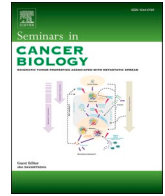




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# Long non-coding RNAs regulated NF- $\kappa$ B signaling in cancer metastasis: Micromanaging by not so small non-coding RNAs

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## ABSTRACT

Cancer metastasis is a major reason for the cancer-associated deaths and a role of long non-coding RNAs (lncRNAs) in cancer metastasis is increasingly being realized. Among the many oncogenic pathways, NF- $\kappa$ B signalling's involvement in cancer metastasis as a key inflammation-regulatory transcription factor has been a subject of interest for long time. Accumulating data from *in vitro* as well as *in vivo* studies along with analysis of clinical cancer tissues points to regulation of NF- $\kappa$ B signalling by lncRNAs with implications toward the onset of cancer metastasis. lncRNAs FOXD2-AS1, KRT19P3 and the NF- $\kappa$ B interacting lncRNA (NKILA) associate with lymph node metastasis and poor prognosis of individual cancers. The role of epithelial-mesenchymal transition (EMT) in cancer metastasis is well known. EMT is regulated by NF- $\kappa$ B and regulation of NF- $\kappa$ B/EMT-induced metastasis by lncRNAs remains a hot topic of research with indications for such roles of lncRNAs MALAT1, SNHG15, CRNDE and AC007271.3. Among the many lncRNAs, NKILA stands out as the most investigated lncRNA for its regulation of NF- $\kappa$ B. This tumor suppressive lncRNA has been reported downregulated in clinical samples representing different human cancers. Mechanistically, NKILA has been consistently shown to inhibit NF- $\kappa$ B activation via inhibition of I $\kappa$ B $\alpha$  phosphorylation and the resulting suppression of EMT. NKILA is also a target of natural anticancer compounds. Given the importance of NF- $\kappa$ B as a master regulatory transcription factor, lncRNAs, as the modulators of NF- $\kappa$ B signaling, can provide alternate targets for metastatic cancers with constitutively active NF- $\kappa$ B.

## 1. Introduction

Cancer is a devastating disease which affects millions of lives every year worldwide. In US alone, American Cancer Society estimated 1,898,160 new cancer cases and 608,570 cancer deaths for the current year 2021 [1]. Globally, the numbers stand at 19.3 million new cancer cases and ~10.0 million cancer deaths for the year 2020, based on the data from 185 countries [2,3]. Gender-wise, female breast cancer became the top-diagnosed cancer, surpassing lung cancer [2]. The overall incidence of breast cancer over the past decade has seen an upward trend largely due to increasing awareness and aggressive screenings [4]. Lung cancer remains the leading cancer in terms of

mortality, accounting for 18 % of all cancer-related deaths globally [2].

Cancer metastasis, the spread of cancer from its primary site of origin to distant organs, is the leading cause of cancer related mortality [5]. For many years, it has been believed that metastasis is responsible for about 90 % of cancer deaths [6–8]. However, based on the recently reported data [9], it could be safe to conclude that 66–90 % of cancer related deaths are due to metastasis. This calls for a better understanding of the cause(s) of cancer metastasis as well as novel therapeutic strategies for countermeasure. In recent years, non-coding RNAs have emerged as an interesting class of molecular factors with wide ranging diagnostic and therapeutic implications [10–14]. In addition to the widely studied small non-coding RNAs, the miRNAs [15–20], there has been steady

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increase in the rather larger non-coding RNAs, the long non-coding RNAs (lncRNAs) [21–23] in cancer progression and metastasis. lncRNAs exceed 200 nucleotides in length and belong to the class of non-coding RNAs because they do not translate into proteins. lncRNAs role in cancer metastasis is now increasingly being appreciated [24,25].

## 2. NF- $\kappa$ B signaling

NF- $\kappa$ B is a master regulator and a major transcription factor that regulates inflammation, immune responses and carcinogenesis [26,27]. NF- $\kappa$ B comprises of five master transcription factors: RelA (p65), Rel B, c-Rel, NF- $\kappa$ B1/p105, and NF- $\kappa$ B2/ p100, which can be activated by various stimuli such as bacterial and viral products (Lipopolysaccharide, dsRNA), cytokines (IL-1 $\beta$ ), UV and ionizing radiation, growth factors, reactive oxygen species (ROS), and oncogenic stress. The five master transcription factors can form a diverse array of dimeric complexes (homo or hetero) as they share conserved Rel homology (RHD) [28]. These stimuli lead to the instigation of the inhibitor of the I $\kappa$ B kinase (IKK) complex which contains three seminal components -IKK1/IKK $\alpha$ , IKK2/IKK $\beta$  and NEMO (NF- $\kappa$ B essential modifier)/IKK $\gamma$ . IKK $\alpha$  and  $\beta$  components are kinases and  $\gamma$  is a regulatory component of the complex. In unstimulated cells, this complex tightly binds NF- $\kappa$ B dimer, inhibits their DNA-binding activity and maintains steady-state localization in the cytoplasm whereas, in stimulated cells, the activated IKK complex phosphorylates I $\kappa$ B proteins, promoting their ubiquitination by the S-phase kinase-associated protein 1 (SKP-1) cullin 1-F-box protein (SCF)/  $\beta$ -transducin repeat-containing protein-dependent E3 ubiquitin ligase-mediated proteasomal degradation [29]. The NF- $\kappa$ B dimers transcriptional activity is regulated by two pathways -canonical and non-canonical. Canonical signaling pathways conglomerate on activation of the IKK complex which is composed of all three seminal components and is induced by pro-inflammatory cytokines whereas the non-canonical pathway requires the IKK $\alpha$  component only. NF- $\kappa$ B signaling is stringently regulated for cellular functioning, and dysregulation of these well-orchestrated events has been observed in cancer [30]. Its role in cancer development was reckoned when the mutation was found in several members of the NF- $\kappa$ B protein family such as in lymphoma, NF- $\kappa$ B was activated through chromosomal translocation [31]. Similarly, in Non-Hodgkin B-cell lymphoma, c-Rel components are amplified and rearranged [32]. The elevated NF- $\kappa$ B activity in tumorous tissue directly contributes to the pro-tumorigenic microenvironment [30]. This microenvironment may ultimately lead to immune suppression and favor tumor escape from immunosurveillance. Thus, the NF- $\kappa$ B pathway in cancer mainly contributes to induction and maintenance of chronic inflammatory microenvironment, although other effects, beyond inflammation, are also believed to be important [33]. Aberrant activation of NF- $\kappa$ B in cancer cells stimulates cell proliferation, prevents apoptosis, regulates tumor angiogenesis and metastasis, and remodels tumor metabolism [30,34,35].

