lncRNAs in NF-κB-Mediated Macrophage Inflammation

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Molecular biology's focus has transitioned from proteins to DNA, and now to RNA. Once considered merely a genetic information carrier, RNA is now recognized as both a vital element in early cellular life and a regulator in complex organisms. Long noncoding RNAs (lncRNAs), which are over 200 bases long but do not code for proteins, play roles in gene expression regulation and signal transduction by inducing epigenetic changes or interacting with various proteins and RNAs. These interactions exhibit a range of functions in various cell types, including macrophages. Notably, some macrophage lncRNAs influence the activation of NF-κB, a crucial transcription factor governing immune and inflammatory responses. Macrophage NF-κB is instrumental in the progression of various pathological conditions including sepsis, atherosclerosis, cancer, autoimmune disorders, and hypersensitivity.

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1. LncRNAs That Modulate Macrophage NF-κB Activity in Sepsis

Sepsis is a life-threatening condition marked by a dysregulated immune response to infection, leading to widespread inflammation, organ dysfunction, and potentially organ failure and death [1]. Often caused by bacteria, viruses, fungi, or other pathogens, a prime stimulant is LPS, an endotoxin found in the cell wall of Gram-negative bacteria [2]. The systemic inflammatory response, particularly post-bloodstream infection, triggers an excessive release of pro-inflammatory cytokines and chemokines. These mediators damage the endothelial cells lining the walls of blood vessels, resulting in increased permeability. This, in turn, leads to fluid leakage, tissue swelling, and subsequently edema [3]. Persistent inflammation can impact multiple organs and systems, with cytokines like TNF-α being key mediators of sepsis [4]. Commonly affected organs include the lungs, heart, kidneys, liver, and even the central nervous system.

NF-κB-mediated inflammation in macrophages, followed by M1 polarization, is pivotal in the pathogenesis of sepsis [5]. Pattern recognition receptors, including Toll-like receptors (TLRs), allow macrophages to identify pathogen-associated molecular patterns on invading microorganisms [2]. Activation of NF-κB, triggered by LPS interaction with TLR4 via the canonical pathway, upregulates numerous pro-inflammatory genes, such as cytokines, chemokines, adhesion molecules, and enzymes like inducible nitric oxide synthase [6]. NF-κB serves as a primary target for immunomodulatory therapies aimed at regulating inflammation and reestablishing immune equilibrium in many diseases, including sepsis. Such strategies might involve inhibiting NF-κB activation or employing targeted therapies to neutralize specific pro-inflammatory cytokines.

The lncRNA nuclear paraspeckle assembly transcript 1 (NEAT1), confined to the nucleus, is instrumental in forming paraspeckles, subnuclear structures involved in antiviral responses [7]. The levels of NEAT1 are increased by more than two-fold in the sera of sepsis patients [8][9][10][11]. Induced by LPS in the human monocytic leukemia cell line THP-1, NEAT1 enhances inflammatory responses by sponging miR-17-5p, thereby stabilizing TLR4 mRNA (the miR-17-5p/TLR4 axis) [11]. In Kupffer cells and the murine macrophages, LPS-induced NEAT1 promotes inflammatory activities via the Let-7q/TLR4 axis [8][9][10][12]. Additionally, NEAT1 also facilitates M1 polarization in macrophages through the miR-125a-5p/TRAF6/TGF-β-activated kinase 1 (TAK1) axis [13], underscoring its potential as a therapeutic target for sepsis.

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), a multifunctional lncRNAs in macrophages, is extensively studied. In late-onset sepsis patients, increased blood MALAT1 levels correlate with disease severity [14]. The expression of MALAT1 increases in activated macrophages, exhibiting an elevation greater than two-fold in mouse peripheral blood mononuclear cells (PBMCs) and more than six-fold in THP-1-derived macrophages, especially following LPS treatment [14][15]. Animal studies show that MALAT1 expression surges with sepsis induction; reducing MALAT1 lessens inflammation and mortality [14][16][17][18], possibly by suppressing M1 and enhancing M2 macrophage polarization [18]. In an LPS-induced septic lung injury model, intravenous MALAT1-specific small interfering RNA (siRNA) decreases inflammatory cytokines and immune cells in bronchoalveolar lavage fluid by inhibiting the p38 mitogen-activated protein kinase (MAPK)/p65 pathway [17].

