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Extended non-coded RNAs Deliver Perspective on the Control of the Cancer-immunity Stage

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Abstract

Developing data from current research reveals fresh insights into the roles played by long non-coding RNAs (lncRNAs) in immuno-oncology. Long non-coding RNAs (lncRNAs) not only influence the aggressiveness of cancer cells but also play a crucial role in controlling different immune cells and stromal cells, which in turn changes the tumor micro-environment and impacts anti-tumor immunity. The significance of predictive indicators derived from long non-coding RNAs (lncRNAs) is underscored by insightful discoveries concerning their involvement in immuno-oncological activities. In this context, we offer a comprehensive overview detailing the diverse functions of lncRNAs originating from immune, tumor, and stromal cells within the tumor microenvironment. We delve into elucidating their intricate processes and functional characteristics, particularly concerning immuno-oncological activities. Additionally, we explore the advantages and drawbacks associated with employing single-cell-based technologies to investigate the mechanisms underlying immune-related lncRNAs in cellular contexts. Through this comprehensive analysis, we aim to shed light on the complex interplay between lncRNAs and the immune system in the context of cancer, providing valuable insights for advancing therapeutic strategies and precision medicine approaches.

Keywords: Long non-coded RNA, cancer, immune cells, tumor micro-environment, immuno-oncology, immune escape, cancer-immune cycle, lncRNA signature

INTRODUCTION

RNA transcripts larger than 200 nucleotides are referred to as long non-coding RNAs (lncRNAs) [1]. Because lncRNAs cannot encode proteins, they were formerly regarded as "waste" from messenger RNA transcription [2]. But in recent years, it has been found that some lncRNAs can encode peptides, and a wealth of studies has transformed our knowledge of how lncRNAs work, particularly in malignancies [3–5]. Recent developments in the study of lncRNAs in particular have revealed their important function in influencing the tumor micro-environment (TME) in a variety of malignancies, the growth and course of which are governed by the dynamic interactions between cancer cells and the TME. Cancer immunity in the TME is mostly mediated by a complex blend of non-malignant components, including fibroblasts, immune cells, and extracellular matrix. The cancer-immunity cycle comprises numerous complex phases. It commences with the release of antigens, which are then recognized by dendritic cells (DCs) and presented on major histocompatibility class I (MHCI) molecules. Subsequently, CD8+ T cells specifically identify the antigen-MHCI complex, which results in CD8+ T cell activation. Following activation, CD8+ T lymphocytes go into the tumor and identify and eliminate malignant cells [6]. Other cells within the tumor micro-environment (TME),

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including stromal cells, macrophages, regulatory T cells (Treg cells), and myeloid-derived suppressor cells (MDSCs), also have significant roles in regulating anti-tumor immunity.

It has been discovered that LncRNAs control the actions of cancer cells, including invasion, proliferation, and the epithelial-mesenchymal transition (EMT). They additionally have a pivotal function in modulating immune cells such as T cells, B cells, macrophages, and dendritic cells, which are closely associated with immune evasion and anti-tumor functions (as mentioned earlier). In this review, we explain the regulatory roles and processes of immune-related lncRNAs originating from various cell types in the TME, examine how these lncRNAs promote or repress the development of cancer, and emphasize their potential clinical utility.

This article encompasses immune-related long non-coding RNAs (lncRNAs) that are extensively engaged in modulating cancer immunity, along with those expressed by immune cells to regulate immune cell functions.

lncRNAs' extracellular significance in the TME

Numerous roles for lncRNAs in the TME have been identified. The fact that certain lncRNAs promote or repress tumors in both cancerous and non-cancerous cells has been extensively shown. For example, it has been discovered that lncRNAs that are involved in oncogenic or anti-tumor actions in cancer cells—like PCAT6, UCA1, NKILA, NEAT1, LUCAT1, HOTAIR, and NRON—also have significant involvement in different kinds of immune cells (Table 1). Below is a more thorough discussion of these lncRNAs' functions.

Table 1. Extracellular significance of lncRNAs in the TME.

LncRNA	Cell type	Disease	Function	Mechanism	References
PCAT6	Cancer cell	NSCLS	Promotes cell growth	Represses LATS2 via the epigenetic repressor EZH2	[7]
	Cancer cell	Breast cancer	Promotes cell proliferation, migration and angiogenesis	Upregulated by VEGF secreted by M2 macrophage and induces the expression of VEGFR2 via ceRNA and deubiquitylation mechanism	[8]
	Cancer cell	Prostate cancer	Promotes cell proliferation, migration and invasion	METTL3-mediated m6A modification	[9]
	Macrophage	Cholangiocarcinoma	Promotes M2 polarization of macrophage	miR-326 and RhoA-ROCK pathway	[10]
SNHG1	Cancer cell	Gastric cancer	Promotes cell proliferation	Promotes DNMT1 expression	[11]
	CD4+ T cell	Breast cancer	Regulates Tregs differentiation	miR-448/IDO	[12]
NKILA	Cancer cell	Breast cancer	Inhibits EMT	Inhibits NF-κB activity	[13]
	Cancer cell	Breast cancer	Suppresses metastasis	Prevents over-activation of NF-κB pathway	[14]
	T cell	Breast cancer	Induces apoptosis of T cells and inhibits CTL infiltration	Inhibits NF-κB activity	[15]
NEAT1	Cancer cell	NSCLC	Promotes cell proliferation	miR-377-3p/E2F3	[16]
	Cancer cell	Prostate cancer	Promotes cancer progression and induces resistance to androgen or AR antagonists	Increased H3K4Me3 and H3AcK9 deposits on the PSMA promoter and transcriptionally activated PSMA	[17]