NF- $\kappa$ B plays a major role in multiple steps of cancer progression and therefore identification of key NF- $\kappa$ B-dependent cancer vulnerabilities can possibly be exploited for cancer therapy [36]. Its role in cancer metastasis is well described [37,38]. In addition to affecting cancer cell proliferation, invasion and angiogenesis [30], NF- $\kappa$ B is profoundly connected to cancer stem cells [37,39] and the process of epithelial-mesenchymal transition (EMT) [40–42] which are well known to influence cancer metastasis.

## 3. lncRNAs as modulators of NF- $\kappa$ B signaling

Even though NF- $\kappa$ B signaling has been investigated for many years, its de-regulation in cancers, often resulting in constitutive activation, is not entirely understood. Non-coding RNAs in general [43] and lncRNAs in particular [44] are now believed to regulate as well as interact with NF- $\kappa$ B signaling, with major implications on tumor progression.

### 3.1. lncRNAs as NF- $\kappa$ B modulators in inflammation and different organs

Given the intricate connection between NF- $\kappa$ B and inflammation, it is not surprising that a number of lncRNAs have been associated with modulation of NF- $\kappa$ B in inflammation. While some reports are from cancer models, as discussed in the next sub-section, there are other reports that have described such activity of lncRNA, but in the model systems other than cancers and we provide a brief overview of such reports here.

lncRNA Gm4419 has been shown to play an important role in NF- $\kappa$ B signaling activation during inflammation in microglial cells with OGD/R (Oxygen-glucose deprivation/Reoxygenation) damage [45]. These deprived microglial cells express abnormally elevated Gm4419. Gm4419 physically interacts and promotes I $\kappa$ B $\alpha$  phosphorylation leading to NF- $\kappa$ B activation. Moreover, inhibition of Gm4419 leads to NF- $\kappa$ B inhibition. Thus, this regulatory role of Gm4419 represents an attractive therapeutic target in OGD/R damage. lncRNA-SLC4A1 is an enhancer RNA (eRNA) that was elevated with elevated H3K27ac modification in unexplained recurrent pregnancy loss (UPRL) [46]. This upregulated lnc-SLC4A1 recruits NF- $\kappa$ B, promotes CXCL8 expression, causes an inflammatory response, affects trophoblast cell migration and apoptosis, eventually leading to UPRL. lncRNA-XIST (X-inactive specific transcript) modulates NF- $\kappa$ B phosphorylation and NLRP3 inflammasome formation in bovine mastitis tissue [47]. In bovine mammary alveolar cells -T (MAC-T), XIST expression was abnormally elevated. XIST silencing significantly elevated the expression of pro-inflammatory cytokines. Moreover, it also suppressed cell proliferation, viability, and stimulated apoptosis under inflammatory conditions via an involvement of NF- $\kappa$ B. Activated NF- $\kappa$ B promoted XIST and NLRP3 inflammasome expression. In turn, XIST generated a negative feedback loop to modulate NF- $\kappa$ B/ NLRP3 inflammasome pathway for intervening in the inflammation process. Thus, XIST inhibits excessive and sustained inflammation process and this sustained activation leads to cell and tissue damage.

A role of lncRNAs in even *Listeria monocytogenes* (Lm) infection and related inflammation has been suggested [48]. lncRNA Cox2 was reported elevated in Lm-infected RAW264.7 cells and its down-regulation resulted in reduction in pro-inflammatory cytokines with reduced nuclear translocation of NF- $\kappa$ B. Even in rheumatoid arthritis, where inflammatory cytokines are functionally involved in disease progression, there is evidence for NF- $\kappa$ B-lncRNA interaction. lncRNA linc00152 is up-regulated in rheumatoid arthritis fibroblast-like synoviocytes through a NF- $\kappa$ B-dependent mechanism [49]. Interestingly, there seems to be a feedback loop wherein linc00152 activates NF- $\kappa$ B pathway through upregulation of TAK1 expression. In osteoarthritis, lncRNA SNHG14 inhibits NF- $\kappa$ B signaling and the resulting inflammation and therefore this lncRNA is downregulated during the disease progression [50]. lncRNA SNHG15 is upregulated along with NF- $\kappa$ B during neuronal damage and microglial inflammation after ischemic stroke [51]. In the inflammatory processes related to non-alcoholic steatohepatitis, a role of lncRNA gm9795 has been suggested [52]. This lncRNA upregulates endoplasmic reticulum stress and the NF- $\kappa$ B signaling. In psoriasis, a very common chronic inflammatory skin condition, lncRNA UCA1 negatively correlates with NF- $\kappa$ B [53]. UCA1 is downregulated in skin lesions of psoriasis patients that are marked by high inflammation and NF- $\kappa$ B activation.