However, several reports have shown contradictory evidence, indicating a significant decrease in MALAT1 expression accompanied by an increase in hsa-miR-346 levels in patients with sepsis. Activated human and mouse macrophages downregulate MALAT1 expression in an NF-κB-dependent manner [15][19]. MALAT1 interacts with NF-κB, inhibiting its DNA-binding activity and, consequently, the expression of pro-inflammatory cytokines [15]. Furthermore, MALAT1 modulates macrophage proliferation by sequestering hsa-miR-346, thereby stabilizing the mRNA of small mothers against decapentaplegic homolog 3 (SMAD3). SMAD3 is a receptor-regulated signaling adaptor that is activated by serine kinases. These conflicting findings underscore the need for future research on MALAT1's role in sepsis.

In sepsis patients, the levels of long noncoding RNA plasmacytoma variant translocation 1 (PVT1) are elevated, showing an increase of more than two-fold compared to the healthy control group. This elevation correlates with increased pro-inflammatory mediators and survival rates. [20][21]. LPS induces PVT1 expression in THP-1 cells, which in turn amplifies NF-κB activity via p38 stimulation [22]. Elevated PVT1 expression, promoting M1 polarization through the miR-29a/high-mobility group box 1 (HMGB1) axis, is observed in heart-infiltrating macrophages of septic mice [23]. HMGB1, released from the cells, can activate TLR4 in both autocrine and paracrine manners [24]. PVT1 is also highly expressed in osteoarthritis patients' serum and in the LPS-stimulated C28/12 chondrocyte cell line, activating the TLR4/NF-κB pathway via the miR-93-5p/HMGB1 axis [25]. Additionally, PVT1 levels rise in myocardial tissues and heart-infiltrating macrophages during sepsis-induced myocardial injury [23].

The expression level of lncRNA MEG3 is significantly reduced in patients with sepsis, and this reduction has prognostic significance [26]. In macrophages, MEG3 overexpression inhibits LPS-induced apoptosis by

downregulating BAX and upregulating Bcl-2. It also suppresses inflammatory factor expression by inhibiting NF-κB signaling [26]. This suggests that the reduced MEG3 expression may exacerbate sepsis by increasing inflammation and inhibiting apoptosis in macrophages. Further research is needed to elucidate MEG3's role in sepsis.

In sepsis patients, the lncRNA colorectal neoplasia differentially expressed (CRNDE) exhibits elevated expression in peripheral blood, with higher levels correlating to improved survival rates [27]. CRNDE intensifies LPS-induced NF-κB activation and subsequent pro-inflammatory cytokine release in THP-1 cells via the miR-181-5p/TLR4 axis [27].

These reports highlight the intricate relationship between lncRNAs and NF-κB in the context of sepsis, impacting inflammatory activation and macrophage polarization. The influence of these lncRNAs on cytokine release, cell polarization, and apoptosis is notable, and their varied expression in sepsis patients suggests potential as biomarkers. Targeting these lncRNAs to regulate NF-κB activation offers promising avenues for immunomodulatory therapies to manage inflammation and restore immune balance in sepsis. However, the contrasting roles of specific lncRNAs, like MALAT1, necessitate further research. A deeper understanding of these lncRNAs' roles could lead to innovative diagnostic and therapeutic strategies, improving management and outcomes in sepsis.

2. LncRNAs That Modulate Macrophage NF-κB Activity in Atherosclerosis

Macrophages are central in atherosclerosis development, marked by arterial plaque build-up. The process initiates with low-density lipoprotein (LDL) cholesterol accumulation in arterial walls, undergoing oxidation and eliciting inflammation [28][29]. Modified LDL attracts monocytes from blood, transforming into macrophages in the arterial wall. These macrophages consume oxidized LDL (oxLDL), forming lipid-laden foam cells and creating fatty streaks, early atherosclerosis signs [30][31]. M1 macrophages exacerbate inflammation by releasing cytokines, attracting more immune cells [32][33]. Chronic inflammation leads to fibrous cap formation over plaques and extracellular matrix accumulation. Macrophages also degrade this matrix, heightening plaque instability and increasing heart attack and stroke risks [30][34]. Macrophages can also contribute to the resolution of inflammation and healing processes [35]. In atherosclerosis, inflammation resolution is overshadowed by ongoing inflammation and plaque growth.

