

Review Article

Lnc-ing inflammation to disease

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Termed ‘master gene regulators’ long ncRNAs (lncRNAs) have emerged as the true vanguard of the ‘noncoding revolution’. Functioning at a molecular level, in most if not all cellular processes, lncRNAs exert their effects systemically. Thus, it is not surprising that lncRNAs have emerged as important players in human pathophysiology. As our body’s first line of defense upon infection or injury, inflammation has been implicated in the etiology of several human diseases. At the center of the acute inflammatory response, as well as several pathologies, is the pleiotropic transcription factor NF- κ B. In this review, we attempt to capture a summary of lncRNAs directly involved in regulating innate immunity at various arms of the NF- κ B pathway that have also been validated in human disease. We also highlight the fundamental concepts required as lncRNAs enter a new era of diagnostic and therapeutic significance.

Master gene regulators: lncRNAs

The ‘noncoding revolution’ [1] has reformed our understanding of how the eukaryotic genomic code is arranged, regulated and transcribed. Simply defined as the transcribed yet untranslated component of the genomic code, noncoding RNAs (ncRNAs) have been classified by base pair length, genomic origin and their functional mechanisms. Representing 70% of the noncoding genome, long ncRNAs (lncRNAs) have played a vital role in substantiating this revolution [2–4]. Collectively classified as ncRNA’s greater than 200 nucleotides in length, lncRNAs are defined by their genomic locale [3,5], epigenetic characteristics [6,7], neighboring protein-coding genes [3,6], tissue specificity [8,9] and their molecular mechanisms (Figure 1). Historically, mutations and alterations at the genomic loci of protein-coding genes were thought to be casual to many human ailments. However, the potency in which lncRNAs can modulate gene expression in a plethora of cellular processes sets a precedent for lncRNAs to play a significant role in the etiology of human disease.

The inflammatory conductor: NF- κ B

The inflammatory response is a highly co-ordinated symphony of transient and sustained tunes orchestrated by a myriad of cells, cytokines, chemokines, regulatory factors and gene products. Given the variety and quantity of components functioning in this complex biological phenomenon, it is not surprising that inflammatory disharmonies underlie a variety of pathophysiological conditions. Discovered over 30 years ago, the pleiotropic transcription factor, NF- κ B, has served as a paradigm for conducting immune homeostasis and maintaining harmonic balance during the inflammatory response [10,11]. Thus, we sought to zoom in on the intersection of lncRNA and NF- κ B functionality in the context of human pathophysiology.

There are essentially two main pathways leading to NF- κ B activation: the canonical and alternative pathways [12]. The canonical pathway (Figure 2a), the focus of this review, involves the activation of an I κ B- α kinase (IKK) complex which contains NF- κ B essential modulator (NEMO) and two kinase subunits, IKK α and IKK β . NEMO tethers and regulates the ubiquitylation of the catalytic IKK α and IKK β subunits. The inactive NF- κ B/I κ B- α complex is maintained in the cytoplasm until IKK α and IKK β mediate the phosphorylation of I κ B- α at two serine residues, respectively, causing I κ B- α to lose

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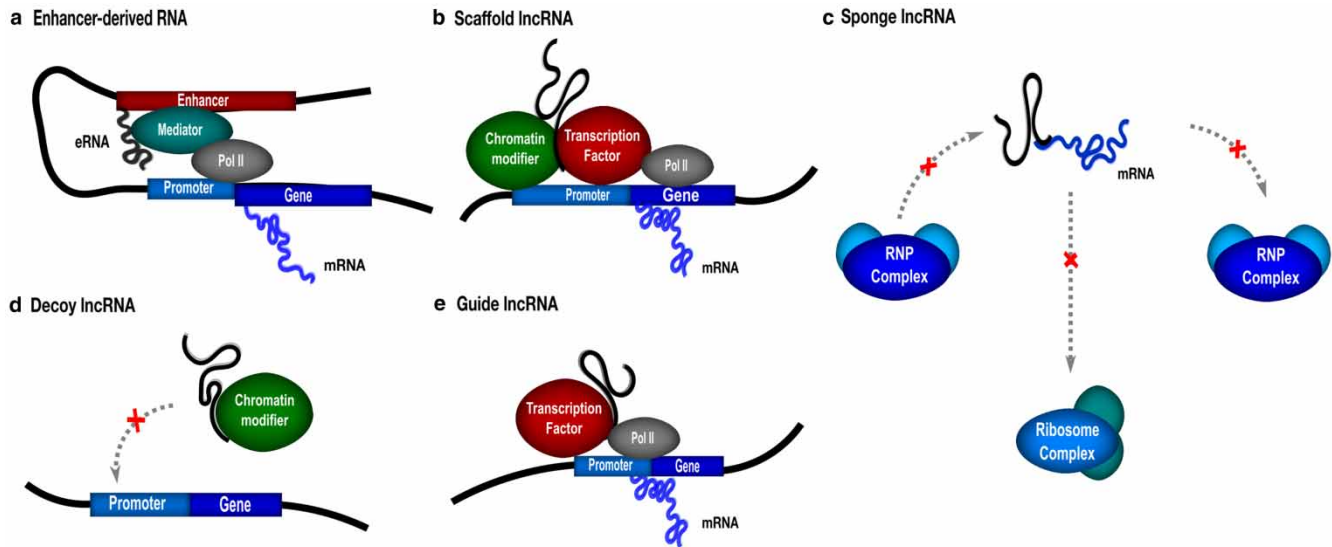


