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Insights from Long Noncoding RNAs into Cancer-immunity Cycle Regulation

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Abstract

Accumulating evidence from recent research offers new perspectives on the functions of long non-coding RNAs (lncRNAs) in immuno-oncology. In addition to modulating the aggressiveness of cancer cells, lncRNAs are essential players in regulating various immune cells and stromal cells, playing a role in reshaping the tumor microenvironment and affecting anti-tumor immunity. The insightful discoveries on the role of lncRNAs in immuno-oncological activities indicate the prognostic value of lncRNA markers. Here, we present an overview of the roles of lncRNAs derived from different cell types in the tumor microenvironment, that is, immune cells, tumor cells, and stromal cells, and summarize their functional characterization and mechanisms in immuno-oncological activities. We also discuss the opportunities and challenges of single-cell-based technologies for analyzing the cellular function of immune-related lncRNAs.

Keywords: Long noncoding RNA, Cancer, Immune cells, Tumor microenvironment, Immuno-oncology, Immune escape, Cancer-immune cycle, lncRNA signature

Introduction

Long non-coding RNA (lncRNAs) are RNA transcripts that are longer than 200 nucleotides [1]. Initially, lncRNAs were considered as "waste" resulting from messenger RNA transcription due to their inability to encode proteins [2]. However, in recent decades, it has been discovered that some lncRNAs have peptide-encoding ability [1], and extensive research has revolutionized our understanding of the function of lncRNAs, especially in cancers [3-5]. In particular, recent advances in the research on lncRNAs have uncovered their substantial role in shaping the tumor microenvironment (TME) in various malignancies, the development and progression of which are controlled by the dynamic interactions between cancer cells and the TME.

In the TME, a complex mixture of non-malignant components, such as immune cells, fibroblasts, and extracellular matrix, is extensively involved in cancer immunity. The cancer-immunity cycle consists of a series of complex steps. Initially, antigens are released, and these are recognized by dendritic cells (DCs) and presented on major histocompatibility class I (MHCI) molecules. Next, the antigen-MHCI complex is specifically recognized by $CD8^+$ T cells, and this triggers $CD8^+$ T cell activation. On activation, $CD8^+$ T cells migrate into the tumor, where they recognize and kill cancerous cells [6]. Other cells in the TME also play pivotal roles in regulating anti-tumor immunity, including immune cells such as regulatory T cells (Treg cells), macrophages, and myeloid-derived suppressor cells (MDSCs), as well as stromal cells such as fibroblasts.

LncRNAs have been found to regulate the behavior of cancer cells, such as invasion, proliferation, and epithelial-mesenchymal transition (EMT), and they also serve as key regulators in immune cells, such as T cells, B cells, macrophages, and dendritic cells, which are closely associated with anti-tumor activities and immune evasion (as discussed above). In this review, we discuss how immune-related lncRNAs derived from different cell types in the TME play promoting or suppressive roles in cancer development, describe the regulatory functions and mechanisms of these lncRNAs, and highlight their potential clinical value. The immune-related lncRNAs discussed here not only include those expressed by immune cells and involved in regulating immune cell activities, but also include those which participate broadly in the regulation of cancer immunity. The latter lncRNAs can be expressed by either immune cells or non-immune cells, including cancer cells and stromal cells.

Multicellular Functions of lncRNAs in the TME

LncRNAs have been implicated in a wide range of functions in the TME. It has been widely demonstrated that some lncRNAs exert tumor promotion or suppression functions not only in cancer cells, but also in non-malignant cells. For instance, lncRNAs, such as PCAT6, UCA1, NKILA, NEAT1, LUCAT1, HOTAIR, and NRON, which are involved in oncogenic or anti-tumor activities in cancer cells, have also been found to play important roles in various types of immune cells (**Table 1**). The roles of these lncRNAs are discussed in more detail below.

