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REVIEW

Targeting of IL-6-Relevant Long Noncoding RNA Profiles in Inflammatory and Tumorous Disease

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Abstract— Interleukin-6 (IL-6) is a critical cytokine with a diverse repertoire of physiological functions. Dysregulation of IL-6 signaling is associated with inflammatory disorders as well as cancers. However, blockade of IL-6 activity *via* antibodies directed against the IL-6 signaling pathway may compromise the efficacy of the immune system; therefore, patients may not have a uniformly satisfactory response to treatment. Long noncoding RNAs (lncRNAs) have been discovered to be evolutionary conserved transcripts of noncoding DNA sequences and have emerged as biomarkers with great predictive and prognostic value, further employed as a targeted anticancer therapy. LncRNAs have been recently implicated in the regulation of IL-6-related signaling and function; they are tightly linked to the development of a range of IL-6 dysregulated diseases. Here, we will highlight those lncRNAs involved in IL-6 signaling, with an emphasis on the mechanisms of lncRNAs that interact with IL-6. Targeting of such lncRNAs related to IL-6 regulation could be, in the near future, a promising therapeutic strategy in the treatment of inflammatory- and tumor-related diseases.

KEY WORDS: IL-6; lncRNA; inflammation; cancer; tumor.

INTRODUCTION

The first clinical use of chimeric antigen receptor (CAR) T cells was to treat an acute lymphoblastic leukemia patient in 2017. However, this revolutionary cancer treatment led to a severe complication where the concentration of interleukin-6 (IL-6) cytokine in circulation increased to 1000 times normal levels. Fortunately, the moribund patient made a miraculous recovery after an infusion of IL-6 targeting agents [1]. This anecdote underscores the importance of, IL-6, which has been risen to a new high level because of its key role in inflammation. Similarly, a growing number of publications have demonstrated that IL-6 plays a vital role in molecular disease processes, including proliferative disorders [2], cancer stem cell formation, and maintenance in various malignant states [3]. In light of such functionality, IL-6-blocking therapeutics would appear to have especially bright prospects [4]. However, concerns have been raised about the possibility of increased long-term adverse events with current treatments targeting IL-6 [5]. For these reasons, more precise IL-6-targeting chemotherapeutic agents will be important to improve patient outcomes.

In the last few years, long noncoding RNAs (lncRNAs), classified as a novel class of transcripts greater than 200 nucleotides, have emerged as important gene expression modulators that have critical roles in the development of human diseases [6]. Knowledge regarding the mechanisms of IL-6 signaling plus the potential of targeting relevant lncRNA suggests a novel therapeutic intervention [7]. It is clear exploration of the

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pathophysiological contributions and the underlying mechanisms of specific lncRNAs in IL-6 dysregulated diseases is a promising research direction. In this review, we attempt to summarize the direct involvement of lncRNAs in various parts of the IL-6 signaling pathway previously validated in human diseases. We also highlight the fundamental barriers that must be overcome for IL-6-related lncRNAs to enter a new era of diagnostic and therapeutic significance.

IL-6 SIGNALING PATHWAYS IN HEALTH AND DISEASE

Many inflammatory states that have a complex relationship with pain, angiogenesis, as well as tumorigenesis and development, are characterized by excessive expression of IL-6. The diverse roles of IL-6 might correlate with two modes of signaling: classical and trans-signaling [8]. Next, IL-6 leads to the activation of the Janus family kinases (JAK)/signal transducer and activator of transcription (STAT3) and mitogen-activated protein kinase (MAPK) cascades to exert its specific actions [9]. IL-6 expression is also regulated by nuclear factor kappa B (NF-κB) or STAT3. To date, IL-6 targeting monoclonal antibodies and JAK inhibitors have been developed to inhibit IL-6 signaling.

Although IL-6 is well known for its pathological character, there are important physiological states of IL-6 that should not be ignored. Firstly, anabolic side effects, such as increased blood lipids, are often observed during IL-6 antagonistic therapies [8]. Furthermore, IL-6 is an important inducer of acute phase proteins even more than IL-1β or tumor necrosis factor alpha (TNF-α) [8]. Inhibition of IL-6 *via* the antibodies directed against IL-6/IL-6R might lead to serious long-term side effects of infection [5]. Moreover, not all patients have a positive response to IL-6 blockade therefore novel drugs with more targeted precision and efficiency should be explored.

LNCRNAS AS PART OF THE IL-6 SIGNALING PATHWAY

LncRNAs, as important transcriptional regulators affecting gene expression and thereby cell homeostasis, have demonstrated vital participation in the expression and signaling-regulation of IL-6. Here, we will discuss their involvement in the onset, progression, and maintenance of several pathologies related to IL-6 dysregulation.