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	CD8+ T cell	Hepatocellular carcinoma	Inhibits CD8+ T cell apoptosis and enhances cytolytic activity	miR-155	[18]
	Myeloid cell	Acute promyelocytic leukemia	Inhibits myeloid differentiation	/	[19]
	DC	Autoimmune disease	Induces immune tolerance in DC	miR-3076-3p/NLRP3	[20]
LUCAT1	Cancer cell	Colorectal cancer	Promotes cell proliferation and chemotherapy resistance	Interacts with PTBP1 to alter alternative splicing of DNA damage related genes	[21]
	Cancer cell	Breast cancer	Promotes breast cancer stemness	miR-5582-3p/TCF7L2	[22]
	Myeloid cell		Inhibits immune response	Interacts with STAT1 to inhibit ISGs	[23]
HOTAIR	Cancer cell	Laryngeal carcinoma	Promotes cell proliferation and PD-L1 expression	miR-30a-5p/GRP78/PD-L1	[24]
	Cancer cell	Glioma	Upregulates PD-L1 and inhibits T cells activation	NF-κB pathway	[25]
	Macrophage	/	Promotes the NF-κB-mediated inflammatory pathway	Activates NF-κB and upregulates IL-6 and iNOS expression via facilitating the degradation of IκBα.	[26]
	Macrophage	/	Regulates glucose metabolism	NF-κB pathway	[27, 28]
NRON	Cancer cell	Hepatocellular carcinoma	Suppresses cell growth and metastasis	Inhibits EMT	[29]
	T cell	/	Represses nuclear factor of activated T cells	/	[30]

It has been determined that the lncRNA PCAT6 is an oncogene in a number of cancer types.

As an example, PCAT6 utilizes epigenetic alterations to enhance the growth and dissemination of cancer cells in non-small-cell lung cancer (NSCLC) and prostate cancer [7, 8]. In triple-negative breast cancer, vascular endothelial growth factor (VEGF) secreted by M2 macrophages activates PCAT6. This leads to the induction of VEGFR2 expression through a competitive endogenous RNA (ceRNA) and deubiquitylation process, which in turn promotes angiogenesis [9]. Further studies have demonstrated that PCAT6 is more extensively expressed in immune cells.

To put it differently, heightened expression of PCAT6 disrupts mitochondrial and metabolic activities, leading to the generation of reactive oxygen species through the miR-326 and RhoA-ROCK pathway. This, in turn, promotes macrophage M2 polarization, which is essential for immunological suppression [10]. In cancer cells, the long non-coding RNA small nucleolar RNA host gene 1 (SNHG1) operates as an oncogene [11]. Conversely, in Treg cells, SNHG1 fosters cell differentiation by elevating indoleamine 2,3-dioxygenase (IDO) levels and sequestering miR-448 [12]. Moreover, the long non-coding RNA nucleus enriched abundant transcript 1 (NEAT1) acts as a promoter of tumor progression by inducing CD8+ T-cell apoptosis and suppressing cytolytic activity [15], while also accelerating tumor growth in non-small-cell lung cancer (NSCLC) and prostate cancers [13, 14]. In certain instances, lncRNAs function as molecules that either promote or repress cancer in malignant and non-malignant cells, respectively. For example, the long non-coding RNA NF-κB-interacting lncRNA (NKILA) exhibits anti-tumor effects in breast cancer by restraining the excessive activation of the NF-κB pathway within tumor cells. NKILA is stimulated by NF-κB and establishes a stable complex by interacting with

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NF-κB/IκB. In breast cancer cell lines, the degradation of NKILA induced by miR-103/107 leads to NF-κB activation, consequently heightening invasiveness [16].

In a similar vein, it has been documented that TGF-β-induced NKILA inhibits EMT in breast cancer by inhibiting the NF-κB pathway that TGF-β induces [17]. However, in the TME, the lncRNA NKILA also takes part in immunological escape. Th1 cells and cytotoxic T lymphocytes (CTLs) have increased production of NKILA, which inhibits NF-κB activity and sensitizes T cells [24]. By causing T cell death and preventing CTL penetration into the malignancy, these modifications regulate immunological escape [18]. All things considered, the research to date has shown the various roles that long non-coding RNAs (lncRNAs) may have in the TME, contingent upon the type of cell involved. Therefore, lncRNAs produced in immune or stromal cells as well as those originating from malignant cells may serve as tumor suppressors or promotors and mediate immunological actions in the TME.

Tumor Cell-generated lncRNAs

In order for an effective anti-tumor immune response to eliminate cancer cells, the cancer-immune sequence, comprising antigen release and presentation, immune cell priming and activation, T-cell trafficking and infiltration, and finally the identification and elimination of cancer cells, must be initiated [6]. Tumor cell-expressed lncRNAs play a major role in immune modulation by controlling antigen presentation and release, priming and activating immune cells, and altering the way immune cells function.