The lncRNA PCAT6 has been identified as an oncogene in various types of cancers. For example, in non-small-cell lung cancer (NSCLC) and prostate cancer, PCAT6 induces an increase in the proliferation and metastasis of cancer cells via epigenetic modifications [7, 8]. In triple-negative breast cancer, PCAT6 is

Table 1. Multicellular functions 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	[9]
	Cancer cell	Prostate cancer	Promotes cell proliferation, migration and invasion	METTL3-mediated m6A modification	[8]
	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	[17]
	Cancer cell	Breast cancer	Suppresses metastasis	Prevents over-activation of NF-κB pathway	[16]
	T cell	Breast cancer	Induces apoptosis of T cells and inhibits CTL infiltration	Inhibits NF-κB activity	[18]
NEAT1	Cancer cell	NSCLC	Promotes cell proliferation	miR-377-3p/E2F3	[13]
	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	[14]
	$CD8^+$ T cell	Hepatocellular carcinoma	Inhibits $CD8^+$ T cell apoptosis and enhances cytolytic activity	miR-155	[15]
	Myeloid cell	Acute promyelocytic leukemia	Inhibits myeloid differentiation	/	[126]
	DC	Autoimmune disease	Induces immune tolerance in DC	miR-3076-3p/NLRP3	[127]

LUCAT1	Cancer cell	Colorectal cancer	Promotes cell proliferation and chemotherapy resistance	Interacts with PTBP1 to alter alternative splicing of DNA damage related genes	[128]
	Cancer cell	Breast cancer	Promotes breast cancer stemness	miR-5582-3p/TCF7L2	[129]
	Myeloid cell	/	Inhibits immune response	Interacts with STAT1 to inhibit ISGs	[130]
HOTAIR	Cancer cell	Laryngeal Carcinoma	Promotes cell proliferation and PD-L1 expression	miR-30a-5p/GRP78/PD-L1	[131]
	Cancer cell	Glioma	Upregulates PD-L1 and inhibits T cells activation	NF-κB pathway	[132]
	Macrophage	/	Promotes the NF-κB-mediated inflammatory pathway	Activates NF-κB and upregulates IL-6 and iNOS expression via facilitating the degradation of IκBα.	[133]
	Macrophage	/	Regulates glucose metabolism	NF-κB pathway	[134]
NRON	Cancer cell	Hepatocellular carcinoma	Suppresses cell growth and metastasis	Inhibits EMT	[135]
	T cell	/	Represses nuclear factor of activated T cells	/	[136]

stimulated by vascular epithelial growth factor (VEGF) secreted by M2 macrophages and induces VEGFR2 expression via a competing endogenous RNA (ceRNA) and deubiquitylation mechanism, thus promoting angiogenesis [9]. Subsequent research has shown that PCAT6 plays a bigger role in immune cells. That is, overexpression of PCAT6 contributes to the accumulation of reactive oxygen species via the miR-326 and RhoA-ROCK pathway and leads to mitochondrial and metabolic function disorders, thus promoting macrophage M2 polarization, which is critical for immune suppression [10] (**Figure 1**). The lncRNA small nucleolar RNA host gene 1 (SNHG1) also acts as an oncogene in cancer cells [11], while in