lncRNA HOTAIR induces NF- $\kappa$ B signaling in immune cells, specifically macrophages, with impact on glucose uptake and metabolism [54]. In T-cells of patients with ankylosing spondylitis, lncRNA LOC645166 is markedly reduced and such downregulation of LOC645166 leads to upregulation of NF- $\kappa$ B through dysregulated ubiquitination machinery thus resulting in increased sensitivity to stimulation by proinflammatory cytokines [55].

Inflammation is central to lung diseases [56] and therefore there are reports connecting lncRNAs with NF- $\kappa$ B in lung cells. For example, lncRNA TUG1 can aid airway remodeling through sponging of miR-181b

that targets HMGB1 (high mobility group box 1) [57]. TUG1 is elevated in asthmatic mice and it activates NF- $\kappa$ B signaling through its effects on HMGB1. lncRNA NKILA regulates NF- $\kappa$ B signaling thereby affecting secretory function of airway epithelial cells during bacterial infections [58]. In LPS-induced pulmonary inflammation, lncRNA MIAT is upregulated [59]. Silencing of MIAT resolves the LPS-mediated injury to lung epithelial cells through inhibition of NF- $\kappa$ B signaling. Even in the acute lung injury (ALI), lncRNAs regulate NF- $\kappa$ B signaling and such role of lncRNA NEAT1 has been reported [60]. NEAT1 is elevated in lung tissues of ALI mice where it activates NF- $\kappa$ B signaling through TRIM37 (tripartite motif-containing 37) and NEAT1's downregulation resolves inflammation.

### 3.2. lncRNAs as NF- $\kappa$ B modulators in human cancers

A number of lncRNAs have been demonstrated to affectively regulate NF- $\kappa$ B signaling in human cancers. For instance, LSINCT5 (Long stress-induced non-coding transcript 5) [61], an oncogenic lncRNA acts as competing endogenous RNA (ceRNA) to specifically bind to miR-451. Rac1, one of the targets of miR-451, is a Rho GTPase family member and mediates glioma cells' metastasis through regulating NF- $\kappa$ B pathway. Targeting miR-451 via LSINCT5-modulated Rac1 expression opens opportunities for potential adjuvant therapy of glioma. In glioma, LSINCT5 is highly expressed and miR-451 expression is remarkably low in gliomas, and the study provided evidence for the regulation of NF- $\kappa$ B in glioma by the LSINCT5/miR-451/Rac1 axis. lncRNA PCAT1 (Prostate Cancer Associated Transcript 1) was also shown to regulate NF- $\kappa$ B and revealed to be a novel therapeutic target in castration-resistant prostate cancer (CRPC) [62]. PCAT1 expression correlated with CRPC progression. PCAT1 perturbed the complex PHLPP/FKBP51/IKK $\alpha$  by binding to FKBP51-binding protein 51 (FKBP51) and displacing PH and leucine-rich repeat protein phosphatase (PHLPP), leading to NF- $\kappa$ B and Akt activation. Targeting PCAT1 restored binding of PHLPP to FKBP51 leading to suppression of NF- $\kappa$ B and Akt. Another study demonstrated lncRNA-ANRIL (antisense noncoding RNA in the INK4 locus) involvement in the progression of gastric cancer via regulation of NF- $\kappa$ B signaling and this study suggested NF- $\kappa$ B signaling as a potential biomarker for prognosis and treatment [63]. Tet methylcytosine dioxygenase 2 (TET 2) inhibited ANRIL function and forestalled cancer progression. Higher ANRIL expression stimulates cancer whereas higher TET2 expression inhibits cancer progression and endured better condition in patients indicating their negative correlation.

lncRNA-BORG (BMP/OP-responsive genes) has gained interest for its role in the metastasis and disease recurrence of TNBC (triple negative breast cancer) [64]. Given the clinical challenges posed by the recurrent breast cancers [65], this lncRNA could be of possible diagnostic/prognostic importance. BORG seems to play a role in the survival of TNBC cells by making them resistant to chemotherapy such as doxorubicin [66]. It was induced upon chemotherapeutic and environmental stress in TNBC. This resistance in BORG-expressing TNBCs was due to their ability to activate NF- $\kappa$ B. Thus, BORG can be a therapeutic target to suppress TNBC recurrence. lncRNA-PACER (P50-associated COX-2 extragenic RNA) regulates the expression of COX-2 and is expressed upstream to COX-2 [67]. COX-2 is a key player in tumor development [68]. In mammary epithelial cells and macrophages, upon LPS-stimulation, COX-2, and PACER expressions are markedly elevated. When PACER is inhibited, COX-2 expression is also drastically alleviated. This suggests PACER's modulatory role on COX-2 expression. The mechanism behind this role is that upon LPS stimulation, PACER gets elevated and this obstructs the inhibitory p50/p50 homodimer binding with COX-2 promoter and promotes active heterodimer p60/p50 binding and ultimately leads to COX-2 activation. Thus, in COX-2 associated cancers, PACER can be a therapeutic target [67]. Another lncRNA that has been shown to play a role in NF- $\kappa$ B related inflammation in macrophages is Tnfaip3 [69].