EXPRESSION AND BREAKDOWN OF ANTIGENS

Research have demonstrated that lncRNAs may hasten the growth of tumors by affecting the expression of MHC molecules and the synthesis of tumor antigens. As an example, calreticulin (CALR), a calcium-binding chaperone found in cancer cells, influences antigen presentation by facilitating the folding of MCH-I [20]. Conversely, in lung cancer, ncRNA-RB1 functions as a tumor suppressor by upregulating CALR expression [19]. The surface expression of CALR acts as a “kill me” signal to encourage macrophage phagocytosis [21]. Macrophage cellular uptake is inhibited by ncRNA-RB1 knockdown, which also stops CALR from being translocated to the cell surface and from being expressed [19]. Humans and mice both contain the immunogenic lncRNA LIMIT (lncRNA generating MHC-I and immunogenicity of tumor) [22].

Heat shock factor-1 (HSF1) is liberated from HSP90 as a result of LIMIT activating the guanylate-binding protein gene clusters, which are stimulated by IFN-γ. HSF1 activation and MHC-I transcription follow from this. Consequently, LIMIT might be a viable epigenetic target for immuno-modulators [22]. Increased T cell infiltration in head and neck cancer is caused by the overexpression of LINC02195, another lncRNA that also increases MHC-I expression [23]. Additionally, HLA-G is known to be implicated in tumor escape. As a result, HOTAIR, another lncRNA, can function as a ceRNA and promote HLA-G expression in gastric and cervical malignancies [24, 25].

The Stimulation and Initialization

Important inhibitors of immunological priming and activation are immune checkpoint molecules. The most often used immune checkpoint inhibitor in clinical settings, programmed cell death 1 ligand 1 (PD-L1), is the subject of much research on how lncRNAs influence this mechanism [26]. According to recent research, lncRNAs function as ceRNAs that can directly sponge adsorb miRNAs in a variety of malignancies, thereby controlling the expression of PD-L1. Furthermore, via targeting miRNAs, the lncRNA UCA1 promotes the survival and metastatic capability of gastric cancer cells and may promote immune evasion through upregulating PD-L1 expression [27]. UCA1 stimulates PD-L1 expression and reduces cytokine release in CD8+ T cells in thyroid cancer, which prevents CD8+ T cells from having a cytotoxic effect and encourages cancer development [28]. Additionally, the conserved lncRNA MALAT1 in mammals can interact competitively with miRNAs to favorably control the expression of PD-L1 in NSCLC and diffuse large B-cell lymphoma [29, 30], hence promoting CD8+ T cell death [29].

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Table 2. LncRNAs derived from the cancer cells in the TME.

Immune-related function	LncRNA	Functions and Mechanisms	References
Antigen release and presentation	NcRNA-RB1	Promotes the expression and translocation of CALR, thus enhancing phagocytosis of macrophages	[19]
	LncRNA LIMIT	Activates HSF1 and the transcription of the MHC-I machinery	[22]
	LINC02195	Upregulates the expression of MHC-I	[23]
Priming and activation	LncRNA UCA1	Upregulates the expression of PD-L1 and inhibits the cytotoxic effect of CD8+ T cells	[27]
	LncRNA MALAT1	Upregulates the expression of PD-L1 through ceRNA network	[29, 30]
	LncRNA SNHG14	Upregulates the expression of PD-L1 and forms a positive feedback loop	[31]
	LncMX1-215	Down-regulates the expression of PD-L1 by preventing H3K27 acetylation on PD-L1 promoters	[33]
Regulation of T cells	LINC00301	Drives Treg infiltration by facilitating TGF-β1 secretion	[36]
	LINC00240	Suppresses NKT cell activity by inhibiting the expression of MICA	[37, 38]
Regulation of TAMs	LncRNA XIST	Recruits MDSCs and TAMs	[39]
	Lnc-BM LncRNA LNMAT1	Induces TAMs migration by promoting expression of CCL2	[40–42]
	LncRNA RPPH1 LncRNA PCAT6 LINC00662	Boosts macrophage M2 polarization	[44–46]
	LncRNA MALAT1	Prevents macrophage M1 polarization	[47]
Regulation of TANs	LncRNA HOTTIP	Induces PD-L1 expression of neutrophils and inhibits T cell proliferation by promoting IL-6 expression	[48]
	LINC01116	Recruits TANs	[49]
Regulation of CAFs	LncRNA POU3F3 lncRNA Gm26809	Mediates the reprogramming of normal fibroblasts into CAFs	[50, 51]

Furthermore, it has been found that SNHG14 increases the expression of PD-L1 and SNHG14 by elevating the abundance of zinc finger E-box binding homeobox 1. Due to its ability to prevent CTL activation and promote immunological escape, a positive feedback loop is responsible for maintaining the high expression of PD-L1 [31]. Furthermore, it has been discovered that the lncRNA LINC00473 increases PD-L1 expression in pancreatic cancer [32]. These results suggest that lncRNAs facilitate cancer cells' immunological escape.

Notably, lncMX1-215, another lncRNA, has been shown to inhibit tumor growth by PD-L1 negative regulation. lncMX1-215 can downregulate IFNα-driven expression of PD-L1 and galectin-9 and can effectively reduce the proliferation and migration of head and neck cancer cells when triggered by the virus. Regarding the underlying mechanism, PD-L1 and galectin-9 promoters are not subjected to H3K27 acetylation due to the direct interaction between lncMX1-215 and GCN5, an H3K27 acetylase [33–35] (Table 2). This has the effect of negatively limiting PD-L1 and galectin-9 expression.

IMMUNE CELL INHIBITION

Studies have suggested a possible link between lncRNA expression and immune infiltration. For example, the elevation of CXCL13 due to the lncRNA BM466146 is associated with enhanced T-cell infiltration in breast cancer [34]. Similarly, in hepatocellular carcinoma (HCC), increased expression of the lncRNA NNT-AS1 triggers activation of the TGF-β signaling pathway, leading to a decrease in CD4+ lymphocyte infiltration [35]. The manner in which lncRNAs produced from tumor cells affect immune cell activity in the TME is still being studied.