NF-κB, activated by stimuli such as oxidative stress, cytokines, and oxLDL, exacerbate atherosclerosis by promoting lipoprotein uptake, foam cell formation, and attracting more immune cells [30][36]. This activation also destabilizes plaques by encouraging matrix metalloproteinase (MMP) secretion, increasing plaque rupture risks [37]. Chronic NF-κB activation sustains the inflammation characteristics of advanced atherosclerosis in conditions like coronary artery diseases (CADs) and myocardial infarction (MI) [38]. Given its crucial role in macrophage activation atherosclerosis progression, NF-κB presents a potential target for therapies aimed at reducing inflammation and slowing atherosclerosis progression [39].

Increased NEAT1 expression levels in the PBMCs and sera of atherosclerosis patients have been noted [40][41]. The expression level of NEAT1 was found to be increased by more than two-fold in PBMCs of CAD patients [40]. NEAT1, induced by oxLDL in THP-1 cells, contributes to pro-inflammatory responses by enhancing p65 phosphorylation, followed by paraspeckle formation [42][43]. It is also induced in bone marrow-derived macrophages (BMDMs) treated with titanium particles and promotes NF-κB activation, NLRP3 inflammasome formation, and M1 polarization via the miR-188-5p/Bruton's tyrosine kinase (BTK) axis [44]. NEAT1 also stimulates pro-inflammatory cytokine and reactive oxygen species (ROS) production and subsequent foam cell formation by sponging miR-342-3p in THP-1 cells [43] or miR-128 in the murine macrophage-like cell line RAW264.7 [45]. These reports agree with NEAT1 being expressed in activated macrophages and enhancing pro-inflammatory changes. One contradicting study, however, reported decreased NEAT1 in the PBMCs of post-MI patients and enhanced macrophage inflammation in NEAT1-knockout mice [46].

Elevated lncRNA PVT1 levels have been detected in the serum of atherosclerosis patients [47]. Inhibiting PVT1 in animal models reduces atherosclerotic plaques by increasing HDL levels and suppressing the MAPK/NF-κB pathway and pro-atherogenic factors [47]. In serum samples of atherosclerosis patients and during oxLDL-induced THP-1 cell foam cell differentiation, there is a notable increase in lncRNA small nucleolar RNA host gene (SNHG)16 and a decrease in miR-17-5p [48]. SNHG16 amplifies macrophage proliferation and pro-inflammatory responses in atherosclerosis through the miR-17-5p/NF-κB axis [48].

LncRNA X-inactive specific transcript (XIST), known for its role in X-chromosome inactivation, has been found to be elevated more than two-fold in the serum of atherosclerosis patients, oxLDL-treated vascular smooth muscle cells, and the U937 human monocytic leukemia cell line [49]. XIST influences atherosclerosis by promoting proliferation and inhibiting apoptotic cell death through the miR-599/TLR4 axis [49]. This finding aligns with other studies that show that apoptosis inhibition aggravates atherogenesis by increasing macrophage proliferation and plaque formation [50][51].

LncRNA H19 is found at elevated levels in the serum of atherosclerosis patients [52][53][54][55]. OxLDL stimulates H19 expression in macrophages [56], aorta vascular smooth muscle cells [52][53], and human umbilical vein endothelial cells (HUVECs) [57]. In macrophages, H19 augments oxLDL-induced lipid accumulation, ROS generation, and NF-κB activation [56][58]. Similarly, in HUVECs, H19 heightens NF-κB activation by increasing p38 and p65 activity [59]. These findings suggest that H19 could be a promising therapeutic target for atherosclerosis treatment.