MALAT1

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) was originally identified as a regulator of cancer cell survival and metastasis [10]. Recently, increasing evidence has suggested a vital regulatory effect for MALAT1 in IL-6 relevant inflammation. IL-6 is a hub gene in the cellular response to lipopolysaccharide (LPS) treatment and induces MALAT1 upregulation in cardiomyocytes [11]. MALAT1 in turn aggravates cardiac inflammation, demonstrating increased levels of blood cytokines including IL-6, which is achieved through the MAPK/NFκB pathway [12]. During cerebral ischemic reperfusion injury associated with diabetes mellitus, MALAT1 in the microglia was significantly upregulated, promoting IL-6 production *via* MyD88 signaling [13].

MALAT1 has also been found to be involved in endothelial cell functions [14]. In endothelial cells, MALAT1 can be upregulated by IL-6 through an extracellular signal-regulated kinase (ERK)-dependent mechanism [15], and may promote IL-6 production through activation of amyloid antigen 3 [14]. Intervention with MALAT1 contributes to changes in IL-6 production by regulating NF-κB and p38 MAPK signaling pathways as well as miR-146a sponging in pulmonary microvascular endothelial cells of acute lung injury [16, 17].

However, other studies have described MALAT1 as an inflammation inhibitor. Li S *et al.* reported that MALAT1 suppressed oxidized low-density lipoprotein (ox-LDL)-induced IL-6 release *via* sponging miR-155, thus alleviating the inflammation persisting in atherosclerosis [18]. MALAT1 could also mitigate inflammatory injury by upregulating miR-19b and inhibiting NF-κB pathways in murine chondrogenic ATDC5 cells [19]. Remarkably MALAT1 was shown to function as a lncRNA 'decoy' and directly interacted with NF-κβ subunits, leading to attenuated NF-κβ occupancy at its target promoters [20]. In the neural microvasculature of ischemic stroke, silencing of MALAT1 significantly aggravated oxygen and glucose depravation-induced expression of IL-6, suggesting that MALAT1 plays an anti-inflammatory role in reducing tissue damage [21]. These seemingly conflicting findings underscore the obscurity of lncRNA functions. Importantly, cell-type and tissue specificity should be considered in the study of the relationship between lncRNA and IL-6.

NEAT1

LncRNA nuclear-enriched abundant transcript 1 (NEAT1) is involved in various types of cancers. Recently,

NEAT1 expression was reported to be significantly upregulated in patients with sepsis, and positively correlated with serum IL-6 [22]. NEAT1 can also induce neuropathic pain development in chronic constriction injury (CCI) rats *via* regulation of the miR-381/HMGB1 axis [23]. This molecule also participated in inflammation through sponging miR-128 in ox-LDL-induced macrophages [24]. Remarkably, downregulation of NEAT1 inhibited neuroinflammation or neovascularization *via* inhibiting IL-6 production [23, 25].

In autoimmune diseases, NEAT1 was reported to be abnormally increased in systemic lupus erythematosus (SLE) patients and predominantly expressed in human monocytes. There was a positive correlation between NEAT1 and clinical disease activity in lupus patients. NEAT1 was further identified as activating the MAPK signaling pathway with upregulation of IL-6 expression [26]. Osteopontin (OPN), which has been reported to upregulate the expression of matrix metalloprotease 13 (MMP13) and IL-6, was significantly increased in osteoarthritis (OA). Finally, NEAT1 could rescue miR-181c expression so as to inhibit OPN expression and synoviocyte proliferation [27].

Other lncRNAs Involved in IL-6 Dysregulated Diseases

Inflammation Relevant Diseases. As the human body's first line of defense upon injury and inflammation, IL-6 has been implicated in the etiology of various diseases besides infection. HOX antisense intergenic RNA (HOTAIR) is a lncRNA significantly induced in LPS-macrophages and implicated in the carcinogenic process [28]. HOTAIR was also obviously upregulated in ox-LDL induced macrophages and contributed to atherosclerosis development by downregulating miR-330-5 [29]. HOTAIR regulates the activation of NF-κB and its target gene IL-6 expression by facilitating the degradation of IκBα [28]. Other lncRNAs were also be found to be involved in NF-κB/IL-6 activation.