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T Cells

It has been demonstrated that the high-expression lncRNA LINC00301 promotes TGF-β1 production, which in turn promotes Treg cell infiltration and subsequently reduces the CD8+ T-cell population in the TME [36]. Through the ceRNA pathway, LINC00240 promotes STAT3 expression in cervical cancer. MHC class I-related chain (MIC)-A is one of STAT3's downstream targets and is essential for the activation of natural killer T (NKT) cells. Consequently, LINC00240 blocked MICA expression, which in turn caused NKT cell activity to be suppressed [37].

Macrophages

Recent research has shown that certain lncRNAs have an impact on the recruitment of macrophages. In a comprehensive RNA study across various cancers, it was discovered that an lncRNA involved in calcium-dependent kinase activation (CamK-A) functions as an oncogene. By stimulating pregnancy-upregulated nonubiquitous CaM kinase (PNCK), which aids in TME remodeling including angiogenesis and macrophage recruitment, CamK-A can activate NF-κB [38]. Through the recruitment of MDSCs and macrophages by the lncRNA XIST/miR-133a-3p/RhoA signaling pathway, which intensifies colitis-associated colorectal tumorigenesis and devFurthermore, it was shown that a novel long noncoding RNA (lncRNA) linked to brain metastasis in breast cancer, called lnc-BM, activates JAK2 kinase and mediates the phosphorylation of STAT3, hence enhancing the STAT3-dependent production of CCL2 and ICAM1. ICAM1 promotes vascular cooptation, and CCL2 crosses the blood-brain barrier to cause macrophage migration into the brain [40]. Interleukin (IL)-6 and oncostatin M, which are secreted by the recruited macrophages, further initiate STAT3 phosphorylation. This study illustrates a self-reinforcing cycle that intensifies the metastasis of breast cancer induced by lnc-BM [41]. It has also been documented that lncRNA-induced CCL2 plays a role in bladder cancer via recruiting macrophages.

LncRNA lymph node metastasis-associated transcript 1, or LNMAT1, has been demonstrated to induce CCL2 expression by recruiting hnRNPL to the CCL2 promoter. elopment, CXCR4 plays a critical role in aggravating colitis-associated colorectal cancer [39]. Through the excretion of VEGF-C, the macrophages attracted by CCL2 facilitate lymphatic metastasis [42].

Based on their functional condition and activation stage, macrophages can be broadly categorized as either traditionally activated (M1 phenotype) or alternatively activated (M2 phenotype) [43]. M2 macrophages are involved in wound healing and have the ability to trigger carcinogenesis and immunosuppression in tumors, whereas M1 macrophages secrete pro-inflammatory cytokines that are part of the type I T helper cell (TH1) response against infections and cancer [43]. Numerous studies on cancer have shown how important lncRNAs are for macrophage polarization. According to one study, cancer cells use exosomes to transfer the long noncoding RNA RPPH1 to macrophages, where it increases M2 polarization and provides a positive feedback loop that increases colorectal cancer cells' ability to invade and proliferate [44]. PCAT6 trafficking from tumor cells has been shown to stimulate macrophage polarization toward the M2 subgroup in non-small cell lung cancer (NSCLC). Additionally, it was discovered that M2 macrophages stimulated EMT and metastasis through the PCAT6/miR-326/KLF1 axis [45]. It has been discovered that LINC00662 paracrinely promotes M2 macrophage polarization in HCC [46], while lncRNA MALAT1 knockdown suppresses angiogenesis and promotes M1 macrophage polarization [47]. Therefore, in HCC, MALAT1 might function as a tumor-promoting marker.

Neutrophils

Tumor-associated neutrophils (TANs) are now recognized as an essential part of the tumor microenvironment (TME) and are involved in immunosuppression and inflammation associated with tumors. In ovarian cancer, the long non-coding RNA HOTTIP suppresses T-cell proliferation and cancer cell evasion by enhancing IL-6 secretion. This, in consequence, promotes the expression of PD-L1 on neutrophils through the phosphorylation of STAT3 [48]. LINC01116 stimulates the expression of IL-1β in gliomas, which aids in the build-up of TANs in the TME. Neutrophils that have infiltrated the

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body secrete diverse cytokines that support the proliferation of cancer cells. Therefore, a bad prognosis for patients with gliomas is indicated by higher expression of LINC01116 in glioma tissues [49].

Fibroblasts

In cancer, activated stromal cells known as fibroblasts, which are also termed cancer-associated fibroblasts (CAFs), are commonly observed. Through interactions with cancer cells, CAFs can accelerate the growth and spread of tumors. Research on how lncRNAs control fibroblasts to promote tumor growth has shown that lncRNAs produced from tumor cells primarily control fibroblasts through exosomes. The lncRNA POU3F3, which is carried by exosomes produced by cancer cells, induces the conversion of fibroblasts into cancer-associated fibroblasts (CAFs) in esophageal squamous cell carcinoma. These activated fibroblasts secrete inflammatory cytokines such as IL-6, which promote the growth and cisplatin resistance of esophageal squamous cell carcinoma (ESCC) cells [50]. Additionally, in melanomas, tumor-secreted exosomal lncRNA Gm26809 was found to transform NIH/3T3 fibroblasts into CAFs, evident from the increased expression of α-smooth actin and fibroblast activation protein. Coculturing melanoma cells with CAFs significantly enhanced cell migration and proliferation [51].

