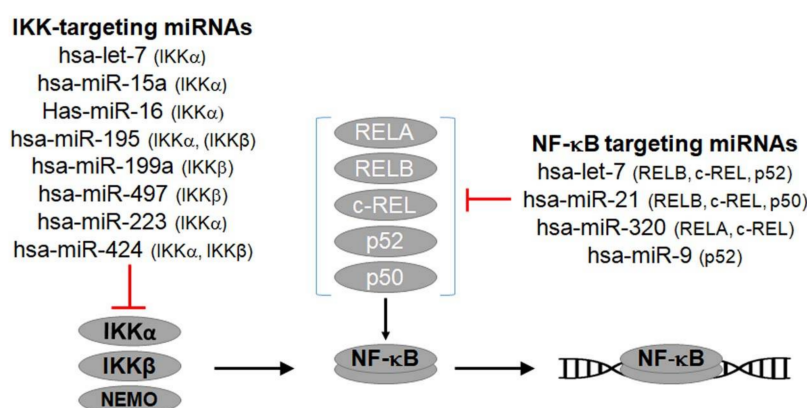


Figure 1. IKK and NF- κ B targeting miRNAs. MiRNAs targeting at least one of the NF- κ B signaling components such as one of the upstream NF- κ B activating kinases, IKK α or IKK β , or one of the NF- κ B transcription factor subunits. For a comprehensive list of NF- κ B targeting miRNAs, see Supplementary Table S1.

MiR-506 was shown to directly target and downregulate the expression of the NF- κ B p50 subunit, leading to the generation of reactive oxygen species (ROS) and the induction of p53-dependent lung cancer cell apoptosis. Interestingly, the p53-dependent induction of miR-506, suggested that miR-506 in lung cancer cells is part of a regulatory network linking p53 and NF- κ B signaling [142]. In prostate cancer, the tumor suppressive miR-497 regulates NF- κ B signaling by targeting IKK β , which activates canonical NF- κ B signaling leading to inhibition of prostate cancer cell proliferation, migration, and invasion. Importantly, miR-497 expression is reduced in prostate cancer cells, leading to a more aggressive tumor phenotype [143].

The miR-520/373 family has also been shown to act as tumor suppressors in breast cancer, by targeting the RELA/p50 NF- κ B subunit. The miR-520/373 family was identified in a genome-wide screen of miRNAs impacting on NF- κ B signaling, using a luciferase-based reporter assay in HEK293T cells [144]. This screen identified 13 families of miRNAs, out of which let-7 and miR-181 are known to participate in NF- κ B feedback loops [145,146] (discussed in the next section). MiR-520/373 was further analysed and was shown to inhibit NF- κ B in estrogen-negative breast cancer cells, which further resulted in downregulation of NF- κ B targets such as the pro-inflammatory cytokines IL-6, IL-8, CXCL1, and ICAM-1, leading to the inhibition of tumor-related inflammation, and suppression of tumor growth and metastasis [144]. In another functional screen for miRNAs regulating NF- κ B, using a NF- κ B reporter cell-line, miR-517a/c were found as potent activators of NF- κ B signaling, upregulating the expression of the reporter more than 40-fold. In this case, the identified target of miR-517a/c leading to activation of NF- κ B was TNIP1, an inhibitor of NF- κ B signaling [147].

MiRNA-126a was shown to target the NF- κ B inhibitor, I κ B α , leading to canonical NF- κ B activation thereby contributing to pathogenesis of ulcerative colitis [148], but paradoxically was shown to act as tumor suppressor for colon cancer [149].

MiRNA-223 was shown to suppress canonical NF- κ B signaling in basal keratinocytes to dampen neutrophilic inflammation [150]. MiR-223 limits inflammation and prevents DNA damage and

hematological and non-hematological malignancies [151]. MiR-223 is one of the most abundant miRNAs in macrophages and responds to stimuli to control the production of IL-6 and IL-1 β [152]. MiR-223 was also associated with macrophage differentiation through targeting IKK α [153]. However, the role of miR-223 in cancer is cell-context dependent [150]. For example, miR-223 promotes the migration and invasion of gastric cancer cells, but has opposite effects in esophageal cancer cells and human cervical cancer [154–156].

Several miRNA sites were identified in IKK α including sites for let-7, miR-223, miR-16, and miRNA-142-5p and two target sites for miR15a, one of which overlapped the putative miR-16 site. Further experiments showed that miR15a, miR-16 and miR-223, which target IKK α and are downregulated during macrophage differentiation, they were responsible at least in part for the increase in IKK α protein expression observed during macrophage differentiation [153]. Regulation of IKK α by these miRNAs may contribute to cancer development [157].

MiR-199a negatively regulates the expression of IKK β in ovarian cancer cells, and inhibits the secretion of pro-inflammatory cytokines, thereby causing suppression of tumor progression and chemoresistance [158]. IKK β is also targeted by miR-497 in prostate cancer cells and inhibits their cell proliferation, migration, and invasion in vitro [143].

5. NF- κ B-miRNA Feedback Loops and Transcriptional Regulatory Networks

Multiple feedback loops operating in a specific cell type can act in concert, creating functional networks that control cell fate. There are several NF- κ B-miRNA feedback loops in the context of inflammation in normal cells and also during cancer development. These NF- κ B-miRNA transcriptional regulatory loops may act in both physiological and pathological conditions, linking pro-inflammatory responses to oncogenic signals [11].

NF- κ B signaling during inflammation is self-limiting. A novel feedback loop that has been identified recently involves miR-146a and miR-155, the combinatory action of which controls NF- κ B activity during inflammation [18]. Their action is based on a two-step mechanism. First, miR-155 is rapidly upregulated by NF- κ B only within the first 12 h of inflammatory response and, by targeting SHIP1, it activates the IKK signalosome complex in a PI3K/Akt-dependent manner, forming a positive feedback loop necessary for signal amplification. Secondly, miR-146a is rather gradually upregulated by NF- κ B and forms a negative feedback loop by targeting IRAK1 and TRAF6, ultimately attenuating NF- κ B activity in the late phase of inflammation. The combined action of these two positive (NF- κ B-miR-155) and negative (NF- κ B-miR-146a) NF- κ B-miRNA regulatory loops provides optimal NF- κ B activity during inflammatory stimuli, and eventually lead to the resolution of the inflammatory response [18].

Knockout of miR-146a in C57BL/6 mice leads to myeloid sarcomas and some lymphomas, and the animals exhibit chronic myeloproliferation in their bone marrow. The development of myeloid malignancies correlated with increased canonical NF- κ B activity. Genetic ablation of NF- κ B p50 suppressed myeloproliferation suggesting that NF- κ B was required for myeloproliferative disease [159].

MiR-9 is induced by pro-inflammatory signals in a NF- κ B-dependent manner in human monocytes [160]. MiR-9 targets the *NFKB1* gene, which encodes the p105/p50 precursor subunit and renders lung cancer cells sensitive to ionizing radiation [160]. In ovarian cancer, miR-9 also targets *NFKB1* and its downregulation in this cancer type, as compared to normal ovarian tissue is considered an additional tumor-promoting mechanism [161]. The fact that miR-9 is positively regulated by inflammation-induced canonical NF- κ B (RelA/65-p50) signaling, taken together with the finding that miR-9 targets *NFKB1* (p105/p50), suggests a negative feedback loop mechanism fine tuning the inflammatory response with an impact in cancer.

Another negative feedback-loop in acute myeloid leukemia (AML), bearing *KIT* driver mutations, involves miR-29b and NF- κ B. MiR-29b targets the Sp1 transcription factor. In *KIT*-driven AML, *KIT* upregulates Sp1, which in turn binds NF- κ B and transactivates *KIT*. Sp1 escapes from miR-29b

downregulation through a negative feedback loop, in which Sp1-induced NF- κ B recruits HDACs in the miR-29b promoter leading to its transcriptional repression [162].

A positive feedback loop that keeps NF- κ B in an activated state operates in breast cancer cells after chemotherapy. In these cells, chemotherapy activates NF- κ B which targets and downregulates miR-448 by binding to its promoter, leading to increased expression of the miR-448 target special AT-rich sequence-binding protein-1 (SATB1). SATB1 upregulation ultimately leads to Twist1 expression, a regulator of EMT; and it also further enhances NF- κ B activity, forming a positive feedback loop that simultaneously promotes EMT [163].