Figure 1. Molecular mechanisms of lncRNAs.

(a) **Enhancer-derived RNAs** are short RNAs transcribed from regulatory enhancer regions. eRNAs bind to a mediator, a multiprotein complex, to elicit chromatin looping and long-range chromatin contacts with a parental enhancer and target gene promoters, leading to the activation target genes. (b) **Scaffold** lncRNAs function by binding to chromatin modifiers, transcriptional and/or repressive factors within a single complex, resulting in DNA binding at target gene promoters. (c) **Sponge** lncRNAs function as molecular ‘sinks’ for miRNAs and/or mRNAs to regulate translation and/or inhibit the formation of RNP complexes. (d) **Decoy** lncRNAs function as ‘sponges’ for transcription factors and chromatin modifiers, titrating them away from target gene loci. (e) Guide RNAs act as molecular cues for transcription factors and chromatin modifiers at target gene loci.

its binding affinity to the NF- κ B complex. The newly released and activated NF- κ B complex is a heterodimeric complex consisting of the subunits p65/RelA and p50. This active form of NF- κ B, free from I κ -B α , then translocates into the nucleus where it binds to and transcriptionally activates the promoters of hundreds of genes including several inflammatory cytokines such as TNF- α , IL-6, Cox2 and IL-1 [13,14]. This canonical NF- κ B pathway is highly autoregulatory, with NF- κ B itself and/or its gene targets increasing the transcriptional activation of I κ -B α , which in turn recruits NF- κ B back into the cytoplasm [15,16]. Dysregulation of any of the molecular components of the NF- κ B pathway has been consistently linked to several human disorders from cancer to autoimmune diseases. During the ‘noncoding revolution’, several lncRNAs within the canonical NF- κ B pathway were identified. Recent findings in the field reveal several steps of this signal transduction pathway to be regulated by these lncRNAs. In this review, we shed light on their regulatory roles in inflammatory-related diseases.

Inflammation and disease-specific lncRNAs

In 2012, Rinn and Chang [17] described a ‘guilt-by-association’ functional lncRNA discovery pipeline that integrated transcriptional and epigenetic sequencing data to formulate a hypothesis for the function of a given lncRNA. The resultant hypothesis could then be experimentally validated. Today, this pipeline has been expanded upon with the advent of chromatin conformation capture (3C) techniques to characterize *trans*-acting lncRNAs and eRNAs. It is now routinely possible to obtain single-cell transcriptome [18,19] and 3C information [20,21], providing unprecedented detail on the intricacies of lncRNA functionality and their relationship to 3D chromatin architecture, as well as unveiling the extent of cellular heterogeneity. Early studies have alluded to lncRNAs playing a functional role in immunoregulation [7]. This has since been extensively validated by the discovery of numerous lncRNAs in the contexts of infection, immunity and disease. One such study used a microarray-based approach to identify lncRNA expression profiles in NF- κ B-activated MDA-MB-231 breast cancer cells. Of the 23 up-regulated lncRNAs following lipopolysaccharide (LPS)-mediated NF- κ B activation, NF- κ B-interacting lncRNA (NKILA) was up-regulated 12-fold [22]. Cytoplasmically located, NKILA binds to the repressive NF- κ B/I κ -B α complex, masking the I κ -B α phosphorylation sites required for the release, activation and translocation of NF- κ B (Figure 2a(i)). The same study also revealed NKILA expression to be inversely proportional to breast cancer metastasis and patient prognosis.