Overall, the research presented in this section suggests that long non-coding RNAs (lncRNAs) produced from tumor cells have a role in the regulation of immune cells and multiple cancer types at different phases of the cancer-immune cycle. Therefore, their impact on the expression of particular proteins by immune cells and the actions of these cells may be linked to the processes behind their impacts on the cancer-immune cycle. Through their effects on events of the cancer-immune cycle, immune cells and stromal cells other than cancer cells may also have an impact on anti-tumor activity. Consequently, lncRNAs connected to these cells are the main topic of the following two sections.

IMMUNE CELL-DERIVED LNCRNAS

Modulation of Immune Cell Differentiation

According to a number of studies, lncRNAs play a critical role in regulating the activation and differentiation of lymphoid and myeloid cells [52–55]. Furthermore, T cell-derived lncRNAs may have an impact on T cell development and function, according to bioinformatics mining investigations [56–58]. According to the findings of Zhang and colleagues, the lncRNA lnc-DC interacts with STAT3 in the cytoplasm, initiating the STAT3 pathway, which influences the maturation and differentiation of dendritic cells [59]. According to another study conducted by Jonathan and his associates, the pro-apoptotic gene Bcl2l11 is maintained by the lncRNA Morrbid, which controls the longevity of myeloid cells [60]. Furthermore, it was found that the long noncoding RNA lnc-MC enhances the expression of activin A receptor type 1B, which promotes activation of the TGF-β signaling pathway. The involvement of long noncoding RNAs (lncRNAs) in the formation and differentiation of immune cells has been extensively documented, with recent research focusing on elucidating whether these lncRNAs promote or hinder tumor growth. One study identified a positive correlation between the expression of EGFR/Foxp3 in patients with HCC and the upregulation of lnc-epidermal growth factor receptor (EGFR) in Tregs. By using c-CBL, lnc-EGFR targets EGFR and prevents its interaction and ubiquitination. Tumor growth and immune escape are facilitated by the modulation of EGFR by lnc-EGFR, which leads to Treg differentiation and CTL inhibition [61–63]. In breast cancer, inhibition of SNHG1 has been observed to decrease IDO expression and prevent Treg differentiation, consequently restraining tumor growth [12] (Table 3).

Expression of Antigens

The TME's main antigen-presenting cell is the dendritic cell. Once antigens have been phagocytosed, they undergo cytokine stimulation to mature, express co-stimulatory molecules like CD80/86/40 and deliver antigens to T cells to trigger immunological responses [63]. It has been discovered that lnc-DC silencing inhibits HLA-DR expression and decreases DCs' capacity to absorb antigens, which in turn lessens DCs' capacity to promote T-cell proliferation. Stated differently, lnc-DC has the ability to increase inflammatory cytokine release and T-cell priming [64]. To start an immunological response,

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Table 3. LncRNAs derived from the immune cells in the TME.

Immune-related function	LncRNA	Functions and Mechanisms	References
Modulation of immune cell differentiation	Lnc-EGFR	Modulates Treg differentiation and CTL suppression	[62]
	LncRNA SNHG1	Promotes Treg differentiation by upregulation of IDO	[12]
Antigen presentation	Lnc-DC	Impairs the antigen uptake of DCs by downregulating the expression of HLA-DR	[64]
	Lnc-Dpf3	Targets HIF-1α and suppresses Ldha	[65]
Regulation of CD8+T cells	Lnc-Tim3	Maintains exhausted CD8+ T cells by inducing expression of the anti-apoptotic proteins	[66]
	LncRNA NEAT1	Promotes CD8+ T cell apoptosis through miR-155/Tim-3 pathway	[15]
Regulation of other immune cells	LncRNA-MM2P	Promotes macrophage M2 polarization	[67]
	LncRNA NIFK-AS1 LncRNA Cox-2	Inhibits macrophage M2 polarization	[68, 69]
	LincRNA-p21 LncRNA TUC339 LncRNA ANCR	Inhibits macrophage M1 polarization	[70–73]
	LncRNA Pvt1	Inhibits MDSCs by upregulating HIF-1a	[74–76]
Regulation of tumor cells	LncRNA HISLA	Enhances the aerobic glycolysis by stabilizing HIF-1a	[77]
	LncRNA AFAP1-AS1	Promotes migration and invasion by inhibiting miR-26a expression and upregulating ATF2	[78]

DC trafficking is also necessary. It has been established that chemokine receptor type 7 (CCR7) ligands play a significant role in DC migration. By stopping its degradation, CCR7 stimulation increases the expression of lnc-Dpf3 and causes a metabolic reprogramming toward glycolysis. This stimulates DC migration by causing DCs to activate the HIF-1α pathway. On the other hand, lnc-Dpf3 has the ability to directly target HIF-1α and decrease the transcription of Ldha, a glycolytic gene that depends on HIF-1α. Due to this, a negative feedback loop is created, which hinders DCs' ability to migrate and metabolize glycogen, terminates CCR7-mediated DC migration, and supports immunological homeostasis [65] (Table 3).