In LPS-induced septic acute kidney injury, long non-coding RNA plasmacytoma variant translocation 1 (PVT1) was shown to increase the levels of IL-6 by inhibiting the JNK/NF-κB signaling pathway [30]. Ins another example, lncRNA Gm4419 contributed to oxygen glucose deprivation/reoxygenation injury in cerebral microglial cells *via* IκB phosphorylation and NF-κB activation [31]. Suppression of lncRNA KCNQ1 overlapping transcript 1 (KCNQ1OT1) may also prevent myocardial ischemia/reperfusion injury *via* p38 MAPK/NF-κB signal pathway [32].

LncRNAs acting on the IL-6/STAT3 pathway have also been identified. In patients with sepsis, lncRNA downregulated in liver cancer (lnc-DILC) negatively regulated the expression of IL-6 by modulating the signaling pathway STAT3/toll-like receptor 4 (TLR4) axis. LncRNA H19 may also regulate endothelial cell aging *via* inhibition of STAT3 signaling [33]. LncRNA X inactivate-specific transcript (XIST) downregulation was shown to inhibit neuro-inflammation by reducing the expression of inflammatory cytokines through upregulating miR-544 and downregulating STAT3 in CCI rats [34].

LncRNAs, novel intracellular molecular effectors of IL-6 in cells of the innate immune system, are also involved in the molecular pathophysiology of autoimmune diseases and may provide novel targets for therapeutic intervention. For example, lncRNA profiling has revealed that differentially expressed lncRNAs are associated with disease activity in peripheral blood mononuclear cells (PBMCs) from patients with rheumatoid arthritis (RA) [35]. Several other lncRNAs, such as lncRNA growth arrest-specific transcript 5 (GAS5), RP11-445H22.4, and lncRNA maternally expressed gene 3 (MEG3) were found to be closely related to osteoarthritis (OA). Moreover, MEG3 knockdown mitigated inflammatory injury *via* the upregulation of miR-203 in ATDC5 cells [36]. Contrastingly, GAS5 and RP11-445H22.4 may ameliorate inflammatory injury in cartilage ATDC5 chondrocytes by inactivation of NF-κB and MAPK/ERK pathways with suppression of inflammatory cytokines secretion including IL-6 [37, 38]. Overexpression of GAS5 aggravated IL-6 secretion in macrophages and mechanistic analysis showed GAS5 to be an endogenous sponge directly inhibiting miR-221 expression [39].

Tumorigenesis and Metastasis. IL-6-activated STAT3 facilitates survival in multiple cancer cell lines and a number of lncRNAs were induced. Such a finding suggests the existence of interplay between coding and noncoding genetic material [40]. Bone marrow expression of lncRNA H19 was positively associated with circulating IL-6 level in multiple myeloma. Knockdown of H19 inhibited multiple myeloma cell growth *via* the NF-κB pathway [41]. Interestingly, lncRNAs H19 and HULC may regulate cholangiocarcinoma cell migration and invasion by targeting IL-6 and chemokine receptor CXCR4 through a ceRNA manner [42]. LINC00460 was markedly increased and facilitates nasopharyngeal carcinoma tumorigenesis through regulating sponging miR-149-5p/IL-6 signal pathway [43]. Su K. *et al.* have reported on a positive feedback loop between lncRNA upregulated in cervical cancer (lnc-UICC) and IL-6/STAT3 pathway to promote cervical cancer

Table 1. Most Relevant lncRNAs Involved in Dysregulated IL-6 Signaling Pathway and their Target Molecules