Ultimately, NKILA functions as an NF- κ B negative-feedback regulator, preventing cancer-associated inflammation and metastasis (Figure 2a(i)) [22].

Since its discovery almost a decade ago, HOX Antisense Intergenic RNA's (HOTAIR's) function has extended from being a spatial marker of the anterior-posterior anatomical axis, to being a potent oncogenic factor and prognostic biomarker. HOTAIR is a *trans*-acting transcriptional repressor that functions by 'guiding' and 'scaffolding' the Polycomb Repressive Complex 2 (PRC2) complex to its target loci [23]. Recent studies have observed dysregulated HOTAIR expression in several cancers where it has been implicated in carcinogenic processes such as proliferation, apoptosis and metastasis. HOTAIR expression modulates and is modulated by a spectrum of immunoregulatory factors including TNF- α [24]. Recently, Özeş et al. [25] demonstrated that TNF- α stimulation in A2780p ovarian cancer cells resulted in a 16-fold increase in HOTAIR expression, which was mediated by the binding of NF- κ B at the HOTAIR promoter. In turn, this aberrant HOTAIR expression induced a DNA damage response (DDR). Increased HOTAIR expression also correlates with the significant reduction in I κ B- α protein levels (Figure 2a(v)) in the same cells, which subsequently lead to increased NF- κ B nuclear translocation and activation. Taken together, these findings implicate the HOTAIR-NF- κ B-DDR-positive feedback loop as a causative mechanism of the persistent DNA damage and reduced genomic integrity observed in ovarian cancer [26,27]. Furthermore, this HOTAIR-NF- κ B-DDR loop and the resultant up-regulation of NF- κ B target genes are thought to lead to the acquisition of chemotherapy resistance [28,29]. Preliminary evidence in septic cardiomyopathy also appears to corroborate the involvement of this loop in deregulated immunity [30]. It is therefore tempting to speculate if, and how, the HOTAIR-NF- κ B-DDR feedback loop lies at interface between innate immunity and autoimmunity.