Optimization of CD8+ T Cell Cytotoxic Consequences

At the moment, lncRNAs are thought to be significant modulators of CD8+ T cell activity. Ji and his associates, for instance, found that lnc-Tim3 is a critical regulator of CD8+ T cell survival and exhaustion. In HCC, CD8+ T cells express lnc-Tim3 at high levels, and there is a negative correlation between this expression with the generation of IL-2 and IFN-γ. These results imply that CD8+ T cell exhaustion is encouraged by lnc-Tim3. A thorough investigation into this effect showed that lnc-Tim3 might selectively bind to Tim-3 to inhibit the interaction between Tim-3 and Bat3, which would cause Bat3 to localize to the nucleus. Moreover, it was shown that lnc-Tim3 improved the transcriptional activation of RelA and p53 and induced the expression of p21, MDM2, and Bcl-2, anti-apoptotic proteins, which allowed Tim-3+ tired CD8+ to survive. The involvement of the lncRNA NEAT1 in aiding hepatocellular carcinoma (HCC) evade immune surveillance via the miR-155/Tim-3 pathway in CD8+ T cells was identified. This process leads to the promotion of CD8+ T-cell apoptosis and inhibition of cytolysis [15] (Table 3). This investigation explored the functions of lncRNAs derived from CD8+ T cells in the progression of HCC.

Alteration with Additional Immune Cells

Cao and his colleagues attempted to identify the lncRNAs of macrophages that affect macrophage polarization in light of the mounting evidence for the critical role of lncRNAs in regulating immune cell development and function. They found that lncRNA-MM2P serves as a regulator of macrophage M2 polarization through the use of lncRNA arrays. In other words, by preventing STAT6 phosphorylation, it was discovered that inhibiting lncRNA-MM2P reduced angiogenesis of M2 and

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inhibited macrophage polarization to M2 [67]. Conversely, it has been discovered that the lncRNAs NIFK-AS1 and Cox-2 inhibit macrophage M2 polarization [68, 69]. Moreover, suppression of lncRNAs may encourage macrophage polarization into pro-inflammatory M1 subsets, including lncRNA-p21, lncRNA TUC339, and lncRNA ANCR [70–72]. (Table 3).

Immature cells that have been pathologically activated, known as MDSCs, are involved in the immunosuppression that tumors induce. These cells aid in the immunological escape of cancerous cells by significantly suppressing the T cell-induced anticancer response [73]. It has been discovered that the lncRNA Pvt1 suppresses the functional control of MDSCs. HIF-1a causes Pvt1 to be increased in MDSCs during hypoxic stress, which significantly reduces MDSC function. Consequently, it was discovered that Pvt1 knockdown decreased MDSCs' capacity to suppress the immune system, hastening the growth of tumors and preventing anti-tumor immune responses [74]. Additional research has shown that some lncRNAs, such as Lnc-C/EBPβ and Lnc-chop, inhibit the ability of MDSCs to suppress the immune system by controlling target transcripts, such as cyclooxygenase-2, nitric oxide synthase 2, arginase-1, and NADPH oxidase 2, all of which are strongly associated with the TME's ability to suppress the immune system [75, 76].

Tumor Cell Modification by Extracellular Vesicles

Researchers have found that extracellular vesicles transport long non-coding RNAs (lncRNAs) from immune cells to tumor cells. For example, the lncRNA HIF-1α-stabilizing long non-coding RNA (HISLA), which is transferred to breast cancer cells by extracellular vesicles from tumor-associated macrophages (TAMs), enhances the aerobic glycolysis of cancer cells by preventing PHD2 and HIF-1α from binding and stabilizing HIF-1α. In a feed-forward loop, TAMs and tumor cells are linked by the delivery of lactic acid by glycolytic tumor cells, which promotes HISLA production in TAMs [77]. An additional illustration is the lncRNA AFAP1-AS1 from exosomes produced from M2 macrophages, which has the ability to suppress the expression of miR-26a and increase ATF2, hence facilitating the migration, invasion, and lung metastasis of esophageal cancer cells [78].

Thus far, research has shown that a number of long noncoding RNAs (lncRNAs) produced from immune cells play a key role in regulating both tumor cells and different kinds of immune cells. LncRNAs are expressed in immune cells, including MDSCs and CD8+ T lymphocytes, and they play a role in controlling their cytotoxic effects, antigen presentation, and differentiation. To better clarify how lncRNAs originating from immune cells influence other types of immune cells, more research is necessary.

lncRNAs Generated within Stromal Cells

The most significant stromal elements in the TME are stromal CAFs [79]. Ding and associates discovered FLJ22447, an as-yet-unidentified long noncoding RNA, to be significantly elevated during the conversion of normal fibroblasts to cancer-associated fibroblasts (CAFs). They dubbed this lnc-CAF. In terms of how it works, lnc-CAF prevents p62-dependent autophagy-lysosome degradation of IL-33 and directly increases IL-33 to sustain the proliferative effect of IL-33 on tumor cells. By means of exosomal lnc-CAF, tumor cells subsequently cause stromal fibroblasts to express higher amounts of lnc-CAF [80] (Table 4).

By altering the activity of tumor cells, exosomes from CAFs that carry lncRNAs may contribute to the etiology and progression of tumors. H19 and CCAL, two lncRNAs linked to colorectal cancer, are found in greater abundance in the stroma of colorectal cancer patients than in the tumor nests. Exosomes released by CAF carry them to cancer cells. By triggering the β-catenin pathway, lncRNA H19 and CCAL can both encourage aggression and chemoresistance [81, 82]. Likewise, miR-14 is transported to oral squamous cell carcinoma (OSCC) cells through exosomes derived from cancer-associated fibroblasts (CAFs) overexpressing lncRNA TIRY. This promotes invasion and metastasis of cancer cells [83]. lncRNAs from CAF-derived exosomes were able to alter cancer cells' metabolic pathways in addition to increasing their aggressiveness. For example, researchers found that the CAF-specific

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Table 4. LncRNAs derived from the stromal cells in the TME.