One of the most well-defined regulatory networks that link inflammation and cancer has been extensively studied by Iliopoulos et al. and is formed by two distinct and complimentary feedback-loops involving either NF- κ B, Lin28, let-7 miRNA and IL-6 or IL-6, miR-21, and miR-181b-1 miRNAs, PTEN, CYLD, and NF- κ B [145,146]. During oncogenesis, proinflammatory signals that are mediated by NF- κ B, upregulate Lin28, which downregulates the tumor suppressor let-7 miRNA [164] which targets IL-6. Let-7 downregulation results in increased IL-6 levels, further activating NF- κ B, generating a feedback loop that sustains inflammation and promotes oncogenesis [145]. NF- κ B can also remain active by a complimentary feedback-loop that involves miR-21 and miR-181b-1. IL-6 activates STAT3, an inducer of miR-21 and miR-181b-1 expression, which respectively target PTEN and CYLD. PTEN and CYLD inhibition further leads to NF- κ B activation [146]. Therefore, the combined action of NF- κ B and STAT3 leading to the induction of miR-21 and miR-181b-1 and let-7 downregulation, ultimately act as a feedback mechanism linking inflammation to cancer. In addition to NF- κ B, STAT3 can also be further upregulated as a result of this feedback mechanism, since miR-181a/b induction by STAT3 can also activate the IL-6/STAT3 signaling pathway [146]. More recently, studies on the interplay between NF- κ B and STAT3, two of the main transcription factors that regulate inflammation [44–46] have revealed that feedback mechanisms that involve these two factors also include several miRNAs [165]. Studies revealed the existence of a negative feedback loop mechanism between STAT3 and NF- κ B involving miR-146b. In this mechanism, STAT3 targets miR-146b, which downregulates NF- κ B, reducing IL-6 production. The reduction of IL-6 is the final step of a negative feedback loop, since IL-6 activates STAT3, contributing to chronic inflammation. This is also a mechanism linking inflammation and cancer in breast tissue, whereas in normal tissue miR-146b is upregulated, leading to resolution of inflammation, in breast cancer it is downregulated, leading to chronic inflammation, through deregulation of the above feedback loop and cancer development [166].

A constitutively activated feedforward circuit composed of I κ B α /NF- κ B(p65) and miR-196b-3p, was shown to drive castration-resistant prostate cancer (CRPC) development. Constitutive activation of I κ B α /RelA(p65) in this circuit was independent of the activation of the canonical IKK β /NF- κ B pathway [167].

The availability of genomic data makes it possible to improve our knowledge of novel regulatory networks that exist in physiological or pathological conditions. Using bioinformatics tools and analysis we were able to identify candidate miRNAs regulated by NF- κ B (Table 1) or targeting NF- κ B pathway components (Figure 1 and Supplementary Table S1). Another such tool that offers a pathway-based approach, is the server of Diana miRpath for finding specific miRNAs involved in pathways or regulatory networks [168]. We believe that the exploitation of unbiased genomic data in conjunction with experimental validation may confirm biologically relevant findings and relate them to specific functions and (physiological or pathological) conditions.

6. Final Thoughts: Possible Therapeutic Approaches

In the current review, we focused on the interplay between NF- κ B and miRNAs impacting on inflammation and cancer development. The functional role of miRNAs in these processes is due to their action as epigenetic switches that interconnect signaling pathways and cellular processes, integrating in larger regulatory networks. In this conceptual framework, the expression of miRNAs may offer the possibility to: (a) fine-tune the activity of a process in time, such as the expression of

miR-155 and miR-146b regulating NF- κ B expression and inflammation intensity and duration [18]; (b) amplify or attenuate the activity of a signaling pathway, by taking part in feedback-loops, such as the NF- κ B-miRNA amplifying loops in inflammation linked to cancer [145,146]; and (c) interconnect TF-miRNA opposing regulatory pathways such as the p53-miRNA and NF- κ B-miRNA networks. Certain NF- κ B-regulated miRNAs can regulate p53, and vice versa, hence they can shift the balance towards apoptosis or cell survival and determine the fate of a cancer cell [11]. The complexity of epigenetic regulation requires taking into account aspects such as the expression of specific TFs and miRNAs and their possible interconnection.

Based on the dynamic nature of NF- κ B signaling combined with the diverse actions and multiple targets of miRNAs, we believe that the NF- κ B-miRNA feedback regulatory loop mechanisms discussed above or possibly novel ones yet to be discovered, should be considered when studying inflammatory responses linked to cancer initiation, progression, and development. Understanding of the NF- κ B-miRNA transcription factor regulatory networks may offer opportunities for pharmacological exploitation and personalized treatments.

Supplementary Materials: The following are available online at <http://www.mdpi.com/2227-9059/6/2/40/s1>, Table S1: Validated miRNAs for targeting at least one of NF- κ B signaling components. (# Denotes the number of NF- κ B genes targeted).

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References

- Hanahan, D.; Weinberg, R.A. Hallmarks of cancer: The next generation. *Cell* **2011**, *144*, 646–674. [[CrossRef](#)] [[PubMed](#)]
- Dawson, M.A.; Kouzarides, T. Cancer epigenetics: From mechanism to therapy. *Cell* **2012**, *150*, 12–27. [[CrossRef](#)] [[PubMed](#)]
- Rodríguez-Paredes, M.; Esteller, M. Cancer epigenetics reaches mainstream oncology. *Nat. Med.* **2011**, *17*, 330. [[CrossRef](#)] [[PubMed](#)]
- Perkins, N.D. Integrating cell-signalling pathways with NF- κ B and IKK function. *Nat. Rev. Mol. Cell Biol.* **2007**, *8*, 49–62. [[CrossRef](#)] [[PubMed](#)]
- Penzo, M.; Massa, P.E.; Olivotto, E.; Bianchi, F.; Borzi, R.M.; Hanidu, A.; Li, X.; Li, J.; Marcu, K.B. Sustained NF- κ B activation produces a short-term cell proliferation block in conjunction with repressing effectors of cell cycle progression controlled by E2F or FoxM1. *J. Cell. Physiol.* **2009**, *218*, 215–227. [[CrossRef](#)] [[PubMed](#)]
- Perkins, N.D. The diverse and complex roles of NF- κ B subunits in cancer. *Nat. Rev. Cancer* **2012**, *12*, 121–132. [[CrossRef](#)] [[PubMed](#)]
- Hayden, M.S.; Ghosh, S. NF- κ B, the first quarter-century: Remarkable progress and outstanding questions. *Genes Dev.* **2012**, *26*, 203–234. [[CrossRef](#)] [[PubMed](#)]
- Chen, W.; Li, Z.; Bai, L.; Lin, Y. NF- κ B in lung cancer, a carcinogenesis mediator and a prevention and therapy target. *Front. Biosci. (Landmark Ed.)* **2011**, *16*, 1172–1185. [[CrossRef](#)] [[PubMed](#)]
- Taniguchi, K.; Karin, M. Nf- κ B, inflammation, immunity and cancer: Coming of age. *Nat. Rev. Immunol.* **2018**. [[CrossRef](#)] [[PubMed](#)]
- Perkins, N.D. Nf- κ B: Tumor promoter or suppressor? *Trends Cell Biol.* **2004**, *14*, 64–69. [[CrossRef](#)] [[PubMed](#)]
- Markopoulos, G.S.; Roupakia, E.; Tokamani, M.; Chavdoula, E.; Hatziapostolou, M.; Polytarchou, C.; Marcu, K.B.; Papavassiliou, A.G.; Sandaltzopoulos, R.; Kolettas, E. A step-by-step microRNA guide to cancer development and metastasis. *Cell. Oncol.* **2017**, *40*, 303–339. [[CrossRef](#)] [[PubMed](#)]
- Markopoulos, G.S.; Roupakia, E.; Tokamani, M.; Vartholomatos, G.; Tzavaras, T.; Hatziapostolou, M.; Fackelmayer, F.O.; Sandaltzopoulos, R.; Polytarchou, C.; Kolettas, E. Senescence-associated microRNAs target cell cycle regulatory genes in normal human lung fibroblasts. *Exp. Gerontol.* **2017**, *96*, 110–122. [[CrossRef](#)] [[PubMed](#)]