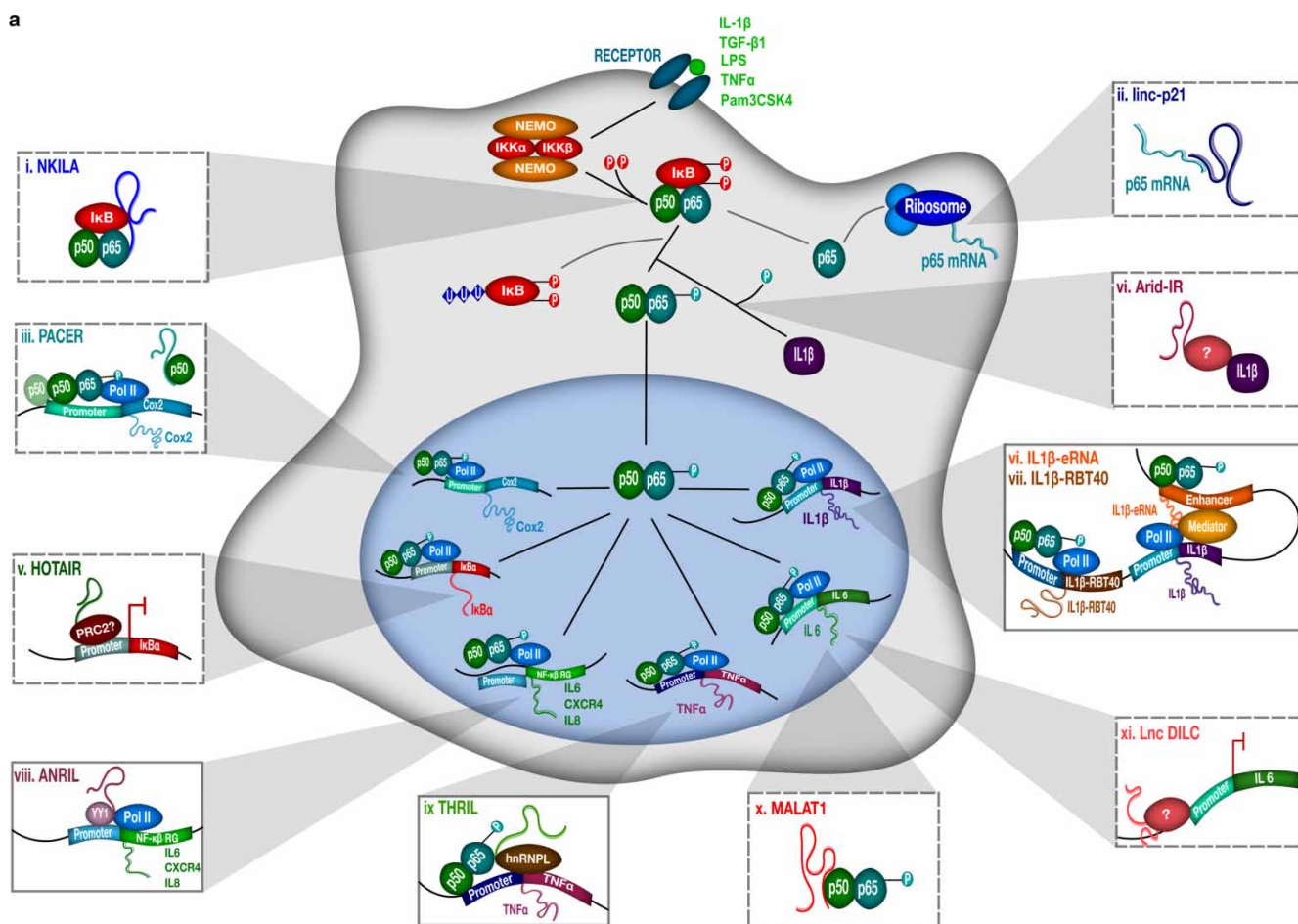
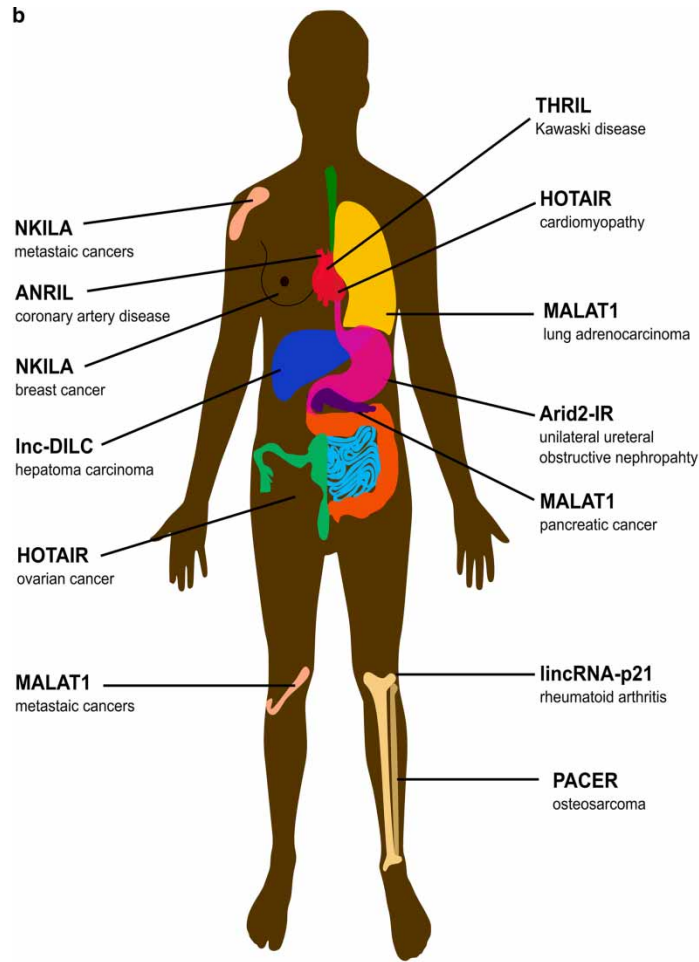


Figure 2. LncRNAs in the NF- κ B signalling pathway.



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Figure 2. LncRNAs in the NF- κ B signalling pathway.