In ovarian cancer, GCLnc1 is involved in cell growth and tumor

**Table 1**

lncRNAs that regulate NF- $\kappa$ B Signaling in human cancers.

lncRNA	Cancer	NF- $\kappa$ B Signaling regulation Effects	References
ANRIL	Gastric	Targets Tet methylcytosine dioxygenase 2 and promotes tumor progression	[63]
BORG	Breast	Provides resistance against Doxorubicin in triple negative breast cancers	[66]
GCLnc1	Ovarian	Elevates NOTCH1 and induces EMT	[70]
LINC00173	Pancreatic	Inhibits SPHK1 and induces apoptosis	[72]
LINC00467	Bladder	Stabilizes NF- $\kappa$ B and promotes its nuclear translocation	[71]
LSINCT5	Glioma	Highly expressed lncRNA that targets miR-451 and regulates metastasis	[61]
MALAT1	OSCC	Induces EMT	[95]
PACER	Breast	Correlates positively with COX-2 expression	[67]
PCAT1	Prostate	Correlates with progression of castrate resistant prostate cancer and activates NF- $\kappa$ B-Akt	[62]

ANRIL: antisense noncoding RNA in the INK4 locus, BORG: BMP/OP-responsive genes, EMT: Epithelial-Mesenchymal Transition, LSINCT5: Long stress-induced non-coding transcript 5, MALAT1: Metastasis associated lung adenocarcinoma transcript 1, OSCC: Oral Squamous Cell Carcinoma, PACER: P50-associated COX-2 extragenic RNA, PCAT: Prostate Cancer Associated Transcript 1, SPHK1: Sphingosine Kinase 1, TSCC: Tongue squamous cell carcinoma.

metastasis. It was reported elevated in epithelial ovarian cancer tissues in a study that evaluated 57 paired ovarian cancer and paracancerous tissues [70]. In the mechanistic studies performed in ovarian cancer cells OVC1 and SKOV3, knockdown of this lncRNA induced apoptosis and reduced cell viability. GCLnc1 induced NOTCH1 which, in turn, induced NF- $\kappa$ B signaling. LINC00467 was evaluated in bladder cancer using bioinformatic tools and was found to be highly expressed in bladder cancer tissues [71]. It correlated negatively with patient prognosis and, moreover, confirmatory experiments *in vitro* as well as *in vivo* validated the positive effect of LINC00467 on bladder cancer cells proliferation and invasion. Further, LINC00467 stabilized NF- $\kappa$ B and promoted its translocation to the nucleus, thus providing a mechanism for bladder cancer progression. LINC00173, on the other hand, suppresses tumor growth and in a study performed on pancreatic cancer models, both *in vitro* using PANC-1 and MiaPaCa-2 cells and *in vivo* in pancreatic cancer xenografts, LINC00173 was found to inhibit cell proliferation and promote apoptosis through reduced expression of SPHK1 (sphingosine kinase 1) expression with resulting repressed NF- $\kappa$ B signaling [72]. Based on these reports, it can be concluded that the studies detailing a modulatory role of lncRNAs on NF- $\kappa$ B signaling have slowly been emerging (Table 1).

### 4. lncRNAs-regulated cancer metastasis: evidence from *in vivo* studies

Patients with cancer metastasis most often carry a grave prognosis, and metastasis remains a major cause of cancer-related fatalities [73]. Thus, a comprehensive understanding of the etiology of metastases is important. The biological convolution that depicts metastasis necessitates a complex experimental model and the modeling to a large extent is only possible using animal models [74]. Models of metastasis are genetically modified mice and transplantable models (syngeneic or xenografts) [75,76]. Additionally, experimental models of cancer metastasis can also provide insights into the mechanisms of cancer metastasis [38,75]. In the area of cancer research, the value of the experimental *in vivo* model has been characterized on the basis of analogy shared amid human cancer and the animal that is being represented [77]. This approach leads to defining of the best cancer prototype and value assignments. It is generally recognized that one system/cancer model alone is not enough to understand the complexity observed among cancer patients in the clinics. The pertinent model(s) for study can be chosen by understanding the strengths and identifying the weaknesses of

the available set of models. *In vivo* models of cancer metastasis have served an important value to investigate the disparity of phenotypes linked with metastatic progression [78]. It is challenging to develop an *in vitro* model system that can faithfully replicate all myriad challenges that disperse tumor cells face, therefore, *in vivo* models will continue to be the pivotal workhorse in metastasis research for foreseeable future.