13. Bartel, D.P. Metazoan microRNAs. *Cell* **2018**, *173*, 20–51. [[CrossRef](#)] [[PubMed](#)]
14. Bartel, D.P. MicroRNAs: Genomics, biogenesis, mechanism, and function. *Cell* **2004**, *116*, 281–297. [[CrossRef](#)]
15. Taganov, K.D.; Boldin, M.P.; Baltimore, D. MicroRNAs and immunity: Tiny players in a big field. *Immunity* **2007**, *26*, 133–137. [[CrossRef](#)] [[PubMed](#)]
16. Boldin, M.P.; Baltimore, D. MicroRNAs, new effectors and regulators of NF- κ B. *Immunol. Rev.* **2012**, *246*, 205–220. [[CrossRef](#)] [[PubMed](#)]
17. Mehta, A.; Baltimore, D. MicroRNAs as regulatory elements in immune system logic. *Nat. Rev. Immunol.* **2016**, *16*, 279. [[CrossRef](#)] [[PubMed](#)]
18. Mann, M.; Mehta, A.; Zhao, J.L.; Lee, K.; Marinov, G.K.; Garcia-Flores, Y.; Baltimore, D. An NF- κ B-microRNA regulatory network tunes macrophage inflammatory responses. *Nat. Commun.* **2017**, *8*, 851. [[CrossRef](#)] [[PubMed](#)]
19. Hobert, O. Gene regulation by transcription factors and microRNAs. *Science* **2008**, *319*, 1785–1786. [[CrossRef](#)] [[PubMed](#)]
20. Martinez, N.J.; Walhout, A.J. The interplay between transcription factors and microRNAs in genome-scale regulatory networks. *Bioessays* **2009**, *31*, 435–445. [[CrossRef](#)] [[PubMed](#)]
21. Chariot, A. The NF- κ B-independent functions of IKK subunits in immunity and cancer. *Trends Cell Biol.* **2009**, *19*, 404–413. [[CrossRef](#)] [[PubMed](#)]
22. Karin, M.; Greten, F.R. NF- κ B: Linking inflammation and immunity to cancer development and progression. *Nat. Rev. Immunol.* **2005**, *5*, 749–759. [[CrossRef](#)] [[PubMed](#)]
23. Bradford, J.W.; Baldwin, A.S. Chapter three-IKK/nuclear factor- κ B and oncogenesis: Roles in tumor-initiating cells and in the tumor microenvironment. In *Advances in Cancer Research*; Tew, K.D., Fisher, P.B., Eds.; Academic Press: Cambridge, MA, USA, 2014; Volume 121, pp. 125–145.
24. Grivennikov, S.I.; Greten, F.R.; Karin, M. Immunity, inflammation, and cancer. *Cell* **2010**, *140*, 883–899. [[CrossRef](#)] [[PubMed](#)]
25. Takahashi, H.; Ogata, H.; Nishigaki, R.; Broide, D.H.; Karin, M. Tobacco smoke promotes lung tumorigenesis by triggering IKK β -and JNK1-dependent inflammation. *Cancer Cell* **2010**, *17*, 89–97. [[CrossRef](#)] [[PubMed](#)]
26. Zaynagetdinov, R.; Stathopoulos, G.T.; Sherrill, T.P.; Cheng, D.-S.; McLoed, A.G.; Ausborn, J.A.; Polosukhin, V.V.; Connelly, L.; Zhou, W.; Fingleton, B. Epithelial nuclear factor- κ B signaling promotes lung carcinogenesis via recruitment of regulatory T lymphocytes. *Oncogene* **2012**, *31*, 3164. [[CrossRef](#)] [[PubMed](#)]
27. Greten, F.R.; Eckmann, L.; Greten, T.F.; Park, J.M.; Li, Z.-W.; Egan, L.J.; Kagnoff, M.F.; Karin, M. IKK β links inflammation and tumorigenesis in a mouse model of colitis-associated cancer. *Cell* **2004**, *118*, 285–296. [[CrossRef](#)] [[PubMed](#)]
28. Karin, M. NF- κ B as a critical link between inflammation and cancer. *Cold Spring Harb. Perspect. Biol.* **2009**, *1*, a000141. [[CrossRef](#)] [[PubMed](#)]
29. Xia, Y.; Shen, S.; Verma, I.M. Nf- κ B, an active player in human cancers. *Cancer Immunol. Res.* **2014**, *2*, 823–830. [[CrossRef](#)] [[PubMed](#)]
30. Stathopoulos, G.T.; Sherrill, T.P.; Cheng, D.S.; Scoggins, R.M.; Han, W.; Polosukhin, V.V.; Connelly, L.; Yull, F.E.; Fingleton, B.; Blackwell, T.S. Epithelial NF- κ B activation promotes urethane-induced lung carcinogenesis. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 18514–18519. [[CrossRef](#)] [[PubMed](#)]
31. Basseres, D.S.; Ebbs, A.; Levantini, E.; Baldwin, A.S. Requirement of the NF- κ B subunit p65/RelA for K-Ras-induced lung tumorigenesis. *Cancer Res.* **2010**, *70*, 3537–3546. [[CrossRef](#)] [[PubMed](#)]
32. Ben-Neriah, Y.; Karin, M. Inflammation meets cancer, with NF- κ B as the matchmaker. *Nat. Immunol.* **2011**, *12*, 715–723. [[CrossRef](#)] [[PubMed](#)]
33. Vlantis, K.; Wullaert, A.; Sasaki, Y.; Schmidt-Supprian, M.; Rajewsky, K.; Roskams, T.; Pasparakis, M. Constitutive IKK2 activation in intestinal epithelial cells induces intestinal tumors in mice. *J. Clin. Investig.* **2011**, *121*, 2781–2793. [[CrossRef](#)] [[PubMed](#)]
34. Xia, Y.; Yeddula, N.; Leblanc, M.; Ke, E.; Zhang, Y.; Oldfield, E.; Shaw, R.J.; Verma, I.M. Reduced cell proliferation by IKK2 depletion in a mouse lung-cancer model. *Nat. Cell Biol.* **2012**, *14*, 257–265. [[CrossRef](#)] [[PubMed](#)]
35. Basseres, D.S.; Ebbs, A.; Cogswell, P.C.; Baldwin, A.S. IKK is a therapeutic target in Kras-induced lung cancer with disrupted p53 activity. *Genes Cancer* **2014**, *5*, 41–55. [[PubMed](#)]