(a) Activating (solid boxes) and inhibitory (dashed boxes) lncRNAs of the NF- κ B canonical pathway. (i) **NKILA** scaffolding lncRNA prevents I κ B and NF- κ B dissociation, maintaining NF- κ B in an inhibited cytosol-retained state. (ii) **linc-p21** binds to and sequesters p65 mRNA, preventing its translation. (iii) **PACER** functions as a decoy binding and titrating p50 away from the NF- κ B-activated Cox2 locus, promoting Cox2 transcription. (iv) **ARID-IR** may promote IL-1 β -mediated NF- κ B phosphorylation. (v) **HOTAIR** acts as a scaffold for transcriptional repressor PRC2 at the I κ B α promoter, preventing I κ B α expression. (vi) **IL-1 β -eRNA** and (vii) **IL-1 β -RBT40** activate IL-1 β expression by mediating chromatin looping, resulting in contacts between the IL-1 β promoter and its upstream enhancer, subsequently resulting in IL-1 β transcription. (viii) **ANRIL** functions as a molecular scaffold for transcription factor YY1 at the NF- κ B locus, activating NF- κ B transcription. (ix) **THRIL** functions as a scaffold for NF- κ B and hnRNPL at the TNF α locus, allowing for its transcriptional activation. (x) **MALAT1** functions as a decoy, binding the NF- κ B sequestering it away from its target promoters. (xi) **lnc-DILC** binds to the IL-6 promoter possibly along with a currently unknown transcriptional repressor to prevent IL-6 expression.

(b) lncRNAs associated with inflammatory human diseases. **NKILA**: breast cancer; **THRIL**: Kawasaki disease and *cardiovascular disorders*; **ANRIL**: cardiovascular disease; **lnc-DILC**: hepatoma carcinoma; **HOTAIR**: cardiomyopathy and several cancers including ovarian cancer; **MALAT1**: several cancers, including lung, pancreatic, brain, liver and breast cancer; **Arid2-IR**: ureteral obstructive nephropathy; **lincRNA-p21**: rheumatoid arthritis; **PACER**: several cancers including osteosarcoma.

As previously described [13,14] the active NF- κ B heterodimer complex consists of p65/RelA and p50 subunits. The nuclear translocation of these heterodimers results in the transcriptional activation of NF- κ B target genes. The p50 subunit, however, can also form p50/p50 homodimers. Termed 'inactive', the p50/p50 homodimer functions as a TNF- α transcriptional repressor in tumor-associated macrophages [31]. The same is true for Cox2 expression in LPS-stimulated macrophages, where p50/p50 occupancy at the Cox2 promoter prevents p50/p65-mediated transcriptional activation (Figure 2a(ii)) [32]. This effect is offset by the Cox2 antisense

'decoy' p50-associated Cox2 extragenic RNA (PACER). PACER directly binds to p50 sequestering p50/p50 homodimers away from the Cox2 promoter promoting p50/p65 occupancy which increases the expression of Cox2 (Figure 2a(iii)) [32]. Although functionally relevant in the acute inflammatory response, persistent Cox2 expression also promotes oncogenesis and cancer progression in various cancers. Incessant Cox2 expression in human osteosarcoma 143B and MG63 cells is potentiated by increased PACER expression and activity in an NF- κ B-dependent manner [33]. The attenuated cellular proliferation and invasion observed during PACER knockdown positions PACER as a potential target for therapeutic intervention in human osteosarcomas.

TNF- α and heterogenous nuclear ribonucleoprotein L (hnRNPL)-related immunoregulatory long intergenic ncRNA (lincRNA; THRIL) expression has been associated with Kawasaki disease (KD). Characterized by systemic vascular inflammation and elevated circulatory TNF- α during its acute phase, this pediatric disease can lead to extensive cardiovascular damage [34]. Attenuated THRIL expression in acute KD patients and Pam3CSK4-stimulated THP1-derived macrophages suggests that THRIL may be regulated by or regulate TNF- α expression. THRIL was found to directly bind hnRNPL, the complex required to maintain basal TNF- α levels. This binding event is crucial for hnRNPL occupancy at the TNF- α promoter [35]. These findings suggest that THRIL functions as a 'guide' or 'scaffold' lincRNA at the TNF- α promoter. Intriguingly, increased TNF- α expression was reflected by a decrease in THRIL expression in THP-1 cells following stimulation [35]. Decreased THRIL expression, in turn, led to decreased TNF- α expression. Indeed, this was validated by RNAi-mediated THRIL knockdown assays, which led to a strong reduction in the expression of TNF- α and that of other NF- κ B regulated cytokines including IL-6 and IL-8 [35]. These findings unravel a novel lincRNA-mediated negative-feedback loop that tightly regulates basal and stimulated TNF- α expression levels (Figure 2a(xi)). In effect, THRIL appears to prevent disproportionate inflammatory responses, such as those observed in KD and inflammatory bowel disorders.