lncRNA	Target	Cell type or tissue	Effect	Disease	Reference
MALAT1	miR-125b and MAPK/NFκB.	Rat sepsis model (*in vivo*)	Aggravate cardiac inflammation and dysfunction	Sepsis	[12]
	MyD88/IRAK1/ TRAF6 signaling.	Rat microglia line HAPI (*in vitro*) and cerebral I/R injury model in diabetic rats (*in vivo*)	Promote inflammatory response	Cerebral ischemia/ reperfusion (I/R) injury in diabetes mellitus	[13]
	Serum amyloid antigen 3 (SAA3)	Human umbilical vein endothelial cells (*in vitro*) and Diabetic model (*in vivo*)	Upregulate inflammatory mediators IL-6 and TNF-α, *et al.* for diabetes-induced vascular complications.	Diabetes mellitus	[14]
	miR-146a	LPS-induced ALI rats (*in vivo*)	Promote inflammatory response	Acute lung injury (ALI)	[16]
	NF-κB and p38 MAPK pathways	Pulmonary microvascular endothelial cells (PMVEC) of rats (*in vitro*) and ALI rats (*in vivo*)	Promote inflammatory response	Acute lung injury (ALI)	[17]
	miR-155 and SOCS1	Human coronary artery endothelial cells (HCAECs) stimulated with ox-LDL	Alleviate inflammation	Atherosclerosis	[18]
	miR-19b and Wnt/β-catenin and NF-κB pathways	Murine chondrogenic ATDC5 cells induced with LPS (*in vitro*)	Alleviated inflammatory injury	Osteoarthritis	[19]
	NF-κB pathways	Macrophages activated with LPS (*in vitro*)	An autonegative feedback regulator of NF-κB to help fine-tune innate immune responses	Innate immune	[20]
	Bim and E-selectin	Mouse brain microvascular endothelial cells (BMECs) (*in vitro*)	Inhibit inflammation to reduce tissue damages	Ischemic stroke	[21]
NEAT1	miR-381/HMGB1 axis.	Chronic constriction injury (CCI) rat model (*in vivo*)	Induce neuropathic pain	Chronic constriction injury	[23]
	miR-128	RAW264.7 macrophages induced with ox-LDL (*in vivo*)	Participate in ox-LDL-induced inflammation and oxidative stress	Atherosclerosis	[24]
	NF-κB/miR-1246 pathway	Human corneal fibroblasts (HCFs) stimulated with LPS (*in vitro*) and CRNV rat model stimulated with LPS (*in vivo*)	Induced secretion of inflammatory factors to promote CRNV progression.	Corneal neovascula-rization (CRNV)	[25]
	MAPK pathway	Human monocytes stimulated with LPS (*in vitro*)	Promote inflammation	Systemic lupus erythematosus	[26]
	miR-181c	Human synoviocyte (*in vitro*)	Inhibit synoviocyte proliferation	Osteoarthritis	[27]
HOTAIR	NF-κB	Macrophages stimulated with LPS (*in vitro*)	Promote inflammatory and immune response	Inflammation	[28]
	miR-330-5p	Human macrophages THP-1 cells induced with ox-LDL (*in vitro*)	Promote development of atherosclerosis	Atherosclerosis	[29]
PVT1	Bind TNF-α and inhibit JNK/ NF-κB pathway	HK-2 cells induced with LPS (*in vitro*)	Promote inflammatory response	Septic acute kidney injury (AKI)	[30]
KCNQ1OT1	AdipoR1 and p38 MAPK/NF-κB pathway.	Cardiac muscle H9c2 cells induced under condition of oxygen glucose deprivation(*in vitro*)	Promote myocardial ischemia/ reperfusion injury	Acute myocardial infarction	[32]

H19	STAT3 signaling	Endothelial cells from aged mice (*in vitro*)	Promote proliferation of endothelial cells	Atherosclerosis	[33]
MEG3	miR-203	ATDC5 cells induced with LPS (*in vitro*)	Promote inflammatory injury	Osteoarthritis	[36]
GAS5	NF-κB and Notch pathways	ATDC5 chondrocytes stimulated by LPS (*in vitro*)	Ameliorate LPS-induced inflammatory injury	Osteoarthritis	[37]
	miR-221	THP-1 macrophage stimulated with ox-LDL (*in vitro*) and atherosclerotic rat model (*in vivo*)	Trigger inflammatory response	Atherosclerosis	[39]
RP11-445H22.4	miR-301a/CXCR4/NF-κB and MAPK/ERK pathways	ATDC5 chondrocytes stimulated by LPS (*in vitro*)	Ameliorate inflammatory injury	Osteoarthritis	[38]
LINC00460	miR-149-5p/IL-6 signal pathway	NPC cells (*in vitro*) and tumor xenografts established by CNE-1/SUNE-1 cells (*in vivo*)	Promote NPC progression	Nasopharyngeal carcinoma (NPC)	[43]
UICC	IL-6/STAT3 signaling	Caski, SiHa, HeLa, Ms751 and C33a cells (*in vitro*) and tumor xenografts established by HeLa cells overexpressing UICC *(in vivo*)	Promote tumorigenesis and metastasis in cervical cancer	Cervical cancer	[44]
BM	JAK2 kinase	Breast cancer cells (*in vitro*) and murine models *(in vivo*)	Promote breast cancer brain metastases	Breast cancer	[45]
TSLNC8	Transketolase/STAT3 axis	HCC cells *(in vitro*) and tumor xenografts (*in vivo*)	Suppresses proliferation and metastasis of HCC cells	Hepatocellular carcinoma (HCC)	[46]
CUDR	NF-κB signaling	Human embryonic stem cells-derived hepatocyte-like stem cells (*in vitro*)	Aggravate hepatocyte-like stem cells malignant transformation	Hepatocellular carcinoma	[47]
DILC	IL-6/STAT3 signaling	Liver cancer stem cells (LCSCs) both (*in vitro*) and tumor xenografts *(in vivo*)	Connect hepatic inflammation with LCSC expansion	Hepatocellular carcinoma	[7]
	IL-6/STAT3 signaling	Colorectal cancer cells (*in vitro*)	Suppress cancer growth and metastasis	Colorectal cancer	[48]

tumorigenesis and metastasis [44]. Another feedback loop, lnc-BM/JAK2 and IL-6/STAT3 signaling was also reported to mediate recruitment of macrophages enhancing breast cancer brain metastases (BCBM) [45].