36. Kim, C.; Pasparakis, M. Epidermal p65/NF- κ B signalling is essential for skin carcinogenesis. *EMBO Mol. Med.* **2014**, *6*, 970–983. [[CrossRef](#)] [[PubMed](#)]
37. Koliarakis, V.; Pasparakis, M.; Kollias, G. IKK β in intestinal mesenchymal cells promotes initiation of colitis-associated cancer. *J. Exp. Med.* **2015**, *212*, 2235–2251. [[CrossRef](#)] [[PubMed](#)]
38. Kawauchi, K.; Araki, K.; Tobiume, K.; Tanaka, N. P53 regulates glucose metabolism through an IKK-Nf- κ B pathway and inhibits cell transformation. *Nat. Cell Biol.* **2008**, *10*, 611. [[CrossRef](#)] [[PubMed](#)]
39. Johnson, R.F.; Witzel, I.-I.; Perkins, N.D. P53-dependent regulation of mitochondrial energy production by the RelA subunit of NF- κ B. *Cancer Res.* **2011**, *71*, 5588–5597. [[CrossRef](#)] [[PubMed](#)]
40. Mauro, C.; Leow, S.C.; Anso, E.; Rocha, S.; Thotakura, A.K.; Tornatore, L.; Moretti, M.; De Smaele, E.; Beg, A.A.; Tergaonkar, V.; et al. NF- κ B controls energy homeostasis and metabolic adaptation by upregulating mitochondrial respiration. *Nat. Cell Biol.* **2011**, *13*, 1272–1279. [[CrossRef](#)] [[PubMed](#)]
41. Tornatore, L.; Thotakura, A.K.; Bennett, J.; Moretti, M.; Franzoso, G. The nuclear factor κ B signaling pathway: Integrating metabolism with inflammation. *Trends Cell Biol.* **2012**, *22*, 557–566. [[CrossRef](#)] [[PubMed](#)]
42. Oeckinghaus, A.; Hayden, M.S.; Ghosh, S. Crosstalk in NF- κ B signaling pathways. *Nat. Immunol.* **2011**, *12*, 695–708. [[CrossRef](#)] [[PubMed](#)]
43. Lin, W.-W.; Karin, M. A cytokine-mediated link between innate immunity, inflammation, and cancer. *J. Clin. Invest.* **2007**, *117*, 1175–1183. [[CrossRef](#)] [[PubMed](#)]
44. Mantovani, A.; Allavena, P.; Sica, A.; Balkwill, F. Cancer-related inflammation. *Nature* **2008**, *454*, 436. [[CrossRef](#)] [[PubMed](#)]
45. Colotta, F.; Allavena, P.; Sica, A.; Garlanda, C.; Mantovani, A. Cancer-related inflammation, the seventh hallmark of cancer: Links to genetic instability. *Carcinogenesis* **2009**, *30*, 1073–1081. [[CrossRef](#)] [[PubMed](#)]
46. Balkwill, F.R.; Mantovani, A. Cancer-Related Inflammation: Common Themes and Therapeutic Opportunities. *Semin. Cancer Biol.* **2012**, *22*, 33–40. [[CrossRef](#)] [[PubMed](#)]
47. Aggarwal, B.B.; Sung, B. Nf- κ B in cancer: A matter of life and death. *Cancer Discov.* **2011**, *1*, 469–471. [[CrossRef](#)] [[PubMed](#)]
48. Allavena, P.; Garlanda, C.; Borrello, M.G.; Sica, A.; Mantovani, A. Pathways connecting inflammation and cancer. *Curr. Opin. Genet. Dev.* **2008**, *18*, 3–10. [[CrossRef](#)] [[PubMed](#)]
49. DiDonato, J.A.; Mercurio, F.; Karin, M. Nf- κ B and the link between inflammation and cancer. *Immunol. Rev.* **2012**, *246*, 379–400. [[CrossRef](#)] [[PubMed](#)]
50. Liang, Y.; Zhou, Y.; Shen, P. NF- κ B and its regulation on the immune system. *Cell Mol. Immunol.* **2004**, *1*, 343–350. [[PubMed](#)]
51. Disis, M.L. Immune regulation of cancer. *J. Clin. Oncol.* **2010**, *28*, 4531–4538. [[CrossRef](#)] [[PubMed](#)]
52. Hoesel, B.; Schmid, J.A. The complexity of Nf- κ B signaling in inflammation and cancer. *Mol. Cancer* **2013**, *12*, 86. [[CrossRef](#)] [[PubMed](#)]
53. Baud, V.; Karin, M. Is Nf- κ B a good target for cancer therapy? Hopes and pitfalls. *Nat. Rev. Drug Discov.* **2009**, *8*, 33. [[CrossRef](#)] [[PubMed](#)]
54. Baldwin, A.S. Regulation of cell death and autophagy by IKK and Nf- κ B: Critical mechanisms in immune function and cancer. *Immunol. Rev.* **2012**, *246*, 327–345. [[CrossRef](#)] [[PubMed](#)]
55. Cartwright, T.; Perkins, N.D.; Wilson, C.L. NFKB1: A suppressor of inflammation, ageing and cancer. *FEBS J.* **2016**, *283*, 1812–1822. [[CrossRef](#)] [[PubMed](#)]
56. Moghaddam, S.J.; Li, H.; Cho, S.-N.; Dishop, M.K.; Wistuba, I.I.; Ji, L.; Kurie, J.M.; Dickey, B.F.; DeMayo, F.J. Promotion of lung carcinogenesis by chronic obstructive pulmonary disease—Like airway inflammation in a k-ras-induced mouse model. *Am. J. Respir. Cell Mol. Biol.* **2009**, *40*, 443–453. [[CrossRef](#)] [[PubMed](#)]
57. Meira, L.B.; Bugni, J.M.; Green, S.L.; Lee, C.-W.; Pang, B.; Borenshtein, D.; Rickman, B.H.; Rogers, A.B.; Moroski-Erkul, C.A.; McFaline, J.L. DNA damage induced by chronic inflammation contributes to colon carcinogenesis in mice. *J. Clin. Invest.* **2008**, *118*, 2516–2525. [[CrossRef](#)] [[PubMed](#)]
58. Caetano, M.S.; Zhang, H.; Cumpian, A.M.; Gong, L.; Unver, N.; Ostrin, E.J.; Daliri, S.; Chang, S.H.; Ochoa, C.E.; Hanash, S.; et al. Il6 blockade reprograms the lung tumor microenvironment to limit the development and progression of k-ras-mutant lung cancer. *Cancer Res.* **2016**, *76*, 3189–3199. [[CrossRef](#)] [[PubMed](#)]
59. Sansone, P.; Storci, G.; Tavolari, S.; Guarnieri, T.; Giovannini, C.; Taffurelli, M.; Ceccarelli, C.; Santini, D.; Paterini, P.; Marcu, K.B.; et al. Il-6 triggers malignant features in mammospheres from human ductal breast carcinoma and normal mammary gland. *J. Clin. Invest.* **2007**, *117*, 3988–4002. [[CrossRef](#)] [[PubMed](#)]

60. Wang, D.J.; Ratnam, N.M.; Byrd, J.C.; Guttridge, D.C. Nf- κ B functions in tumor initiation by suppressing the surveillance of both innate and adaptive immune cells. *Cell Rep.* **2014**, *9*, 90–103. [[CrossRef](#)] [[PubMed](#)]
61. Wang, Y.; Cui, H.; Schroering, A.; Ding, J.L.; Lane, W.S.; McGill, G.; Fisher, D.E.; Ding, H.-F. Nf- κ B2 p100 is a pro-apoptotic protein with anti-oncogenic function. *Nat. Cell Biol.* **2002**, *4*, 888. [[CrossRef](#)] [[PubMed](#)]
62. Jacque, E.; Billot, K.; Authier, H.; Bordereaux, D.; Baud, V. Relb inhibits cell proliferation and tumor growth through p53 transcriptional activation. *Oncogene* **2013**, *32*, 2661–2669. [[CrossRef](#)] [[PubMed](#)]
63. De Donatis, G.M.; Le Pape, E.; Pierron, A.; Cheli, Y.; Hofman, V.; Hofman, P.; Allegra, M.; Zahaf, K.; Bahadoran, P.; Rocchi, S.; et al. Nf- κ B2 induces senescence bypass in melanoma via a direct transcriptional activation of EZH2. *Oncogene* **2016**, *35*, 2813. [[CrossRef](#)] [[PubMed](#)]
64. Wang, Y.; Xu, J.; Gao, G.; Li, J.; Huang, H.; Jin, H.; Zhu, J.; Che, X.; Huang, C. Tumor-suppressor Nf κ B2 p100 interacts with ERK2 and stabilizes PTEN mRNA via inhibition of mir-494. *Oncogene* **2016**, *35*, 4080–4090. [[CrossRef](#)] [[PubMed](#)]
65. Xiao, Z.; Jiang, Q.; Willette-Brown, J.; Xi, S.; Zhu, F.; Burkett, S.; Back, T.; Song, N.Y.; Datta, M.; Sun, Z.; et al. The pivotal role of IKK α in the development of spontaneous lung squamous cell carcinomas. *Cancer Cell* **2013**, *23*, 527–540. [[CrossRef](#)] [[PubMed](#)]
66. Xie, Y.; Xie, K.; Gou, Q.; Chen, N. I κ B kinase α functions as a tumor suppressor in epithelial-derived tumors through an NF- κ B-independent pathway (review). *Oncol. Rep.* **2015**, *34*, 2225–2232. [[CrossRef](#)] [[PubMed](#)]
67. Song, N.-Y.; Zhu, F.; Wang, Z.; Willette-Brown, J.; Xi, S.; Sun, Z.; Su, L.; Wu, X.; Ma, B.; Nussinov, R.; et al. IKK α inactivation promotes Kras-initiated lung adenocarcinoma development through disrupting major redox regulatory pathways. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, E812–E821. [[CrossRef](#)] [[PubMed](#)]
68. Lawrence, T.; Bebién, M.; Liu, G.Y.; Nizet, V.; Karin, M. IKK α limits macrophage NF- κ B activation and contributes to the resolution of inflammation. *Nature* **2005**, *434*, 1138–1143. [[CrossRef](#)]
69. Liu, B.; Willette-Brown, J.; Liu, S.; Chen, X.; Fischer, S.M.; Hu, Y. IKK α represses a network of inflammation and proliferation pathways and elevates c-myc antagonists and differentiation in a dose-dependent manner in the skin. *Cell Death Differ.* **2011**, *18*, 1854–1864. [[CrossRef](#)] [[PubMed](#)]
70. Li, N.; Wu, X.; Holzer, R.G.; Lee, J.H.; Todoric, J.; Park, E.J.; Ogata, H.; Gukovskaya, A.S.; Gukovsky, I.; Pizzo, D.P.; et al. Loss of acinar cell IKK α triggers spontaneous pancreatitis in mice. *J. Clin. Investig.* **2013**, *123*, 2231–2243. [[CrossRef](#)] [[PubMed](#)]
71. Liu, B.; Yang, Y.; Chernishof, V.; Loo, R.R.; Jang, H.; Tahk, S.; Yang, R.; Mink, S.; Shultz, D.; Bellone, C.J.; et al. Proinflammatory stimuli induce IKK α -mediated phosphorylation of pias1 to restrict inflammation and immunity. *Cell* **2007**, *129*, 903–914. [[CrossRef](#)] [[PubMed](#)]
72. Yang, L.; Cui, H.; Wang, Z.; Zhang, B.; Ding, J.; Liu, L.; Ding, H.F. Loss of negative feedback control of nuclear factor- κ B2 activity in lymphocytes leads to fatal lung inflammation. *Am. J. Pathol.* **2010**, *176*, 2646–2657. [[CrossRef](#)] [[PubMed](#)]
73. Natoli, G.; De Santa, F. Shaping alternative NF- κ B-dependent gene expression programs: New clues to specificity. *Cell Death Differ.* **2006**, *13*, 693–696. [[CrossRef](#)] [[PubMed](#)]
74. Wang, V.Y.; Huang, W.; Asagiri, M.; Spann, N.; Hoffmann, A.; Glass, C.; Ghosh, G. The transcriptional specificity of NF- κ B dimers is coded within the κ B DNA response elements. *Cell Rep.* **2012**, *2*, 824–839. [[CrossRef](#)] [[PubMed](#)]
75. Kolovos, P.; Georgomanolis, T.; Koeflerle, A.; Larkin, J.D.; Brant, L.; Nikolicc, M.; Gusmao, E.G.; Zirkel, A.; Knoch, T.A.; van Ijcken, W.F.; et al. Binding of nuclear factor κ B to noncanonical consensus sites reveals its multimodal role during the early inflammatory response. *Genome Res.* **2016**, *26*, 1478–1489. [[CrossRef](#)] [[PubMed](#)]
76. Dejardin, E.; Droin, N.M.; Delhase, M.; Haas, E.; Cao, Y.; Makris, C.; Li, Z.W.; Karin, M.; Ware, C.F.; Green, D.R. The lymphotoxin- β receptor induces different patterns of gene expression via two NF- κ B pathways. *Immunity* **2002**, *17*, 525–535. [[CrossRef](#)]
77. Jin, J.; Xiao, Y.; Chang, J.H.; Yu, J.; Hu, H.; Starr, R.; Brittain, G.C.; Chang, M.; Cheng, X.; Sun, S.C. The kinase TBK1 controls IgA class switching by negatively regulating noncanonical NF- κ B signaling. *Nat. Immunol.* **2012**, *13*, 1101–1109. [[CrossRef](#)] [[PubMed](#)]
78. Bren, G.D.; Solan, N.J.; Miyoshi, H.; Pennington, K.N.; Pobst, L.J.; Paya, C.V. Transcription of the relb gene is regulated by NF- κ B. *Oncogene* **2001**, *20*, 7722–7733. [[CrossRef](#)] [[PubMed](#)]