In atherosclerosis and CAD patients, MALAT1 levels rise more than two-fold and subsequently fall after treatment [60][61][62]. MALAT1 impacts various macrophage processes like foam cell formation, autophagy, and pyroptosis [63][64][65]. OxLDL prompts NF-κB-dependent MALAT1 expression in THP-1 cells. MALAT1 then enhances lipid uptake and foam cell formation by promoting scavenger receptor CD36 expression [61][63][64]. MALAT1 also enhances NF-κB activation and subsequent inflammation by sponging miR-330-5p [64]. Further, oxLDL-induced autophagy in macrophage is mediated by MALAT1, which activates the MAPK/NF-κB pathway and inhibits sirtuin 1 (SIRT1), a key transcription factor deacetylase [65][66]. NLRP3 inflammasome-mediated pyroptosis, a programmed cell death

as a defense mechanism against intracellular pathogens, is also influenced by MALAT1 [67]. In diabetic atherosclerosis models, a cinnamic acid derivative reduces inflammasome activation and pyroptosis by suppressing MALAT1 [68]. Extracellular vesicles (EVs) such as exosomes are crucial for cell-to-cell communication, transferring proteins and lncRNAs [69]. M1 macrophages have been found to release MALAT1-containing EVs, which regulate myocyte proliferation and angiogenesis in MI models [70]. These findings underscore MALAT1's role in atherosclerosis: it is upregulated in activated macrophages and influences various processes including lipid uptake, foam cell formation, and cell death.

However, contrary reports exist regarding the role of MALAT1 in atherosclerosis. It was observed that in atherosclerosis patients and oxLDL-treated THP-1 cells, MALAT1 levels decrease [61]. Reduced MALAT1 leads to increased lipid and total cholesterol accumulation in THP-1 cells via the miR-17-5p/ATP-binding cassette subfamily A member 1 (ABCA1) axis [61]. ABCA1 is known to facilitate cholesterol efflux, thereby reducing foam cell formation [71]. Additionally, MALAT1 deficiency in certain mouse models has been linked to accelerated macrophage inflammation and atherosclerosis [72]. Exosomal MALAT1 from oxLDL-treated HUVECs promotes a transition from M1 to M2 macrophages [73]. These findings suggest potential anti-atherogenic properties of MALAT1, highlighting the need for further research to clarify its role in atherosclerosis.

Notably, the expression levels of lncRNA HOX transcript antisense intergenic RNA (HOTAIR) are decreased in the peripheral blood lymphocytes of atherosclerosis patients and oxLDL-treated RAW264.7 cells [74]. HOTAIR overexpression reduces pro-inflammatory cytokine expression while boosting anti-inflammatory cytokines, achieved by inhibiting NF-κB activity. This suppression occurs through HOTAIR's enhancement of fragile X-related protein 1 (FXR1) levels, a protein moving between the nucleus and cytoplasm and associating with polyribosomes [74][75].

These reports underscore the complex relationship between various lncRNAs and macrophage NF-κB in atherosclerosis. These lncRNAs impact crucial aspects such as lipid uptake, foam cell formation, inflammation, and cell death in macrophages. Given their link to NF-κB activation, targeting these lncRNAs for NF-κB modulation presents a promising approach to managing atherosclerosis by restoring immune equilibrium and curbing inflammatory activation. It is intriguing that certain lncRNAs, such as MALAT1 and HOTAIR, have been identified to play conflicting roles in atherosclerosis. Variations in the stages of atherosclerosis or CAD examined, the measurement techniques utilized, environmental factors, or the experimental model systems employed could account for these discrepancies. Alternatively, the overall impact of these lncRNAs may differ based on the dominant signaling pathways activated in particular contexts or disease states. Despite the conflict, their significant influence on macrophage function and disease progression is evident. Further research is essential to unravel the full potential of these lncRNAs in atherosclerosis treatment.

3. LncRNAs That Modulate Macrophage NF-κB Activity in Cancer

The role of macrophage inflammation in cancer is multifaceted and contradictory. M1 macrophages, typically anti-tumorigenic, can attack tumor cells and stimulate immune responses. Conversely, M2 macrophages often aid tumor growth by supporting angiogenesis, suppressing immune responses, and facilitating tissue remodeling [76]. Generally, tumor-associated macrophages (TAMs) exhibit an M2 phenotype, supporting tumor growth and metastasis and contributing to an immunosuppressive tumor environment [77][78]. Given their significant impact on cancer progression, TAMs are being investigated as therapeutic targets, with strategies focusing on inhibiting their tumor-promoting functions or reprogramming them to combat tumors.