Some lncRNA could also behave like a tumor inhibitor through IL-6/STAT3 signaling pathway. Tumor suppressive lncRNA on chromosome 8p12 (TSLNC8) is frequently deleted and downregulated in HCC tissues but is a tumor suppressor that inactivates the IL-6/STAT3 signaling pathway [46]. LncRNA prostate cancer associated transcript 29 (PCAT29) suppressed cell viability *via* IL-6/STAT3/miR-21 pathway [47].

IL-6 has been previously shown to exhibit enhanced activity in cancer stem cells (CSCs) and cooperation with lncRNAs to trigger the malignant transformation of CSCs. IL-6 and lncRNA CUDR cooperation aggravates hepatocyte-like stem cells malignant transformation through NF-κB signaling, and in turn, phosphorylated NF-κB promotes the expression and phosphorylation of STAT3. This molecule binds to the promoter region of miRNAs and lncRNAs to increase telomerase activity which leads to the malignant transformation of hepatocyte-like stem cells [47]. Through its mediation of cross-talk between TNF-α/NF-κβ signaling and IL-6/STAT3 cascade, DILC was reported to be an important tumor suppressor and is thought to be a potentially critical determinant in both the inflammatory microenvironment and CSC expansion [7, 48]. The most relevant lncRNAs involved in pathological processes dysregulating IL-6 signaling pathway are summarized in Table 1.

FUTURE DIRECTIONS

The effect of lncRNA on IL-6 activity is still under investigation. However, the promise of such molecules as biological markers remains clear. For example, lncRNAs may be able to predict whether a patient will develop a disease in which IL-6 signaling dysregulation is vitally involved. Thus, lncRNAs will further help to determine the use of IL-6 targeting strategies. However, for the specific purpose of determining drug types for IL-6 targeting to be administered, *i.e.*, monoclonal antibodies or small molecules for IL-6 signaling, specific lncRNAs can provide efficient and specific directions on which might achieve better efficiency in the context of serious diseases or complications. The lncRNAs may even help to determine the treatment program, therapy duration of length, or become treatment biomarker responses to minimize the adverse effects. Furthermore, some lncRNAs, such as lncRNA-SRLR, which behaves by evoking IL-6/STAT3 axis, may serve as a predictive biomarker for inherent drug resistance, and therefore as a therapeutic target to enhance responses to a specific kind of drug [49].

Increasing evidence has shown that lncRNAs which mediate IL-6 dysregulated diseases have great therapeutic potential, providing advantages over traditional IL-6-targeting agents. For instance, development of neutralizing antibodies against the IL-6-targeting-antibody-proteins leads to a loss of responsiveness after initially successful treatment. Additionally, small molecules are also less likely to disrupt protein-protein or protein-DNA interacting surfaces. One vital advantage of lncRNA-mediated control is the ability to tightly control gene expression *via* mechanisms such as protein- or DNA-binding. In addition, the regulatory relationship between components of IL-6 signaling pathway and lncRNAs seems to be reciprocal. The key point here lies in the determination of lncRNAs that play the pivotal role in the vicious circle, and challenges still remain before the clinical use of lncRNA-targeting therapeutics is possible.

Finally, several drugs have been reported to exert beneficial effects at least partly through regulation of expression for some lncRNAs related to IL-6 signaling. For example, emodin may attenuate cell apoptosis and inflammation as it was demonstrated to release IL-6 induced by LPS by inhibiting the NF-κB pathways *via* upregulation of TUG1 in murine chondrogenic ATDC5 cells [50]. Understanding the pharmacological interactions between drugs and lncRNAs will be of great help for appropriate drug-design. Besides, the interactions between drugs and lncRNAs are closely related to cell and tissue type. We should maximize the efficiency and minimize side effects of drugs with the help of local delivery by making efforts to fully evaluate innovative personalized treatment.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflicts of Interest. The authors have no conflict of interest to declare.

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