79. Jacque, E.; Tchenio, T.; Piton, G.; Romeo, P.H.; Baud, V. Rela repression of relb activity induces selective gene activation downstream of tnf receptors. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 14635–14640. [[CrossRef](#)] [[PubMed](#)]
80. Madge, L.A.; May, M.J. Classical NF- κ B activation negatively regulates noncanonical NF- κ B-dependent cxcl12 expression. *J. Biol. Chem.* **2010**, *285*, 38069–38077. [[CrossRef](#)] [[PubMed](#)]
81. Ramakrishnan, P.; Wang, W.; Wallach, D. Receptor-specific signaling for both the alternative and the canonical NF- κ B activation pathways by NF- κ B-inducing kinase. *Immunity* **2004**, *21*, 477–489. [[CrossRef](#)] [[PubMed](#)]
82. Lam, L.T.; Davis, R.E.; Ngo, V.N.; Lenz, G.; Wright, G.; Xu, W.; Zhao, H.; Yu, X.; Dang, L.; Staudt, L.M. Compensatory IKK α activation of classical NF- κ B signaling during IKK β inhibition identified by an RNA interference sensitization screen. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 20798–20803. [[CrossRef](#)] [[PubMed](#)]
83. Shembade, N.; Pujari, R.; Harhaj, N.S.; Abbott, D.W.; Harhaj, E.W. The kinase IKK α inhibits activation of the transcription factor NF- κ B by phosphorylating the regulatory molecule tax1bp1. *Nat. Immunol.* **2011**, *12*, 834–843. [[CrossRef](#)] [[PubMed](#)]
84. Pelzer, C.; Thome, M. IKK α takes control of canonical NF- κ B activation. *Nat. Immunol.* **2011**, *12*, 815–816. [[CrossRef](#)] [[PubMed](#)]
85. Gloire, G.; Horion, J.; El Mjiyad, N.; Bex, F.; Chariot, A.; Dejardin, E.; Piette, J. Promoter-dependent effect of IKK α on NF- κ B/p65 DNA binding. *J. Biol. Chem.* **2007**, *282*, 21308–21318. [[CrossRef](#)] [[PubMed](#)]
86. Araki, K.; Kawachi, K.; Tanaka, N. IKK/Nf- κ B signaling pathway inhibits cell-cycle progression by a novel rb-independent suppression system for E2F transcription factors. *Oncogene* **2008**, *27*, 5696. [[CrossRef](#)] [[PubMed](#)]
87. Sfikas, A.; Batsi, C.; Tselikou, E.; Vartholomatos, G.; Monokrousos, N.; Pappas, P.; Christoforidis, S.; Tzavaras, T.; Kanavaros, P.; Gorgoulis, V.G.; et al. The canonical NF- κ B pathway differentially protects normal and human tumor cells from ros-induced DNA damage. *Cell. Signal.* **2012**, *24*, 2007–2023. [[CrossRef](#)] [[PubMed](#)]
88. Batsi, C.; Markopoulou, S.; Vartholomatos, G.; Georgiou, I.; Kanavaros, P.; Gorgoulis, V.G.; Marcu, K.B.; Kolettas, E. Chronic NF- κ B activation delays rasv12-induced premature senescence of human fibroblasts by suppressing the DNA damage checkpoint response. *Mech. Ageing Dev.* **2009**, *130*, 409–419. [[CrossRef](#)] [[PubMed](#)]
89. Guttridge, D.C.; Albanese, C.; Reuther, J.Y.; Pestell, R.G.; Baldwin, A.S., Jr. NF- κ B controls cell growth and differentiation through transcriptional regulation of cyclin d1. *Mol. Cell Biol.* **1999**, *19*, 5785–5799. [[CrossRef](#)] [[PubMed](#)]
90. Park, K.J.; Krishnan, V.; O'Malley, B.W.; Yamamoto, Y.; Gaynor, R.B. Formation of an IKK α -dependent transcription complex is required for estrogen receptor-mediated gene activation. *Mol. Cell* **2005**, *18*, 71–82. [[CrossRef](#)] [[PubMed](#)]
91. Hu, M.C.; Lee, D.F.; Xia, W.; Golfman, L.S.; Ou-Yang, F.; Yang, J.Y.; Zou, Y.; Bao, S.; Hanada, N.; Saso, H.; et al. I κ B kinase promotes tumorigenesis through inhibition of forkhead foxo3a. *Cell* **2004**, *117*, 225–237. [[CrossRef](#)]
92. Chiu, C.F.; Chang, Y.W.; Kuo, K.T.; Shen, Y.S.; Liu, C.Y.; Yu, Y.H.; Cheng, C.C.; Lee, K.Y.; Chen, F.C.; Hsu, M.K.; et al. NF- κ B-driven suppression of foxo3a contributes to egfr mutation-independent gefitinib resistance. *Proc. Natl. Acad. Sci. USA* **2016**, *113*, E2526–E2535. [[CrossRef](#)] [[PubMed](#)]
93. De Smaele, E.; Zazzeroni, F.; Papa, S.; Nguyen, D.U.; Jin, R.; Jones, J.; Cong, R.; Franzoso, G. Induction of gadd45 β by NF- κ B downregulates pro-apoptotic JNK signalling. *Nature* **2001**, *414*, 308–313. [[CrossRef](#)] [[PubMed](#)]
94. Papa, S.; Zazzeroni, F.; Bubici, C.; Jayawardena, S.; Alvarez, K.; Matsuda, S.; Nguyen, D.U.; Pham, C.G.; Nelsbach, A.H.; Melis, T.; et al. Gadd45 β mediates the Nf- κ B suppression of JNK signalling by targeting MKK7/JNKK2. *Nat. Cell Biol.* **2004**, *6*, 146–153. [[CrossRef](#)] [[PubMed](#)]
95. Wuerzberger-Davis, S.M.; Chang, P.Y.; Berchtold, C.; Miyamoto, S. Enhanced G₂-M arrest by nuclear factor- κ B-dependent p21^{waf1/cip1} induction. *Mol. Cancer Res.* **2005**, *3*, 345–353. [[CrossRef](#)] [[PubMed](#)]
96. Chang, P.Y.; Miyamoto, S. Nuclear factor- κ B dimer exchange promotes a p21^{waf1/cip1} superinduction response in human T leukemic cells. *Mol. Cancer Res.* **2006**, *4*, 101–112. [[CrossRef](#)] [[PubMed](#)]