Regulation of tumor cells	LncRNA	Functions and Mechanisms	References
Promotion the aggressiveness of tumor cells	Lnc-CAF	Upregulates IL-33 and maintains effects of IL-33 on tumor proliferation	[80]
	LncRNA H19 LncRNA CCAL	Promotes aggressiveness and chemoresistance by activating the β-catenin pathway	[81–83]
Reprograms of the metabolic pathways	LINC01614	Enhances glutamine uptake by directly interacting with ANXA2 and p65 to facilitate the activation of NF-κB	[84]
	LncRNA SNHG3	Inhibits mitochondrial oxidative phosphorylation and increases glycolysis and carboxylation, thus enhancing tumor proliferation	[85]

long non-coding RNA LINC01614 enhances glutamine uptake in lung adenocarcinoma (LUAD) cells [84]. Moreover, upon uptake of exosomes by tumor cells, the long non-coding RNA SNHG3 can enhance glycolysis and carboxylation, suppress mitochondrial oxidative phosphorylation, and stimulate tumor cell proliferation [85] (Table 4). Therefore, it appears that CAFs are the main source of lncRNAs that are linked to the spread and metastasis of cancer and are extracted from the stroma.

LncRNAs affect endothelial cells' ability to operate in addition to fibroblasts. It has been found that lncRNA n342419, also known as MANTIS, functions as an endothelial angiogenic facilitator [86]. In addition, lncRNA-MIAT, in conjunction with vascular endothelial growth factor and miR-150-5p, can counteract the microvascular dysfunction caused by diabetes mellitus in the retina [87]. There is still a pressing need for additional research to show how lncRNAs function in cancer-associated endothelium cells.

The Clinical Significance of lncRNAs Connected to Immunity

Immune-related lncRNAs' Potential for Clinical Application

Since lncRNAs significantly affect tumor growth, they could be attractive targets for tumor therapy from a therapeutic standpoint. Technologies aimed at lncRNAs have advanced significantly recently [88], with methods to control lncRNA expression in the cytoplasm and nucleus among them: (1) RNA destabilizing elements (RDE) integrated into the genomic region to inhibit lncRNA transcription [89, 90]. (2) Locked nucleic acid (LNA) GapmeRs [91], antisense oligonucleotides (ASO) [90], and siRNA [3] destabilize lncRNA transcripts. (3) Using aptamers and tiny compounds to prevent lncRNAs from interacting with other people [92]. (4) CRISPR-based lncRNA gene editing [93]. These methods have been verified in models of patient-derived tumor xenografts (PDXs). It has been shown by researchers that brain metastasis of breast cancer can be prevented by siRNA targeting lnc-BM. Lnc-BM stimulates ICAM1 and CCL2 expression, which leads to macrophage chemotaxis into the brain and ultimately promotes brain metastases. In order to investigate a possible treatment approach for the illness, scientists created mouse models with brain metastases and administered siRNAs for lnc-BM coupled with nanoparticles. Depletion of lnc-BM by siRNAs substantially inhibited brain metastasis, as demonstrated by in vivo investigations [41]. Furthermore, lncRNA targeting might increase immunotherapy's efficacy. Immunocheckpoint blockage (ICB) and the elevated level of LIMIT caused by CRISPR activation can work together to enhance antigen presentation by raising MHC-I expression [22].

T cell NKILA silencing in immunocompromised mice prevents them from being eliminated by the immune system, increasing the effectiveness of adoptive T cell treatment [18]. These results point to lncRNAs' potential for treatment in preclinical models. Therapeutic approaches involving lncRNAs have various benefits. Firstly, since certain dysregulated lncRNAs are particular to cancer, these lncRNAs are essential for the creation of tailored treatments. Moreover, lncRNAs interact with other molecules on a variety of regulatory locations, opening up new avenues for the development of novel structure-based drugs [94]. Targeting lncRNAs has therapeutic potential, but like all RNA-based medicines, there are certain challenges in bringing the research into the clinic, including as specificity, immunogenicity, and delivery [95]. Extracellular vesicles, which are immunological tolerant and tissue penetrating, can be used to encapsulate lncRNAs or lncRNA-targeting compounds in order to improve

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delivery and immunogenicity [96, 97]. Using artificial carriers, such as synthetic nanoparticles, offers an option [41].

Altering RNA or nanoparticles could potentially enhance their specificity for the intended target, thereby increasing precision. It is still unclear, though, if straying from the goal might be dangerous for people's safety. While a number of mRNA-based treatments, such as siRNAs or ASOs, have received FDA approval to date, no lncRNA-based treatments have been used in clinical settings [95]. Much progress is needed before lncRNAs or lncRNA-targeted compounds can be utilized in tumor treatment, with the majority of research on lncRNAs and tumor therapy concentrating on mouse models [98–110].