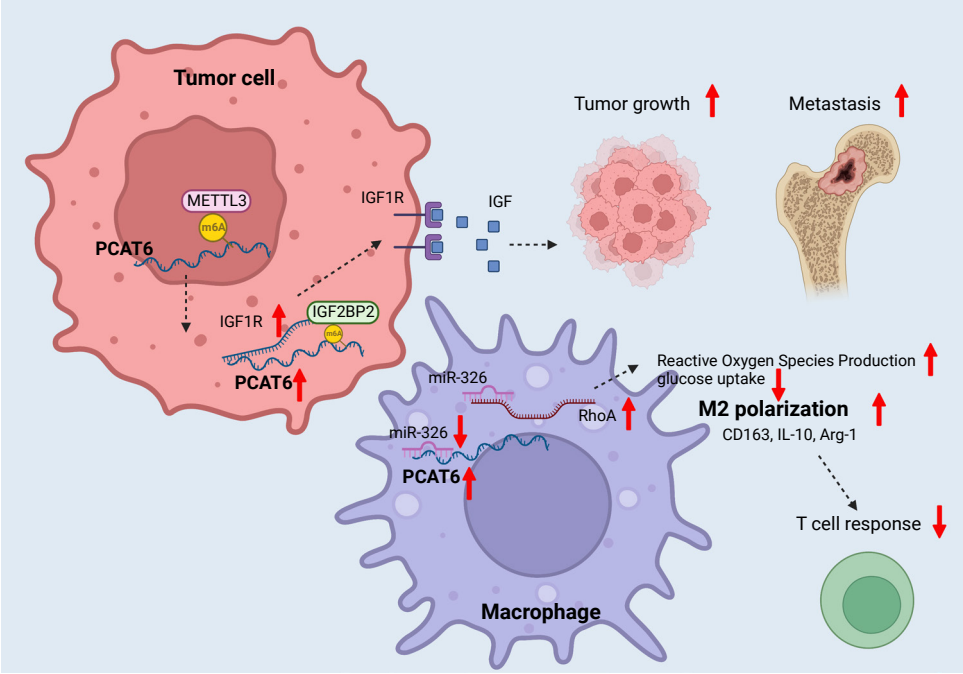

Figure 1. Functions and mechanisms of lncRNA PCAT6 in the TME.

Treg cells, SNHG1 promotes cell differentiation by sponging miR-448 and upregulating indoleamine 2,3-dioxygenase (IDO) [12]. Further, the lncRNA nuclear enriched abundant transcript 1 (NEAT1) accelerates tumor growth in NSCLC and prostate cancers [13,14], as well as acts as a tumor promotor by accelerating $CD8^+$ T-cell apoptosis and inhibiting cytolytic activity [15].

In some cases, lncRNAs play opposing roles as cancer-promoting and cancer-suppressing molecules in malignant and non-malignant cells, respectively. For example, in breast cancer, NF-κB-interacting lncRNA (NKILA), which is upregulated by NF-κB and forms a stable complex by interacting with NF-κB/IκB, plays anti-tumor roles by preventing hyperactivation of the NF-κB pathway in tumor cells. The degradation of NKILA by miR-103/107 targeting activates NF-κB signaling and increases invasiveness in breast cancer cell lines [16]. Similarly, it has been reported that TGF-β-induced NKILA suppresses EMT in breast cancer by negative regulation of the TGF-β-induced NF-κB pathway [17]. On the other hand, the lncRNA NKILA also participates in immune escape in the TME. NKILA expression is upregulated in cytotoxic T lymphocytes (CTLs) and Th1 cells, which suppresses NF-κB activity and sensitizes T cells [24]. These changes control immune escape by inducing apoptosis of T cells and inhibiting CTL infiltration in the cancer [18].

Collectively, the findings so far indicate that lncRNAs may play different roles in the TME depending on cell type and shed light on the multifaceted functions of lncRNAs and the complex regulation of lncRNAs. Thus, not only lncRNAs derived from malignant cells, but also those expressed in immune or stromal cells, could function as tumor suppressors or promotors, and mediate immune activities in the TME.

Tumor Cell-derived lncRNAs

For an anti-tumor immune response to be effective in eliminating cancer cells, a series of events must be initiated; these are collectively referred to as the cancer-immune cycle and include antigen release and presentation, immune cell priming and activation, T-cell trafficking and infiltration, and finally, recognition and killing of cancer cells [6]. lncRNAs expressed by tumor cells are involved in immune modulation mainly via regulation of antigen release and presentation, immune cell priming and activation, as well as reshaping the functions of immune cells.

Antigen release and presentation

Studies have shown that lncRNAs may accelerate tumor advancement by influencing the tumor antigens production and the MHC molecules expression. For example, ncRNA-RB1 serves as a tumor inhibitor in lung cancer by positively regulating the expression of calreticulin (CALR) [19], which is a calcium-binding chaperone in cancer cells that influences antigen presentation by facilitating the folding of MCH-I [20]. CALR is expressed on the cell surface and serves as a "kill me" signal that promotes phagocytosis of macrophages [21]. Knockdown of ncRNA-RB1 inhibits the expression of CALR and prevents the translocation of CALR to the cell surface, and this inhibits the cellular uptake of macrophages [19].