97. Batsi, C.; Markopoulou, S.; Kontargiris, E.; Charalambous, C.; Thomas, C.; Christoforidis, S.; Kanavaros, P.; Constantinou, A.I.; Marcu, K.B.; Kolettas, E. Bcl-2 blocks 2-methoxyestradiol induced leukemia cell apoptosis by a p27(kip1)-dependent g1/s cell cycle arrest in conjunction with NF- κ B activation. *Biochem. Pharmacol.* **2009**, *78*, 33–44. [[CrossRef](#)] [[PubMed](#)]
98. Julien, S.; Puig, I.; Caretti, E.; Bonaventure, J.; Nelles, L.; van Roy, F.; Dargemont, C.; de Herreros, A.G.; Bellacosa, A.; Larue, L. Activation of NF- κ B by akt upregulates snail expression and induces epithelium mesenchyme transition. *Oncogene* **2007**, *26*, 7445–7456. [[CrossRef](#)] [[PubMed](#)]
99. Schmidt, D.; Textor, B.; Pein, O.T.; Licht, A.H.; Andrecht, S.; Sator-Schmitt, M.; Fusenig, N.E.; Angel, P.; Schorpp-Kistner, M. Critical role for nf- κ B-induced junb in vegf regulation and tumor angiogenesis. *EMBO J.* **2007**, *26*, 710–719. [[CrossRef](#)] [[PubMed](#)]
100. Min, C.; Eddy, S.F.; Sherr, D.H.; Sonenshein, G.E. NF- κ B and epithelial to mesenchymal transition of cancer. *J. Cell Biochem.* **2008**, *104*, 733–744. [[CrossRef](#)] [[PubMed](#)]
101. Yan, C.; Boyd, D.D. Regulation of matrix metalloproteinase gene expression. *J. Cell Physiol.* **2007**, *211*, 19–26. [[CrossRef](#)] [[PubMed](#)]
102. Clark, I.M.; Swingler, T.E.; Sampieri, C.L.; Edwards, D.R. The regulation of matrix metalloproteinases and their inhibitors. *Int. J. Biochem. Cell Biol.* **2008**, *40*, 1362–1378. [[CrossRef](#)] [[PubMed](#)]
103. Fanjul-Fernandez, M.; Folgueras, A.R.; Cabrera, S.; Lopez-Otin, C. Matrix metalloproteinases: Evolution, gene regulation and functional analysis in mouse models. *Biochim. Biophys. Acta* **2010**, *1803*, 3–19. [[CrossRef](#)] [[PubMed](#)]
104. Parks, W.C.; Wilson, C.L.; Lopez-Boado, Y.S. Matrix metalloproteinases as modulators of inflammation and innate immunity. *Nat. Rev. Immunol.* **2004**, *4*, 617–629. [[CrossRef](#)] [[PubMed](#)]
105. Fingleton, B. Matrix metalloproteinases as regulators of inflammatory processes. *Biochim. Biophys. Acta* **2017**, *1864*, 2036–2042. [[CrossRef](#)] [[PubMed](#)]
106. Fong, K.M.; Kida, Y.; Zimmerman, P.V.; Smith, P.J. Timp1 and adverse prognosis in non-small cell lung cancer. *Clin. Cancer Res.* **1996**, *2*, 1369–1372. [[PubMed](#)]
107. Aljada, I.S.; Ramnath, N.; Donohue, K.; Harvey, S.; Brooks, J.J.; Wiseman, S.M.; Khoury, T.; Loewen, G.; Slocum, H.K.; Anderson, T.M.; et al. Upregulation of the tissue inhibitor of metalloproteinase-1 protein is associated with progression of human non-small-cell lung cancer. *J. Clin. Oncol.* **2004**, *22*, 3218–3229. [[CrossRef](#)] [[PubMed](#)]
108. Rius, J.; Guma, M.; Schachtrup, C.; Akassoglou, K.; Zinkernagel, A.S.; Nizet, V.; Johnson, R.S.; Haddad, G.G.; Karin, M. NF- κ B links innate immunity to the hypoxic response through transcriptional regulation of hif-1 α . *Nature* **2008**, *453*, 807–811. [[CrossRef](#)] [[PubMed](#)]
109. D'Ignazio, L.; Batie, M.; Rocha, S. Hypoxia and inflammation in cancer, focus on hif and NF- κ B. *Biomedicines* **2017**, *5*, E21. [[CrossRef](#)] [[PubMed](#)]
110. Bandarra, D.; Biddlestone, J.; Mudie, S.; Muller, H.A.; Rocha, S. Hif-1 α restricts NF- κ B-dependent gene expression to control innate immunity signals. *Dis. Models Mech.* **2015**, *8*, 169–181. [[CrossRef](#)] [[PubMed](#)]
111. Triner, D.; Shah, Y.M. Hypoxia-inducible factors: A central link between inflammation and cancer. *J. Clin. Investig.* **2016**, *126*, 3689–3698. [[CrossRef](#)] [[PubMed](#)]
112. D'Ignazio, L.; Bandarra, D.; Rocha, S. NF- κ B and hif crosstalk in immune responses. *FEBS J.* **2016**, *283*, 413–424. [[CrossRef](#)] [[PubMed](#)]
113. Triner, D.; Xue, X.; Schwartz, A.J.; Jung, I.; Colacino, J.A.; Shah, Y.M. Epithelial hypoxia-inducible factor 2 α facilitates the progression of colon tumors through recruiting neutrophils. *Mol. Cell Biol.* **2017**, *37*. [[CrossRef](#)] [[PubMed](#)]
114. Hunter, J.E.; Butterworth, J.A.; Zhao, B.; Sellier, H.; Campbell, K.J.; Thomas, H.D.; Bacon, C.M.; Cockell, S.J.; Gewurz, B.E.; Perkins, N.D. The Nf- κ B subunit c-rel regulates bach2 tumour suppressor expression in b-cell lymphoma. *Oncogene* **2015**, *35*, 3476. [[CrossRef](#)] [[PubMed](#)]
115. Hunter, J.E.; Leslie, J.; Perkins, N.D. C-rel and its many roles in cancer: An old story with new twists. *Br. J. Cancer* **2016**, *114*, 1. [[CrossRef](#)] [[PubMed](#)]
116. Rocha, S.; Campbell, K.J.; Perkins, N.D. P53-and mdm2-independent repression of Nf- κ B transactivation by the arf tumor suppressor. *Mol. Cell* **2003**, *12*, 15–25. [[CrossRef](#)]
117. Campbell, K.J.; Rocha, S.; Perkins, N.D. Active repression of antiapoptotic gene expression by RelA (p65) Nf- κ B. *Mol. Cell* **2004**, *13*, 853–865. [[CrossRef](#)]