The activation of NF-κB in macrophages plays a crucial role in cancer development and progression. In TAMs, NF-κB activation leads to the production of cytokines, growth factors, and enzymes that promote tumor growth and suppress anti-tumor immune responses [79][80]. NF-κB can also alter the immune microenvironment, potentially inducing immune checkpoint molecules that weaken the immune response against tumors [81]. Additionally, NF-κB-activated macrophages can produce angiogenic factors, aiding tumor vascularization [82][83][84]. They can also stimulate matrix metalloproteinases (MMPs), breaking down extracellular matrix barriers and facilitating cancer cell spread [85][86]. Thus, macrophage NF-κB is implicated in various aspects of cancer progression and targeting macrophage NF-κB has emerged as a prominent focus in cancer treatment strategies [87].

LncRNA DC-STAMP domain containing 1-antisense 1 (DCST1-AS1) has been investigated in various cancers, including gastric, colorectal, cervical, breast, glioblastoma, endometrial, and HCC [88][89][90][91][92][93][94]. In these cancers, increased DCST1-AS1 expression correlates with larger tumors and shorter survival and DCST1-AS1 promotes cancer cell proliferation and metastasis, and inhibits apoptosis, by sponging miRNAs [88][89][90][91][92][93][94]. Notably, in oral squamous cell carcinoma, DCST1-AS1 advances tumor progression by enhancing NF-κB activity in cancer cells and macrophages [95]. The expression of DCST1-AS1 showed a more than three-fold increase in oral squamous cell carcinoma cells compared to normal cells [95]. Elevated DCST1-AS1 in cancer cells and M2 macrophages is linked to tumor growth and cancer cell proliferation. NF-κB antagonists revealed that DCST1-AS1 enhances cancer progression and M2 macrophage polarization through NF-κB-mediated mechanisms [95].

The lncRNA FGD5 antisense RNA 1 (FGD5-AS1) shows elevated levels in non-small-cell lung cancer and pancreatic cancer, correlating with metastasis and poor prognosis [96][97]. FGD5-AS1-containing exosomes from these cancers induce M2 macrophage polarization [96]. FGD5-AS1 links acetyltransferase p300, STAT3, and NF-κB, leading to acetylated STAT3/p65 complex and transcriptional activation [96][98]. STATs are crucial transcription factors in macrophage polarization, with STAT1 being integral to M1, and STAT3/6 to M2 polarization. [99]. In cervical cancer, FGD5-AS1, via the miR-129-5p/bone marrow stromal cell antigen 2 (BST2) axis, promotes tumor growth and M2 polarization [100]. BST2, a lipid raft-associated protein, is implicated in cell proliferation and immune response [101][102]. Collectively, FGD5-AS1 augments tumor growth by enhancing cancer progression and M2 macrophage polarization.

The lncRNA AP000439.2 has recently been identified as a prognostic marker for renal cell carcinoma (RCC) patient survival [103][104]. Exosomes from human RCC cell lines have been shown to induce M2 polarization in co-

cultured THP-1 cells [105]. AP000439.2 promotes M2 polarization through the phosphorylation of STAT3 and the NF-κB p65 subunit, which, in turn, enhances the migration potential of cocultured cancer cell lines. The impact of exosomal AP000439.2 on macrophage M2 polarization and RCC growth has been confirmed in a xenograft tumor mouse model [105].

LncRNA Five Prime to Xist (FTX), an evolutionarily conserved regulator of XIST expression, is associated with various conditions including malignancies, endometriosis, and stroke, functioning through miRNA sponging [106][107]. Liu et al. observed decreased FTX levels in cirrhosis patients, linking them to abnormal activation of CD14+ CD16+ monocytes via the miR-545/T cell immunoglobulin and mucin domain 3 (Tim-3) axis [108][109]. Moreover, FTX suppression in THP-1 cells increases NF-κB activity and pro-inflammatory cytokine expression, suggesting that a reduction in FTX might accelerate tumor progression by enhancing inflammation in the tumor microenvironment (TME) [108].