LncRNA inducing MHC-I and immunogenicity of tumor (LIMIT) is an immunogenic lncRNA found in humans and mice [22]. When induced by IFN-γ, LIMIT activates the guanylate-binding protein gene clusters, which release heat shock factor-1 (HSF1) from HSP90. This results in HSF1 activation and MHC-I transcription. Thus, LIMIT may be a potential epigenetic target for immunotherapy [22]. Overexpression of another lncRNA, LINC02195, induces the expression of MHC-I, thereby increasing the infiltration of T cells in head and neck cancer [23]. Further, another lncRNA, HOTAIR, can act as a ceRNA and induce HLA-G expression in gastric and cervical cancers, and HLA-G is known to be involved in tumor escape [24,25] (**Table 2**).

Priming and activation

Immune checkpoint molecules are crucial inhibitors in immune priming and activation. Research on how lncRNAs regulate this process mainly focuses on the modulation of programmed cell death 1 ligand 1 (PD-L1), the most widely used immune checkpoint inhibitor in the clinical setting [26]. In recent studies, lncRNAs were found to regulate the expression of PD-L1 by acting as ceRNAs that were capable of direct sponge adsorption of miRNAs in multiple cancers. In addition, the lncRNA UCA1 facilitates viability and metastatic potential of gastric carcinoma cells by targeting miRNAs, and may lead to immune evasion by upregulating PD-L1 expression [27]. In thyroid carcinoma, UCA1 induces PD-L1 expression and attenuates cytokine secretion in $CD8^+$ T cells, thereby inhibiting the cytotoxic effect of $CD8^+$ T cells and promoting cancer development [28]. Further, the lncRNA MALAT1 is a conserved lncRNA in mammals that can competitively bind with miRNAs to positively regulate the expression of PD-L1 in diffuse large B-cell lymphoma and NSCLC [29,30], facilitating apoptosis of $CD8^+$ T cells [29]. Moreover, SNHG14 was found to increase the level of zinc finger E-box binding homeobox 1, which in turn, upregulates SNHG14 and PD-L1. Thus, the high expression of PD-L1 is maintained by a positive feedback loop, which inhibits the CTLs activation and leads to immune escape [31]. In addition, the lncRNA LINC00473 has also been found to stimulate PD-L1 expression in pancreatic cancer [32]. These findings indicate that lncRNAs promote the immune escape of cancer cells.

Of note, another lncRNA, lncMX1-215, is known to suppress tumor growth by negative regulation of PD-L1. When induced by IFNα, lncMX1-215 can significantly inhibit proliferation and migration of head and neck cancer cells, as well as downregulate IFNα-induced expression of PD-L1 and galectin-9. With regard to the underlying mechanism, the direct interaction between lncMX1-215 and GCN5, an H3K27 acetylase, prevents H3K27

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	Downregulates 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]
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]

acetylation on PD-L1 and galectin-9 promoters, thereby negatively regulating PD-L1 and galectin-9 expression and relieving immunosuppression [33] (**Table 2**).

Regulation of immune cells

Studies have suggested that there is a correlation between lncRNA expression and immune infiltration. For example, the lncRNA BM466146 upregulates CXCL13, which shows a positive association with enhanced T-cell infiltration in breast cancer [34]. Further, overexpression of the lncRNA NNT-AS1 activates the TGF-β signaling pathway in hepatocellular carcinoma (HCC), and this is correlated with a decrease in $CD4^+$ lymphocyte infiltration [35]. Currently, there is ongoing research about how tumor cell-derived lncRNAs modulate immune cell function in the TME.

T cells: The lncRNA LINC00301, which is expressed at high levels in NSCLC, has been shown to facilitate TGF-β1 secretion to drive Treg cell infiltration and then decrease the $CD8^+$ T-cell population in the TME [36]. In cervical cancer, LINC00240 induces STAT3 expression via the ceRNA mechanism. One of the downstream targets of STAT3 is MHC class I-related chain (MIC)-A, which is critical for natural killer T (NKT) cell activation. Accordingly, the expression of MICA was inhibited by LINC00240, and this led to the suppression of NKT cell activity [37].