118. Campbell, K.J.; Witty, J.M.; Rocha, S.; Perkins, N.D. Cisplatin mimics arf tumor suppressor regulation of RelA (p65) nuclear factor- κ B transactivation. *Cancer Res.* **2006**, *66*, 929–935. [[CrossRef](#)] [[PubMed](#)]
119. Msaki, A.; Sanchez, A.M.; Koh, L.F.; Barre, B.; Rocha, S.; Perkins, N.D.; Johnson, R.F. The role of RelA (p65) threonine 505 phosphorylation in the regulation of cell growth, survival, and migration. *Mol. Biol. Cell* **2011**, *22*, 3032–3040. [[CrossRef](#)] [[PubMed](#)]
120. Perkins, N.D. The importance of the p50 Nf- κ B subunit. *Cell Cycle* **2015**, *14*, 2877. [[CrossRef](#)] [[PubMed](#)]
121. Moles, A.; Butterworth, J.A.; Sanchez, A.; Hunter, J.E.; Leslie, J.; Sellier, H.; Tiniakos, D.; Cockell, S.J.; Mann, D.A.; Oakley, F.; et al. A RelA(p65) thr505 phospho-site mutation reveals an important mechanism regulating Nf- κ B-dependent liver regeneration and cancer. *Oncogene* **2016**, *35*, 4623. [[CrossRef](#)] [[PubMed](#)]
122. Klapproth, K.; Sander, S.; Marinkovic, D.; Baumann, B.; Wirth, T. The IKK2/Nf- κ B pathway suppresses myc-induced lymphomagenesis. *Blood* **2009**, *114*, 2448–2458. [[CrossRef](#)] [[PubMed](#)]
123. Cao, S.; Zhang, X.; Edwards, J.P.; Mosser, D.M. Nf- κ B1 (p50) homodimers differentially regulate pro-and anti-inflammatory cytokines in macrophages. *J. Biol. Chem.* **2006**, *281*, 26041–26050. [[CrossRef](#)] [[PubMed](#)]
124. Wang, D.; Paz-Priel, I.; Friedman, A.D. Nf- κ B p50 regulates c/ebp α expression and inflammatory cytokine-induced neutrophil production. *J. Immunol.* **2009**, *182*, 5757–5762. [[CrossRef](#)] [[PubMed](#)]
125. Elsharkawy, A.M.; Oakley, F.; Lin, F.; Packham, G.; Mann, D.A.; Mann, J. The Nf- κ B p50: P50: Hdac-1 repressor complex orchestrates transcriptional inhibition of multiple pro-inflammatory genes. *J. Hepatol.* **2010**, *53*, 519–527. [[CrossRef](#)] [[PubMed](#)]
126. Voce, D.J.; Schmitt, A.M.; Uppal, A.; McNerney, M.E.; Bernal, G.M.; Cahill, K.E.; Wahlstrom, J.S.; Nassiri, A.; Yu, X.; Crawley, C.D. NFKB1 is a haploinsufficient DNA damage-specific tumor suppressor. *Oncogene* **2015**, *34*, 2807. [[CrossRef](#)] [[PubMed](#)]
127. Wilson, C.; Jurk, D.; Fullard, N.; Banks, P.; Page, A.; Luli, S.; Elsharkawy, A.; Gieling, R.; Chakraborty, J.B.; Fox, C. Nf κ B1 is a suppressor of neutrophil-driven hepatocellular carcinoma. *Nat. Commun.* **2015**, *6*, 6818. [[CrossRef](#)] [[PubMed](#)]
128. Kravtsova-Ivantsiv, Y.; Shomer, I.; Cohen-Kaplan, V.; Snijder, B.; Superti-Furga, G.; Gonen, H.; Sommer, T.; Ziv, T.; Admon, A.; Naroditsky, I. Kpc1-mediated ubiquitination and proteasomal processing of Nf- κ B1 p105 to p50 restricts tumor growth. *Cell* **2015**, *161*, 333–347. [[CrossRef](#)] [[PubMed](#)]
129. Martin, B.N.; Wang, C.; Willette-Brown, J.; Herjan, T.; Gulen, M.F.; Zhou, H.; Bulek, K.; Franchi, L.; Sato, T.; Alnemri, E.S. IKK α negatively regulates asc-dependent inflammasome activation. *Nat. Commun.* **2014**, *5*, 4977. [[CrossRef](#)] [[PubMed](#)]
130. Xiao, D.; Jia, J.; Shi, Y.; Fu, C.; Chen, L.; Jiang, Y.; Zhou, L.; Liu, S.; Tao, Y. Opposed expression of IKK α : Loss in keratinizing carcinomas and gain in non-keratinizing carcinomas. *Oncotarget* **2015**, *6*, 25499. [[CrossRef](#)] [[PubMed](#)]
131. Esteller, M. Non-coding RNAs in human disease. *Nat. Rev. Genet.* **2011**, *12*, 861–874. [[CrossRef](#)] [[PubMed](#)]
132. Georgakilas, G.; Vlachos, I.S.; Zagganas, K.; Vergoulis, T.; Paraskevopoulou, M.D.; Kanellos, I.; Tsanakas, P.; Dellis, D.; Fevgas, A.; Dalamagas, T. Diana-mirgen v3. 0: Accurate characterization of microRNA promoters and their regulators. *Nucleic Acids Res.* **2015**, *44*, D190–D195. [[CrossRef](#)] [[PubMed](#)]
133. Niu, J.; Shi, Y.; Tan, G.; Yang, C.H.; Fan, M.; Pfeffer, L.M.; Wu, Z.-H. DNA damage induces Nf- κ B-dependent microRNA-21 up-regulation and promotes breast cancer cell invasion. *J. Biol. Chem.* **2012**, *287*, 21783–21795. [[CrossRef](#)] [[PubMed](#)]
134. Ma, J.; Liu, J.; Wang, Z.; Gu, X.; Fan, Y.; Zhang, W.; Xu, L.; Zhang, J.; Cai, D. NF- κ B-dependent microRNA-425 upregulation promotes gastric cancer cell growth by targeting *PTEN* upon il-1 β induction. *Mol. Cancer* **2014**, *13*, 40. [[CrossRef](#)] [[PubMed](#)]
135. Takata, A.; Otsuka, M.; Yoshikawa, T.; Kishikawa, T.; Hikiba, Y.; Obi, S.; Goto, T.; Kang, Y.J.; Maeda, S.; Yoshida, H.; et al. MicroRNA-140 acts as a liver tumor suppressor by controlling Nf- κ B activity by directly targeting DNA methyltransferase 1 (dnmt1) expression. *Hepatology* **2013**, *57*, 162–170. [[CrossRef](#)] [[PubMed](#)]
136. Takata, A.; Otsuka, M.; Kojima, K.; Yoshikawa, T.; Kishikawa, T.; Yoshida, H.; Koike, K. MicroRNA-22 and microRNA-140 suppress Nf- κ B activity by regulating the expression of Nf- κ B coactivators. *Biochem. Biophys. Res. Commun.* **2011**, *411*, 826–831. [[CrossRef](#)] [[PubMed](#)]
137. Huan, L.; Liang, L.-H.; He, X.-H. Role of microRNAs in inflammation-associated liver cancer. *Cancer Biol Med.* **2016**, *13*, 407. [[PubMed](#)]