The antisense ncRNA in the INK4 locus (ANRIL) was originally identified as a PRC2 'scaffold' lincRNA responsible for the epigenetic silencing of genes at the INK4 locus genes [36]. Transcribed from the high-risk susceptibility locus Chr9q21, dysfunctional ANRIL expression and its multiple small nucleotide polymorphisms (SNPs) have been implicated in a several diseases including atherosclerosis, periodontitis, coronary artery disease, diabetes and numerous cancers. RNA immunoprecipitation assays reported the transcription factor Ying Yang 1 (YY1) as an ANRIL-binding factor, indicating a role for ANRIL in the inflammatory response [37]. Both short and long isoforms of ANRIL (SANRIL and LANRIL) are significantly up-regulated by pro-inflammatory activators LPS, TNF- α , interleukin 1 beta (IL-1 β) and interferon gamma (IFN- γ) [38]. Each of these factors, bar IFN- γ , augments NF- κ B binding at the ANRIL promoter. Subsequently, ANRIL proportionally up-regulates several inflammatory genes, including IL-6, CXCR4 and IL-8. Each of these gene promoters are enriched with both YY1 and ANRIL in human umbilical cord vein endothelial cells and patient-derived peripheral blood mononuclear cells (Figure 2a(vii)) [38]. These results describe a novel activating and 'scaffolding' role for ANRIL in the inflammatory response. Extensive studies of the NF- κ B/ANRIL/YY1 pathway are yet to be pursued in the context of other diseases where ANRIL expression is deregulated.

lincRNA down-regulated in liver cancer (linc-DILC) was recently characterized in 3D hepatoma carcinoma (HCC)-derived spheroids formed in culture under chemotherapeutic selection [39]. Consistently down-regulated in 3D spheroids as compared to traditional 2D monolayers, linc-DILC depletion was specifically detected in cells expressing known cancer stem cell (CSC) markers [39]. CSCs are a distinct subset of tumor-associated cells that have been linked to chemotherapy resistance [40]. TNF- α or IL-1 β stimulation of HCC-derived spheroids increased linc-DILC occupancy ~203 bp upstream of the IL-6 promoter (Figure 2a(xi)) [39]. This lincRNA-DNA-binding event prevented NF- κ B-mediated transcription and secretion of this potent JAK2/STAT3 signaling activator [39]. IL-6 has been previously shown to exhibit enhanced activity in CSCs [41]. RNAi-mediated linc-DILC depletion not only augmented IL-6/STAT3 signaling, but also enhanced CSC-associated marker expression and tumor expansion in the HCC-derived spheroids [39]. These findings place linc-DILC as a potentially critical determinant in both the hepatic inflammatory microenvironment and CSC expansion through its mediation of cross-talk between the TNF- α /NF- κ B and IL-6/STAT3 signaling cascades. Although linc-DILC appears to function as a 'signal' lincRNA, the molecular 'receivers' and 'executors' of this 'signal' at the IL-6 promoter remain enigmatic (Figure 2a(xi)). More extensive validation experiments are required to further elucidate this mechanism and validate linc-DILC's broader relevance to the TNF- α /NF- κ B signaling pathway.

As its name suggests, the nuclear-retained metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) plays a predominant role in tumor development and progression. Initially identified by its overexpression in lung and pancreatic cancers in 2003 [42], a molecular mechanism for MALAT1, in normal