There is evidence from animal studies and experimental metastasis models to support regulation of cancer metastasis by lncRNAs (Table 2). Studies describing such effects of lncRNAs include, lncRNA Myd88 [79] and miR503HG [80] in hepatocellular carcinoma (HCC), LINC01410 in gastric cancer [81], TLR8-AS1 [82] and GClnc1 [70] in ovarian cancer, LINC00467 in bladder cancer [71] and NKILA in lung and esophageal cancers. LncRNA Myd88 is located upstream of the Myd88 gene and positively regulates Myd88 gene expression in HCC [79]. Myd88 is an oncogene that stimulates tumor accumulation, metastasis and equates with a poor prognosis in HCC. The elevated expression of Myd88 gene by lnc Myd88 is via augmenting H3K27ac in the promoter region of Myd88. This hepatocarcinogenesis is promoted through stimulation of NF- $\kappa$ B and PI3K/AKT signaling pathways. Thus, up-regulated Lnc-Myd88 provokes tumor progression and worsens HCC outcome. So, it might be a potential prognostic marker and a novel index for diagnosis. HCC has also been linked with another lncRNA, lncRNA-miR503HG, with resulting affects on metastasis [80]. LncRNA-miR503HG is the host gene for miR-503. It is significantly reduced in HCC and its expression level is significantly linked with recurrence time and overall survival. *In vitro* and *in vivo* studies suggested that enhanced expression of miR503HG noticeably inhibits invasion and metastasis. miR503HG specifically associates with HNRNPA2B1 (heterogeneous nuclear ribonucleoprotein A2/B1) and stimulates its degradation which decreases p65 and p52 mRNA stability, and subsequently disturbs the NF- $\kappa$ B signaling. miR503HG and miR503 are co-expressed and inhibit migration of HCC cells through inhibition of NF- $\kappa$ B signaling pathway. miR503HG imposes its metastatic tumor repression function via regulating HNRNPA2B1 ubiquitination status [80].

LINC01410 upregulation plays a vital role in gastric cancer (GC) carcinogenesis [81]. LINC01410 is a negative regulator of miR-532–5p, a tumor suppressor in GC. *in vitro* and *in vivo* miR-532–5p over-expression study revealed its inhibitory effect on metastasis and

angiogenesis of GC. The underlying mechanism implicated in the effect of LINC01410 on the miR-532–5p-mediated metastatic tumor is that miR-532–5p attenuates the NF- $\kappa$ B pathway by suppressing NCF2 expression. It was also demonstrated in this study that downregulation of miR-532–5p can be ascribed to aberrant upregulated expression of LINC01410 in GC. High expression of LINC01410 stimulates metastasis and angiogenesis by suppressing miR-532–5p leading to upregulation of NCF2 and NF- $\kappa$ B pathway. Intriguingly, NCF2 consequently increases the expression and the promoter activity of LINC01410 through NF- $\kappa$ B, thus amplifying the message. Thus, this manifests a positive feedback loop and directs the malignant behavior in GC. Another lncRNA TLR8-AS1 also activates NF- $\kappa$ B signaling and stabilizes TLR8 mRNA to facilitate chemoresistance and metastasis in ovarian cancer (OC) [82]. The axis TLR8-AS1/TLR8/NF- $\kappa$ B in OC is responsible for modulating the instigative impacts of TLR8-AS1 on OC metastasis. Bioinformatics approach identified TLR8-AS1 as cancer-associated fibroblast-regulated lncRNA in OC and *in vitro* and *in vivo* experiments demonstrated its role in the augmentation of metastasis and chemoresistance. TLR8-AS1 augments TLR8 by stabilizing TLR8 mRNA and thus instigating NF- $\kappa$ B and promoting OC metastasis. TCGA data analysis revealed that TLR8-AS1 is upregulated in OC and high expression is correlated with poor prognosis. Thus, it can be indexed as a possible prognostic indicator for OC. In tongue squamous cell carcinoma (TSCC), lncRNA NKILA has been shown to inhibit lung metastasis in NOD/SCID mice through a mechanism that involves suppression of NF- $\kappa$ B activation [83]. In esophageal squamous cell carcinoma (ESCC), NKILA inhibited metastasis *in vivo* through suppression of MMP14 which involved inhibition of NF- $\kappa$ B [84]. Thus, a number of investigations *in vivo* support a modulation of NF- $\kappa$ B signaling by lncRNAs with resulting effects on cancer metastasis.

## 5. lncRNAs affect NF- $\kappa$ B signaling to regulate lymph node metastasis

For a long time, it has been realized that lymph node metastasis of several primary cancers represents an important mechanism in the overall metastasis of human cancers [85]. Now it is known that cancer patients with lymph node metastasis have poorer prognosis compared to patients without such nodal metastasis and that tumor cells and their secreted factors contribute to mechanisms that help evade immune surveillance [86]. Thus, lymph node metastases have remained important metastases to watch during the tumor progression. lncRNAs are increasingly being realized to be involved in the lymph node metastases of several cancers with indications for their possible role as predictors of lymph node metastasis [87,88].

A few lncRNAs have already been reported to involve regulation of NF- $\kappa$ B as their mechanism of influencing lymph node metastasis (Table 3). For example, FOXD2-AS1, an upregulated lncRNA in TSCC, associates with increased lymphatic metastasis through modulation of NF- $\kappa$ B, as evidenced by deregulated phospho-p65 [89]. High expression

**Table 2**

lncRNAs that influence cancer metastasis *in vivo* through the regulation of NF- $\kappa$ B.