138. Le Sage, C.; Nagel, R.; Egan, D.A.; Schrier, M.; Mesman, E.; Mangiola, A.; Anile, C.; Maira, G.; Mercatelli, N.; Ciafre, S.A.; et al. Regulation of the p27(kip1) tumor suppressor by mir-221 and mir-222 promotes cancer cell proliferation. *EMBO J.* **2007**, *26*, 3699–3708. [[CrossRef](#)] [[PubMed](#)]
139. Voorhoeve, P.M.; Agami, R. Classifying microRNAs in cancer: The good, the bad and the ugly. *Biochim. Biophys. Acta* **2007**, *1775*, 274–282. [[CrossRef](#)] [[PubMed](#)]
140. Kedde, M.; van Kouwenhove, M.; Zwart, W.; Oude Vrielink, J.A.; Elkon, R.; Agami, R. A pumilio-induced RNA structure switch in p27-3' utr controls mir-221 and mir-222 accessibility. *Nat. Cell Biol.* **2010**, *12*, 1014–1020. [[CrossRef](#)] [[PubMed](#)]
141. Karagkouni, D.; Paraskevopoulou, M.D.; Chatzopoulos, S.; Vlachos, I.S.; Tastsoglou, S.; Kanellos, I.; Papadimitriou, D.; Kavakiotis, I.; Maniou, S.; Skoufos, G. DIANA-TarBase v8: A decade-long collection of experimentally supported miRNA–gene interactions. *Nucleic Acids Res.* **2017**, *46*, D239–D245. [[CrossRef](#)] [[PubMed](#)]
142. Yin, M.; Ren, X.; Zhang, X.; Luo, Y.; Wang, G.; Huang, K.; Feng, S.; Bao, X.; He, X.; Liang, P. Selective killing of lung cancer cells by miRNA-506 molecule through inhibiting Nf- κ B p65 to evoke reactive oxygen species generation and p53 activation. *Oncogene* **2015**, *34*, 691. [[CrossRef](#)]
143. Kong, X.-J.; Duan, L.-J.; Qian, X.-Q.; Xu, D.; Liu, H.-L.; Zhu, Y.-J.; Qi, J. Tumor-suppressive microRNA-497 targets IKK β to regulate Nf- κ B signaling pathway in human prostate cancer cells. *Am. J. Cancer Res.* **2015**, *5*, 1795–1804. [[PubMed](#)]
144. Keklikoglou, I.; Koerner, C.; Schmidt, C.; Zhang, J.; Heckmann, D.; Shavinskaya, A.; Allgayer, H.; Gückel, B.; Fehm, T.; Schneeweiss, A. MicroRNA-520/373 family functions as a tumor suppressor in estrogen receptor negative breast cancer by targeting Nf- κ B and TGF- β signaling pathways. *Oncogene* **2012**, *31*, 4150. [[CrossRef](#)] [[PubMed](#)]
145. Iliopoulos, D.; Hirsch, H.A.; Struhl, K. An epigenetic switch involving Nf- κ B, lin28, let-7 microRNA, and il6 links inflammation to cell transformation. *Cell* **2009**, *139*, 693–706. [[CrossRef](#)] [[PubMed](#)]
146. Iliopoulos, D.; Jaeger, S.A.; Hirsch, H.A.; Bulyk, M.L.; Struhl, K. Stat3 activation of mir-21 and mir-181b-1 via PTEN and cyld are part of the epigenetic switch linking inflammation to cancer. *Mol. Cell* **2010**, *39*, 493–506. [[CrossRef](#)] [[PubMed](#)]
147. Olarerin-George, A.O.; Anton, L.; Hwang, Y.-C.; Elovitz, M.A.; Hogenesch, J.B. A functional genomics screen for microRNA regulators of NF- κ B signaling. *BMC Biol.* **2013**, *11*, 19. [[CrossRef](#)] [[PubMed](#)]
148. Feng, X.; Wang, H.; Ye, S.; Guan, J.; Tan, W.; Cheng, S.; Wei, G.; Wu, W.; Wu, F.; Zhou, Y. Up-regulation of microRNA-126 may contribute to pathogenesis of ulcerative colitis via regulating NF- κ B inhibitor κ B α . *PLoS ONE* **2012**, *7*, e52782. [[CrossRef](#)] [[PubMed](#)]
149. Huang, W.; Lin, J.; Zhang, H. Mir-126: A novel regulator in colon cancer. *Biomed. Rep.* **2016**, *4*, 131–134. [[CrossRef](#)] [[PubMed](#)]
150. Zhou, W.; Pal, A.S.; Hsu, A.Y.; Gurol, T.; Zhu, X.; Wirbisky-Hershberger, S.E.; Freeman, J.L.; Kasinski, A.L.; Deng, Q. MicroRNA-223 suppresses the canonical NF- κ B pathway in basal keratinocytes to dampen neutrophilic inflammation. *Cell Rep.* **2018**, *22*, 1810–1823. [[CrossRef](#)] [[PubMed](#)]
151. Haneklaus, M.; Gerlic, M.; O'Neill, L.A.; Masters, S.L. Mir-223: Infection, inflammation and cancer. *J. Intern. Med.* **2013**, *274*, 215–226. [[CrossRef](#)] [[PubMed](#)]
152. Chen, Q.; Wang, H.; Liu, Y.; Song, Y.; Lai, L.; Han, Q.; Cao, X.; Wang, Q. Inducible microRNA-223 down-regulation promotes tlr-triggered il-6 and il-1 β production in macrophages by targeting stat3. *PLoS ONE* **2012**, *7*, e42971. [[CrossRef](#)] [[PubMed](#)]
153. Li, T.; Morgan, M.J.; Choksi, S.; Zhang, Y.; Kim, Y.S.; Liu, Z.G. MicroRNAs modulate the noncanonical transcription factor NF- κ B pathway by regulating expression of the kinase IKK α during macrophage differentiation. *Nat. Immunol.* **2010**, *11*, 799–805. [[CrossRef](#)] [[PubMed](#)]
154. Li, S.; Li, Z.; Guo, F.; Qin, X.; Liu, B.; Lei, Z.; Song, Z.; Sun, L.; Zhang, H.T.; You, J.; et al. Mir-223 regulates migration and invasion by targeting artemin in human esophageal carcinoma. *J. Biomed. Sci.* **2011**, *18*, 24. [[CrossRef](#)] [[PubMed](#)]
155. Li, X.; Zhang, Y.; Zhang, H.; Liu, X.; Gong, T.; Li, M.; Sun, L.; Ji, G.; Shi, Y.; Han, Z.; et al. MiRNA-223 promotes gastric cancer invasion and metastasis by targeting tumor suppressor epb4113. *Mol. Cancer Res.* **2011**, *9*, 824–833. [[CrossRef](#)] [[PubMed](#)]

156. Tang, Y.; Wang, Y.; Chen, Q.; Qiu, N.; Zhao, Y.; You, X. Mir-223 inhibited cell metastasis of human cervical cancer by modulating epithelial-mesenchymal transition. *Int. J. Clin. Exp. Pathol.* **2015**, *8*, 11224–11229. [[PubMed](#)]
157. Aqeilan, R.I.; Calin, G.A.; Croce, C.M. Mir-15a and mir-16-1 in cancer: Discovery, function and future perspectives. *Cell Death Differ.* **2009**, *17*, 215. [[CrossRef](#)] [[PubMed](#)]
158. Chen, R.; Alvero, A.B.; Silasi, D.A.; Kelly, M.G.; Fest, S.; Visintin, I.; Leiser, A.; Schwartz, P.E.; Rutherford, T.; Mor, G. Regulation of IKK β by mir-199a affects Nf- κ B activity in ovarian cancer cells. *Oncogene* **2008**, *27*, 4712. [[CrossRef](#)] [[PubMed](#)]
159. Zhao, J.L.; Rao, D.S.; Boldin, M.P.; Taganov, K.D.; O'Connell, R.M.; Baltimore, D. Nf- κ B dysregulation in microRNA-146a—Deficient mice drives the development of myeloid malignancies. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 9184–9189. [[CrossRef](#)] [[PubMed](#)]
160. Bazzoni, F.; Rossato, M.; Fabbri, M.; Gaudiosi, D.; Mirolo, M.; Mori, L.; Tamassia, N.; Mantovani, A.; Cassatella, M.A.; Locati, M. Induction and regulatory function of mir-9 in human monocytes and neutrophils exposed to proinflammatory signals. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 5282–5287. [[CrossRef](#)] [[PubMed](#)]
161. Guo, L.M.; Pu, Y.; Han, Z.; Liu, T.; Li, Y.X.; Liu, M.; Li, X.; Tang, H. MicroRNA-9 inhibits ovarian cancer cell growth through regulation of Nf- κ B1. *FEBS J.* **2009**, *276*, 5537–5546. [[CrossRef](#)] [[PubMed](#)]
162. Liu, S.; Wu, L.-C.; Pang, J.; Santhanam, R.; Schwind, S.; Wu, Y.-Z.; Hickey, C.J.; Yu, J.; Becker, H.; Maharry, K.; et al. Sp1/NF κ B/HDAC/miR-29b regulatory network in KIT-driven myeloid leukemia. *Cancer Cell* **2010**, *17*, 333–347. [[CrossRef](#)] [[PubMed](#)]
163. Li, Q.Q.; Chen, Z.Q.; Cao, X.X.; Xu, J.D.; Xu, J.W.; Chen, Y.Y.; Wang, W.J.; Chen, Q.; Tang, F.; Liu, X.P.; et al. Involvement of Nf- κ B/mir-448 regulatory feedback loop in chemotherapy-induced epithelial–mesenchymal transition of breast cancer cells. *Cell Death Differ.* **2010**, *18*, 16. [[CrossRef](#)] [[PubMed](#)]
164. Kumar, M.S.; Erkeland, S.J.; Pester, R.E.; Chen, C.Y.; Ebert, M.S.; Sharp, P.A.; Jacks, T. Suppression of non-small cell lung tumor development by the let-7 microRNA family. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 3903–3908. [[CrossRef](#)] [[PubMed](#)]
165. Iliopoulos, D. MicroRNA circuits regulate the cancer-inflammation link. *Sci. Signal.* **2014**, *7*, pe8. [[CrossRef](#)]
166. Xiang, M.; Birkbak, N.J.; Vafaizadeh, V.; Walker, S.R.; Yeh, J.E.; Liu, S.; Kroll, Y.; Boldin, M.; Taganov, K.; Groner, B. Stat3 induction of mir-146b forms a feedback loop to inhibit the Nf- κ B to il-6 signaling axis and stat3-driven cancer phenotypes. *Sci. Signal.* **2014**, *7*, ra11. [[CrossRef](#)] [[PubMed](#)]
167. Jeong, J.-H.; Park, S.-J.; Dickinson, S.I.; Luo, J.-L. A constitutive intrinsic inflammatory signaling circuit composed of mir-196b, Meis2, PPP3CC, and p65 drives prostate cancer castration resistance. *Mol. Cell* **2017**, *65*, 154–167. [[CrossRef](#)] [[PubMed](#)]
168. Papadopoulos, G.L.; Alexiou, P.; Maragkakis, M.; Reczko, M.; Hatzigeorgiou, A.G. Diana-mirpath: Integrating human and mouse microRNAs in pathways. *Bioinformatics* **2009**, *25*, 1991–1993. [[CrossRef](#)] [[PubMed](#)]