Possibilities

A growing number of novel lncRNAs are being found as a result of increased lncRNA study. Further research is needed to find out how these new lncRNAs work in the future. The investigation of lncRNA functions that are exclusive to particular cell types in the TME is limited by the heavy reliance of lncRNA investigations to date on bulk RNA sequencing or microarray detection. To ascertain the function and predictive significance of lncRNAs in particular immune cells, some researchers have carried out investigations on particular isolated cell types or cell lines. Even though these investigations have produced some amazing results, more research is still needed to determine how different cell types contribute to the expression of these lncRNAs. The analysis of lncRNA expression in a single cell can be effectively accomplished by the use of single-cell RNA sequencing, or scrRNA-seq. It might aid in the identification of novel lncRNA-defined cell subtypes [111–120].

More recently, single-cell investigations have made it possible to identify novel lncRNA markers and understand their roles in the development of embryos and stem cells, as well as in viral infectious illnesses. Additionally, single-cell investigations on lncRNAs have been initiated in the field of cancer research. For instance, studies on the scRNA-seq of clear cell renal cell carcinoma (ccRCC) have identified 173 lncRNAs linked with ccRCC metastasis that support immune response, proliferation, and cell adhesion [121–130]. Furthermore, scRNA-seq in HCC filtered out an M2 macrophage polarization-associated lncRNA, which was then discovered to function as a miRNA sponge to enhance glucose metabolism and cell proliferation. Nevertheless, there are presently few research on lncRNAs that use single-cell analysis, in part because low-abundance transcripts are not detected and novel lncRNAs lack annotations. Large-scale information collections and sequencing technology have sparked a revolution in “omics.” It is still very difficult to determine how to interpret this data in order to learn more about the function of immune-related lncRNAs. By effectively understanding omics data through machine learning and deep learning, and by integrating data from medical and pathological pictures, artificial intelligence (AI) can be a useful tool. An integrative technique based on machine learning is developed by Prabhat and colleagues to create a consensus immune-related lncRNA signature (IRLS) with a strong prediction value for colorectal cancer. A lncRNA-based prognostic signature was developed in our previous study using a machine learning-based LASSO algorithm. Digital pathology techniques, such as image segmentation, identification of positively-stained cells, and region annotation, were utilized to evaluate immune infiltration within sub-groups categorized according to the signature [131–137].

CONCLUSION

The functions of lncRNAs expressed by different cells that control cancer immunity in the TME are outlined in this review. Tumor, stromal, and immune cells can all express immune-related RNAs, which are implicated in immuno-regulatory mechanisms. Through the paracrine system or extracellular vesicles, lncRNAs originating from distinct sources can influence the behavior of other cell types. This suggests that the regulation of the TME is not a discrete intracellular process, but rather entails nuanced interactions across multiple cell types. However, a detailed discussion of how lncRNAs interact with other non-coding RNAs to regulate the TME is not provided here. Rather, we also talked about the disadvantages of lncRNA-based therapy approaches. Even though bulk RNA sequencing is currently the primary method used for studies into the expression and characterization of lncRNAs, we think that

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the quick development of single-cell techniques and bioinformatics analytical tools will greatly contribute to further elucidating the regulatory functions and therapeutic significance of immune-related lncRNAs.

Conflicts of Interest

All authors declare no conflict of interest.

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This study did not receive any funds.

Abbreviations

lncRNAs: Long non-coding RNAs;
TME: Tumor Microenvironment;
DC: Dendritic Cell;
MHCI: Major Histocompatibility Class I;
Treg: Regulatory T cell;
MDSC: Myeloid-Derived Suppressor Cell;
EMT: Epithelial-Mesenchymal Transition;
NSCLC: Non-Small-Cell Lung Cancer;
VEGF: Vascular Epithelial Growth Factor;
ceRNA: Competing endogenous RNA;
SNHG1: Small Nucleolar RNA Host Gene 1;
IDO: Indoleamine 2,3-dioxygenase;
NEAT1: Nuclear Enriched Abundant Transcript 1;
NKILA: NF-κB-Interacting lncRNA;
CTLs: Cytotoxic T Lymphocytes;
CALR: Calreticulin;
LIMIT: LncRNA Inducing MHC-I and Immunogenicity of Tumor;
HSF1: Heat Shock Factor-1;
PD-L1: Programmed cell death 1 Ligand 1;
HCC: Hepatocellular Carcinoma;
MIC: MHC class I-related Chain;
NKT: Natural Killer T;
CamK-A: Calcium-dependent Kinase Activation;
PNCK: Pregnancy up-regulated Nonubiquitous CaM Kinase;
TH1: Type I T Helper cell;
TANs: Tumor-Associated Neutrophils;
CAFs: Cancer-Associated Fibroblasts;
ESCC: Esophageal Squamous Cell Carcinoma;
lnc-MC: Long noncoding Monocytic RNA;
EGFR: Epidermal Growth Factor Receptor;
CCR7: Chemokine Receptor type 7;
HISLA: HIF-1α-Stabilizing Long non-coding RNA;
TAMs: Tumor Associated Macrophages;
CCAL: Colorectal Cancer-Associated lncRNA;
OSCC: Oral Squamous Cell Carcinoma;
LUAD: Lung Adenocarcinoma;
RDE: RNA Destabilization Elements;
ASO: Antisense Oligonucleotide;
LNA: Locked Nucleic Acid;
ICB: Immune Checkpoint Inhibitor;
PDX: Patient-Derived tumor Xenograft;

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NPC: Nasopharyngeal Carcinoma;
TILSig: Tumor-infiltrating immune-related lncRNA signature;
scRNA-seq: Single-cell RNA sequencing;
ccRCC: Clear cell Renal Cell Carcinoma;
AI: Artificial Intelligence;
IRLS: Immune-Related lncRNA Signature

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