LncRNA HOTAIR, known for its role in gene regulation and epigenetic modifications, is implicated in various human diseases [110]. It is often overexpressed in cancer, contributing to tumor progression, metastasis, and poor prognosis by altering gene expression related to the cell cycle, apoptosis, and metastasis [110][111]. HOTAIR is also associated with central nervous system disorders, fibrosis, and inflammatory conditions, impacting cellular processes and immune responses [112][113][114][115]. It regulates glucose transporter isoform 1 (GLUT1) expression in human neuroblastoma cells and macrophages by stimulating NF-κB activity, suggesting a role in metabolic reprogramming in cancer [116][117]. In addition, inflammatory activation of macrophages triggers HOTAIR expression, which then promotes NF-κB activation and cytokine gene expression by aiding in the degradation of IκBα [116]. HOTAIR's expression pattern in cancer tissue macrophages remains unexplored and warrants future investigation.

Elevated levels of lncRNA HOXA transcript at the distal tip (HOTTIP) have been observed in AML patients and cell lines, such as U937 and THP-1 [118]. HOTTIP facilitates cell proliferation via the miR-608/DET1- and DDB1-associated 1 (DDA1) axis, with DDA1 being a gene known for its oncogenic properties [118][119]. In squamous cell carcinoma, M1-derived exosomes containing HOTTIP inhibit cancer cell proliferation and induce apoptosis by activating the TLR5/NF-κB pathway [120]. Additionally, exosomal HOTTIP influences the M1 polarization of circulating monocytes [120]. The comprehensive role of HOTTIP in cancer progression remains an area for future exploration.

Cyclooxygenase (COX)2, linked with inflammation in immune cells, is implicated in several cancers [121]. LncRNA p50-associated COX2 extragenic RNA (PACER), located upstream of the COX2 promoter, regulates COX2 expression [122]. PACER, through its association with p50, facilitates p65/p50 heterodimer binding to the COX2 promoter, recruiting p300 histone acetyltransferase [122]. Its expression is upregulated in various cancer tissues, influencing COX2 and PGE_2 synthesis and cancer cell proliferation, migration, and invasion [123][124][125].

LncRNA cardiac hypertrophy-related factor (CHRF) functions as an oncogene, promoting migration and invasion in various tumor types [126]. In a silica-induced pulmonary fibrosis mouse model, CHRF activates inflammatory and

fibrotic pathways via the miR-489/MyD88 and miR-489/SMAD3 axes, with SMAD3 being an adaptor in receptor-regulated signaling [127][128]. CHRF's pro-inflammatory effects are also observed in LPS-induced acute lung injury [129]. However, its specific role in macrophage inflammation within the TME remains unclear, necessitating further research.

LncRNA SNHG1, commonly overexpressed in various cancers as an oncogene, affects cellular signaling via interactions with miRNAs and signaling regulators [130]. In cholangiocarcinoma cell lines, SNHG1 is associated with increased proliferation and invasion, mediated by NF-κB activation through the miR-140/TLR4 axis, contributing to an inflammatory TME [131]. In an LPS-induced acute lung injury model, SNHG1 is upregulated in M1 polarized THP-1 cells, enhancing NF-κB activation and inflammation through interaction with HMGB1 [132]. However, SNHG1's specific role in macrophage-related TME remains unexplored.

These findings highlight the intricate relationship between macrophages, lncRNAs, and NF-κB in cancer, affecting cell proliferation, invasion, inflammation, and macrophage polarization. The dichotomy of macrophages, especially TAMs, underscores their potential as therapeutic targets. Their influence extends to inflammation, TME modulation, angiogenesis, and immunosuppression, making them key in the interplay between cancer cells and the immune system. Understanding lncRNA-driven macrophage NF-κB regulation is essential for developing targeted cancer therapies. Despite advances, many aspects of lncRNA functions in cancer and inflammation require further exploration, presenting exciting opportunities for future research and potential therapeutic interventions.

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