physiology, was elucidated three short years later [43]. The Müller-Tidow laboratory described MALAT1s as a molecular ‘sponge’ sequestering serine/arginine-rich splicing factors to nuclear speckles, which subsequently decreases alternative splicing [43]. However, previous findings have revealed MALAT1 to function as a ‘scaffold’ lncRNA that interacts with PRC2 to regulate the expression of growth control genes in *cis* [44,45]. The mode of action in which MALAT1 functions is still under debate with several different cellular and animal models describing conflicting functions. However, its role in cancer is unanimous. Augmented MALAT1 expression has been demonstrated in several metastatic cancer and solid tumor cells, including lung [46], brain [47], liver [46] and mammary tumors [48], establishing MALAT1 as a definitive marker of metastasis [49,50]. More recently, MALAT1’s significance in innate immunity was elucidated. Functioning as a lncRNA ‘decoy’, MALAT1 directly interacts with NF- κ B subunits p65 and p50 in the nuclei of LPS-stimulated THP1 macrophages (Figure 2a(x)) [51]. This binding event correlates with attenuated NF- κ B occupancy at its target promoters [51]. RNAi-mediated knockdown of MALAT1 led to increased TNF- α and IL-6 expression; however, the same was not observed for IL-1 β [51]. Although NF- κ B occupancy at the IL-1 β promoter was not required for increased IL-1 β expression in Zhao et al.’s (2016) study; NF- κ B occupancy at the IL-1 β -eRNA and IL-1 β -RBT40 lncRNA promoters is crucial for LPS-mediated IL-1 β up-regulation of the same cell line in a different study (Figure 2a(vi,vii)) [52]. These seemingly conflicting findings underscore just how obscure lncRNA functions are and even more so inter-lncRNA effects at the single-cell level.

Rheumatoid arthritis (RA) is an autoimmune disease characterized by an amplified immune response, including enhanced TNF- α production, which ultimately results in chronic synovial inflammation [53]. Methotrexate (MTX) is an anti-rheumatic known to activate certain components of the DNA damage response, including the tumor suppressor p53 [54]. lincRNA p21 (lincRNA-p21) is a p53-inducible lncRNA located 15 kb upstream of *Cdkn1a/p21* [55]. ‘Guiding’ hnRNP-K to p53-responsive genes both in *cis* [55] and in *trans* [56] as well as directly affecting post-transcriptional gene regulation and protein stability, lincRNA-p21 has emerged as a critical effector of p53-regulated processes such as apoptosis [55,57,58]. Recently, lincRNA-p21 was shown to be consistently down-regulated in RA patients [54]. MTX treatment in primary T cells and cell lines induced linc-p21 expression in a DNA-dependent protein kinase catalytic subunit (DNA PKcs)-dependent manner [54]. Furthermore, lincRNA-p21 induction in MTX-treated RA patients diminished NF- κ B functionality [54]. The mechanism of action employed by lincRNA-p21, in this context, does not alter NF- κ B subunit transcript levels; instead, lincRNA-p21 binds and sequesters the p65/RelA mRNA transcript presumably inhibiting its translation (Figure 2a(ii)). Accordingly, significant reductions in phosphorylated p65 protein levels were also observed in patients treated with MTX [54]. These findings suggest that chronic NF- κ B activation in RA patients is corrected by MTX therapy in a lincRNA-p21-dependent manner, thus implicating lincRNA-p21 as a novel therapeutic target for inflammation-associated disorders.

At the time of writing this review, the latest lncRNA discovered in the NF- κ B signaling pathway was AT-rich interactive domain-containing protein 2 (Arid2)-IR. Arid2-IR is transcribed from the second intron of the chromatin modifier complex SWItch/Sucrose Non Fermentable (SWI/SNF) chromatin modeling subunit, Arid2. Upon transforming growth factor beta 1 (TGF- β 1) stimulation, in the kidneys of unilateral ureteral obstructive (UUO) nephropathic mice, mothers against decapentaplegic homolog 3 (Smad3) binding at the Arid2-IR promoter initiates Arid2-IR transcription [59]. Surprisingly, Arid2-IR knockdown did not influence TGF- β 1 signaling in the same model. However, Arid2-IR knockdown inhibited IL-1 β -induced NF- κ B phosphorylation and activation (Figure 2a(vi)). Arid2-IR overexpression in the same animal model resulted in persistent NF- κ B activation and sustained NF- κ B binding at the promoters of pro-inflammatory cytokines: TNF- α and monocyte chemoattractant protein 1 (MCP1) in response to IL-1 β stimulation. Furthermore, reduced renal inflammation was observed, marked by reduced F4/80+ macrophage and CD3+ T-cell occupancies in the tubulointerstitium of UUO kidneys, following Arid2-IR RNAi-mediated knockdown [59]. These findings led the authors to postulate a model where Arid2-IR/NF- κ B signaling promoted renal inflammation. Although not far-fetched, further investigation of this proposed mechanism, particularly in different experimental models, is required.