lncRNA	Target	Cancer	Effects	References
AC007271.3	miR-125b-2–3p	OSCC	Inhibits epithelial marker E-cadherin and induces EMT	[103]
CRNDE	miR-539–5p	HCC	Highly expressed in HCC cells and tissues; induces EMT through NF- $\kappa$ B and Akt	[102]
LINC01410	miR-532–5p	Gastric	Higher expression in GC supports angiogenesis and metastasis	[81]
miR503HG	miR-503	HCC	Inhibits NF- $\kappa$ B and metastasis	[80]
Myd88	Myd88 gene	HCC	Affects acetylation through H3K27 and correlates with poor prognosis	[79]
NKILA	MMP14	ESCC	Inhibits NF- $\kappa$ B and metastasis	[84]
	EMT	TSCC	Inhibits NF- $\kappa$ B activation	[83]
SNHG15	–	RCC	Up-regulated in cancer tissues and induces EMT	[101]
TLR8-AS1	TLR8 gene	Ovarian	Potential prognostic biomarker which also induces chemoresistance	[82]

EMT: Epithelial-Mesenchymal Transition, ESCC: Esophageal Squamous Cell Carcinoma, GC: Gastric Cancer, HCC: HepatoCellular Carcinoma, OSCC: Oral Squamous Cell Carcinoma, RCC: Renal Cell Carcinoma, TSCC: Tongue Squamous Cell Carcinoma.

**Table 3**

lncRNA-mediated lymph node metastasis through NF- $\kappa$ B regulation.

lncRNA	Status	Cancer	Outcomes	References
FOXD2-AS1	Increased in lymph node metastases	TSCC	High expression correlates with poor prognosis	[89]
KRT19P3	Decreased in lymph node metastases	GC	Low expression correlates with advanced TNM staging and poor prognosis	[90]
NKILA	Decreased in lymph node metastases	NSCLC	Low expression correlates with advanced TNM staging	[91]

GC: Gastric Cancer; KRT19P3: Keratin 19 Pseudogene 3, NSCLC: Non-small cell lung cancer, TSCC: Tongue Squamous Cell Carcinoma.



of this lncRNA correlated with poor prognosis as would be expected given its association with lymph node metastasis. KRT19P3 (Keratin 19 Pseudogene 3) is a tumor suppressor lncRNA which is decreased in gastric cancer and such down-regulated expression levels of this lncRNA correlate with increased lymph node metastasis [90]. Lower levels of KRT19P3 also associate with larger tumor size, tumor progression, advanced TNM stages and poor prognosis. The down-regulation of lncRNA NKILA has also been linked to significantly increased lymph node metastasis of primary NSCLC [91] as well as advanced TNM stage.

## 6. lncRNAs connecting NF- $\kappa$ B, EMT and metastasis

Epithelial-Mesenchymal Transition (EMT) is a fundamental process of phenotype transition that is tightly regulated by transcription factors. During this transition, the epithelial cells undergo major morphological and transcriptional transformations, leading to loss of their cell-cell adhesion molecule (E-cadherin) and attainment of mesenchymal-like properties though the gain of mesenchymal markers such as Vimentin, ZEB1/2, N-cadherin and transcription factors (snail, slug, and twist) etc. The transformed cells now loose junctional connections and disengage from the epithelial layers where they arose, and express mesenchymal markers. This mesenchymal phenotype is evident in elevated migratory activity, extracellular matrix production, invasiveness and enhanced resistance to apoptosis and therapies [92–94]. Now the cells can penetrate into blood vessels, lymphatics, and distant body parts where they can form metastatic lesions. NF- $\kappa$ B is well connected with the process of EMT [38,40–42]. Thus, EMT's regulation by NF- $\kappa$ B represents another step wherein regulation by lncRNAs can have major implications.

In a report on oral squamous cell carcinoma (OSCC), lncRNA MALAT1 (Metastasis associated lung adenocarcinoma transcript 1) was linked to NF- $\kappa$ B signaling and EMT [95]. MALAT1 expression correlated with upregulation of mesenchymal markers, N-cadherin, vimentin and downregulation of E-cadherin, an epithelial marker, along with activation of NF- $\kappa$ B and  $\beta$ -catenin. Similar to NF- $\kappa$ B,  $\beta$ -catenin also promotes tumor progression and EMT-mediated metastasis [96–98]. This study revealed MALAT1 as a new prognostic marker in OSCC patients as it plays an essential role in maintaining EMT-mediated metastasis. MALAT1 has also shown to be involved in NF- $\kappa$ B mediated EMT induced by particulate matter in lung bronchial epithelial cells [99] and in the NF- $\kappa$ B mediated resistance to therapy in glioblastoma [100]. lncRNA SNHG15 has been reported up-regulated in renal cell carcinoma (RCC) tissues as well as cell lines [101] and it promotes RCC cells' invasion and migration through NF- $\kappa$ B-mediated induction of EMT. Another lncRNA that plays a role in EMT induction through regulation of NF- $\kappa$ B pathway is CRNDE [102]. This lncRNA was reported elevated in HCC cells and tissues and it inhibited E-cadherin while inducing vimentin. It sponged miR-539–5p in its induction of NF- $\kappa$ B-induced EMT of HCC cells. Finally, lncRNA AC007271.3 has recently been reported to affect EMT in a way that involves NF- $\kappa$ B [103]. This study conducted in OSCC found that AC007271.3 promoted tumorigenesis by up-regulating Slug which was a result of sponging of Slug-targeting miRNA, miR-125b-2–3p. Expression of AC007271.3 correlated with canonical NF- $\kappa$ B and interestingly AC007271.3 inhibited epithelial marker E-cadherin but had no effect on mesenchymal markers tested which still was good enough for the induction of EMT. lncRNA GClncl has been reported to induce EMT in ovarian cancer cells in a NOTCH1-dependent manner with resulting impact on tumor cell metastasis [70].