Over and beyond the lncRNAs discussed here, numerous disease-specific lncRNAs have been linked to NF- κ B signaling. However, their functional mechanisms in this context remain elusive. Some notable cancer-specific examples include DLEU1 and DLEU2 [60], Morrbid [61], LINK-A [62] and CCAT2 [63]. On the other hand, lncRNAs, such as NeST [64], lincRNA-Cox2 [65], Lethe [66], Umlilo [67], IL-1 β -eRNA and IL-1 β -RBT46 [52], have been functionally validated at various arms of the NF- κ B pathway yet their immunoregulatory roles in human disease remain hypothetical.

Perspectives

Considering that lncRNAs contribute to a significant proportion of the human genome, it is not surprising that the largest proportion of SNPs resides at noncoding loci [68]. Although lncRNA SNP catalogs exist in curated databases such as LncVar [69], LincSNP [70] and lncRNASNP [71], extensive validation studies on their functional significance are needed to not only expand upon our understanding of human disease but also to develop more effective therapies against human disease. To date, only two functional lncRNA SNPs in the NF- κ B pathway have been validated: the first found in the ANRIL gene and the other within a novel HOTAIR enhancer [72,73]. Each of these SNPs have been associated with increased disease risk and severity in certain populations. Though largely underrated, functional lncRNA genetic variation may play a larger role in the etiology of human disease than that of their protein-coding counterparts.

As demonstrated in this review, among others, lncRNA functioning at a molecular level has systemic consequences. Thus, the dysregulation of lncRNA expression and functionality contributes to several pathophysiological states with several lncRNAs validated as *bona fide* prognostic and diagnostic markers. This, of course, introduces the need to address lncRNA ‘druggability’ in the development of novel therapeutic approaches. As with determining the precise molecular mechanisms of lncRNAs, developing therapeutic interventions targeted at lncRNAs requires careful consideration of lncRNA expression levels, subcellular localization, cellular specificity, functional binding partners, SNPs, secondary and tertiary structure. Although their capabilities are currently limited, technologies used to suppress mRNAs such as antisense oligonucleotides [74], RNAi [33,39,59,74], genome editing [67,75] and small-molecule inhibitors [76] are attractive strategies in this regard. In the coming years, we envision lncRNAs functioning not only as diagnostic markers for disease, but also as therapeutically relevant targets and agents.

Abbreviations

ANRIL, antisense ncRNA in the INK4 locus; Arid2, AT-rich interactive domain-containing protein 2; CAD, coronary artery disease; CCAT2, colon cancer associated transcript 2; CSC, cancer stem cell; DDR, DNA damage response; DLEU1/2, deleted in lymphocytic leukemia 1/2; hnRNP-K, heterogeneous nuclear ribonucleoprotein K; hnRNPL, heterogenous nuclear ribonucleoprotein L; HOTAIRs, HOX Antisense Intergenic RNAs; HOX, homeobox; IKK, I κ -B α kinase; IL-1 β , interleukin 1 beta; JAK2/STAT3, Janus kinase 2/signal transducer and activator of transcription 3; KD, Kawasaki disease; Lethe, long non-coding RNA named after the “river of forgetfulness”; lincRNA-Cox2, long intergenic RNA Cox2; lincRNA p21, lincRNA-p21; LINK-A, long intergenic non-coding RNA for kinase activation; lnc-DILC, lncRNA down-regulated in liver cancer; lncRNAs, long ncRNAs; LPS, lipopolysaccharide; MALAT1, nuclear-retained metastasis-associated lung adenocarcinoma transcript 1; Morrbid, myeloid RNA regulator of Bim-induced death; ncRNAs, noncoding RNAs; NEMO, NF- κ B essential modulator; NeST, Nettoie Salmonella pas Theiler’s (cleanup Salmonella not Theiler’s); NKILAs, NF- κ B-interacting lncRNAs; PACER, p50-associated Cox2 extragenic RNA; PRC2, polycomb repressive complex 2; RA, rheumatoid arthritis; SNPs, small nucleotide polymorphisms; SWI/SNF, SWItch/Sucrose Non Fermentable; TGF- β 1, transforming growth factor beta 1; Umlilo, upstream master lncRNA of the inflammatory chemokine locus; THP1, Tamm-Horsfall protein-1 monocytic cells; UUU, unilateral ureteral obstructive; YY1, Ying Yang 1.

Competing Interests

The Authors declare that there are no competing interests associated with the manuscript.

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