## 7. lncRNA NKILA: the lncRNA connecting NF- $\kappa$ B, EMT and metastasis

There is evidence for direct interactions of lncRNAs with NF- $\kappa$ B. lncRNA NKILA is a cytoplasmic lncRNA which is upregulated by NF- $\kappa$ B and it masks phosphorylation of I $\kappa$ B thereby preventing further activation of NF- $\kappa$ B [104]. This represents a tight regulation of NF- $\kappa$ B signaling

**Table 4**

NKILA: the lncRNA that regulates NF- $\kappa$ B-mediated EMT and cancer metastasis.

Cancer	Effect on NF- $\kappa$ B signaling	Effect on EMT	References
Breast	Negatively regulates NF- $\kappa$ B	Negatively correlates with EMT phenotype in clinical breast cancer samples	[108]
	Inhibits I $\kappa$ B $\alpha$ phosphorylation	Inhibits IL-6-induced EMT	[110]
ESCC	Suppresses NF- $\kappa$ B activation	Impacts TGF- $\beta$ signaling	[84]
HCC	Suppresses I $\kappa$ B $\alpha$ phosphorylation	Inhibits Slug and EMT	[106]
NSCLC	Inhibits I $\kappa$ B $\alpha$ phosphorylation	Down-regulates Snail through inhibition of EMT	[91]
TSCC	Inhibits I $\kappa$ B $\alpha$ phosphorylation	Inhibits EMT	[83]

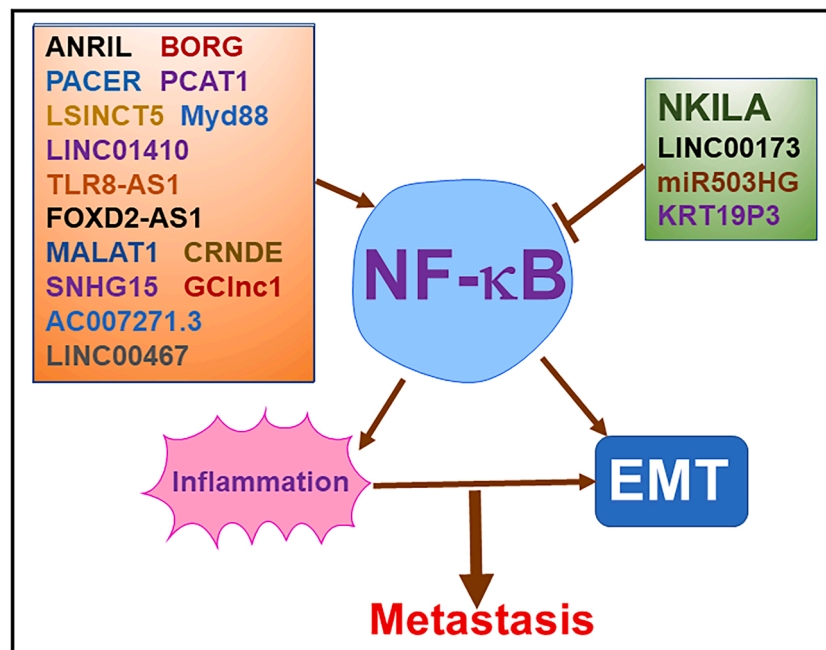
ESCC: Esophageal Squamous Cell Carcinoma, HCC: HepatoCellular Carcinoma, NSCLC: Non-Small Cell Lung Carcinoma, TSCC: Tongue Squamous Cell Carcinoma.

by an endogenous lncRNA with the aim to keep NF- $\kappa$ B activity in check. RNA binding protein co-immunoprecipitation experiments have confirmed binding of NKILA to p65 in osteosarcoma cells [105].

NKILA is perhaps the most well characterized lncRNA in terms of its role in NF- $\kappa$ B-mediated EMT in different human cancer models. Its name, an abbreviation of 'NF- $\kappa$ B interacting lncRNA', is itself an indicator of its activity. Since it is a tumor suppressor lncRNA, therefore, in TSCC patient samples, the levels of NKILA were reported lower than in the matched adjacent non-cancerous tissues [83]. Further, NKILA was shown to inhibit phosphorylation of I $\kappa$ B $\alpha$  which inhibited the activation of NF- $\kappa$ B as well as EMT. In NSCLC as well, NKILA was reported to be expressed at lower levels in cancer tissues, compared to matched adjacent non-cancerous tissues [91]. This study also identified inhibition of I $\kappa$ B $\alpha$  phosphorylation as the mechanism of action of NKILA which inhibited NF- $\kappa$ B and, subsequently, Snail. NKILA is expressed at lower levels in HCC tissues as well [106] and such decreased levels of NKILA in HCC patients associate with relatively larger tumor burden and the positive vascular invasion. Similar to its mechanism in other cancers, in HCC as well, this lncRNA suppresses I $\kappa$ B $\alpha$  phosphorylation and p65 nuclear translocation thus inhibiting NF- $\kappa$ B activation and the induction of EMT.

NKILA was also shown down-regulated in ESCC which resulted in de-repression of NF- $\kappa$ B activation and increased metastasis [84]. This study identified NKILA as the lncRNA of interest upon RNA-seq analysis to compare lncRNAs expression levels between TGF- $\beta$ 1-treated and untreated ESCC cells. NKILA was significantly down-regulated in ESCC tumor tissues and, moreover, its expression was significantly decreased in advanced grade III and IV tumors, compared to early stage grade I and II tumors. NKILA was reported downregulated in nasopharyngeal carcinoma (NPC) as well where it affected metastasis through regulation of NF- $\kappa$ B signaling [107]. This study evaluated 107 paraffin-embedded tissues from NPC patients and found NKILA to be down-regulated in cancer tissues. Low NKILA levels predicted poor survival outcome and metastatic potential *in vitro* and *in vivo*.

Similar to some reports above, NKILA was reported to be upregulated by TGF- $\beta$  and essential for the negative feedback regulation of NF- $\kappa$ B pathway in breast cancer [108]. It suppressed TGF- $\beta$ -induced EMT which mechanistically involved blocking of NF- $\kappa$ B activation [108]. In breast cancer cells, both triple negative MDA-MB-231 as well as the estrogen receptor-positive MCF-7, NKILA regulated EMT in a NF- $\kappa$ B-dependent manner [109]. In just the MDA-MB-231 cells, NKILA was shown to reverse the IL-6 induced EMT, viability and migration of cells [110]. Ectopic expression of NKILA directly inhibited IL-6, VEGF as well as the phosphorylation of I $\kappa$ B $\alpha$  and the nuclear transposition of p65. Based on these studies, the importance of NKILA as the NF- $\kappa$ B modulating lncRNA is unmatched (Table 4).



**Fig. 1. lncRNAs-regulated NF- $\kappa$ B signaling in cancer metastasis.** Several oncogenic lncRNAs upregulate NF- $\kappa$ B signaling while a few tumor suppressive lncRNAs, including NKILA, inhibit NF- $\kappa$ B signaling. Activated NF- $\kappa$ B leads to inflammation and EMT (Epithelial-Mesenchymal Transition) ultimately leading to metastasis and spread of cancer to lymph nodes and other organs.

## 8. Regulation of lncRNAs-NF- $\kappa$ B by anticancer natural compounds

Several naturally occurring compounds from various sources have been proposed as putative anticancer drugs based on the comprehensive *in vitro* and *in vivo* investigations [111–121]. Many of these compounds function *via* inhibition of NF- $\kappa$ B signaling [42]. Additionally, emerging literature suggests regulatory effect of many of these compounds on lncRNAs [122–125].

A few reports have directly assessed an effect of natural compounds on lncRNAs and the NF- $\kappa$ B signaling. For example, the anti-cancer effects of baicalein (5,6,7-trihydroxyflavone), a naturally occurring flavone and a constituent of several ethnic medications [126], were potentiated by lncRNA NKILA in HCC [127]. Moreover, silencing of NKILA abrogated the anticancer effects of baicalein suggesting its involvement in baicalein activity. As a further mechanism, NF- $\kappa$ B nuclear translocation inhibitor JSH-23 attenuated the NKILA effects, thus tying baicalein action with lncRNA NKILA and NF- $\kappa$ B signaling. Bharangin, a diterpenoid quinonemethide and a potent inhibitor of NF- $\kappa$ B activation [128], has been reported to induce expression of tumor suppressor lncRNAs MEG-3 and GAS-5 and suppress oncogenic lncRNA H19 concomitantly with NF- $\kappa$ B inhibition in breast cancer cells [129]. The active fraction of *Polyrhachis vicina* Rogers, a traditional Chinese medicine, was recently shown to possess anti-inflammatory potential through its regulation of lncRNA NKILA [130]. This active fraction upregulated the tumor suppressive NKILA resulting in reduced cell proliferation, invasion, clonogenicity and tumor growth through dysregulated NF- $\kappa$ B signaling. There seems to be an effect of specific diets, such as Mediterranean diet, on the expression of lncRNAs and NF- $\kappa$ B signaling [131] and the identity of individual dietary components responsible for such activity remains to be elucidated. In addition to the few reports discussed above that directly evaluated the effect of a natural anticancer agent on lncRNA(s) and NF- $\kappa$ B signaling, it needs to be pointed out that many such compounds are well known modulators of NF- $\kappa$ B signaling [42] and more recent literature is indicative of a lncRNA-modulating effect of these same compounds [124,132–134]. It will not be surprising if these two seemingly different activities of these

compounds are actually found to be related in future investigations.

## 9. Conclusions and perspectives

The importance of NF- $\kappa$ B as the master regulator of tumorigenesis and cancer progression and metastasis is undeniable. It regulates inflammation, EMT and cancer metastasis (Fig. 1). The studies on lncRNAs as modulators of NF- $\kappa$ B in general, and NF- $\kappa$ B-mediated EMT in particular, have opened up avenues for the possible successful targeting of oncogenic NF- $\kappa$ B signaling in patients with metastatic disease. NF- $\kappa$ B is a key player in metastasis as well the resistance to different therapies and, therefore, modulation of its activity by lncRNAs is important to be completely understood and characterized. The data from *in vivo* and pre-clinical studies as well as the analysis of patients-derived samples provide solid proof in support of the clinical utility of lncRNAs. The best case scenario is their possible utilization as targets for therapy but even their validation as diagnostic and/or prognostic biomarkers is more than a mere consolation. Clearly, the focus for future studies should be on the design of more translational studies aimed at manipulating lncRNA levels through targeted and non-toxic delivery systems.

## Declaration of Competing Interest

The authors report no declarations of interest.

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