Macrophages: The recruitment of macrophages is affected by some lncRNAs, according to recent evidence.. In a pan-cancer RNA analysis, an lncRNA for calcium-dependent kinase activation (CamK-A) was identified as an oncogenic gene. CamK-A can trigger NF-κB activation by activating pregnancy up-regulated nonubiquitous CaM kinase (PNCK), which contributes to TME reshaping, including angiogenesis and macrophage recruitment [38]. A study on colitis-associated colorectal cancer has illustrated the crucial role of CXCR4 in exacerbating colitis-associated colorectal tumorigenesis and progression via the lncRNA XIST/miR-133a-3p/RhoA signaling pathway, which recruits MDSCs and macrophages [39]. In addition, a novel lncRNA associated with breast cancer brain metastasis, lnc-BM, was found to activate JAK2 kinase and

mediate the phosphorylation of STAT3, thus promoting the STAT3-dependent expression of ICAM1 and CCL2. ICAM1 increases vascular cooption, while CCL2 induces macrophage migration into the brain by passing through the blood-brain barrier [40]. The recruited macrophages secrete oncostatin M and interleukin (IL)-6, which in turn further trigger STAT3 phosphorylation. This finding reveals a positive feedback loop that boosts breast cancer metastasis triggered by lnc-BM [41]. The macrophage recruitment function of lncRNA-induced CCL2 has also been reported in bladder cancer. lncRNA lymph node metastasis-associated transcript 1 or LNMAT1 was found to activate CCL2 expression by recruiting hnRNPL to the CCL2 promoter. The macrophages recruited by CCL2 promote lymphatic metastasis via VEGF-C excretion [42].

In general, macrophages can be classified as classically (M1 phenotype) or alternatively activated (M2 phenotype) macrophages according to the activation stage and functional status [43]. M1 macrophages are involved in the type I T helper cell (TH1) response against pathogens and cancer through the secretion of pro-inflammatory cytokines, while M2 macrophages are involved in wound repair and can induce tumorigenesis and immunosuppression in tumors [43]. Various reports on cancer have demonstrated the vital roles of lncRNAs in macrophage polarization. One report found that cancer cells deliver the lncRNA RPPH1 via exosomes to macrophages and boost M2 polarization, which consist of a positive feedback that enhances the viability and invasion of colorectal cancer cells [44]. In NSCLC, transport of PCAT6 from tumor cells was found to promote polarization of macrophages towards the M2 subset. Further, M2 macrophages were found to promote EMT and metastasis via the PCAT6/miR-326/KLF1 axis [45]. In HCC, LINC00662 was found to promote M2 macrophage polarization in a paracrine manner [46], and knockdown of the lncRNA MALAT1 was found to suppress angiogenesis and promote M1 macrophage polarization [47]. Thus, MALAT1 may act as a tumor-promoting marker in HCC.

Neutrophils: Tumor-associated neutrophils (TANs) have emerged as a critical component of the TME that play a role in tumor-related inflammation and immunosuppression. In ovarian cancer, the lncRNA HOTTIP, via upregulation of the secretion of IL-6, promotes PD-L1 expression on neutrophils by STAT3 phosphorylation, which consequently causes inhibition of T-cell proliferation and cancer cell escape [48]. In gliomas, LINC01116 activates IL-1β expression, contributing to the accumulation of TANs in the TME. The infiltrated TANs produce various cytokines to stimulate proliferation of cancer cells. Hence, the elevated expression of LINC01116 in glioma tissues is indicative of poor prognosis in patients [49].

Fibroblasts: Fibroblasts are stromal cells that can be activated in cancer and are commonly known as cancer-associated fibroblasts (CAFs). CAFs can interact with cancer cells to promote tumor metastasis and progression. Studies on how lncRNAs regulate fibroblasts to facilitate tumor advancement have illustrated that tumor cell-derived lncRNAs mainly regulate fibroblasts via exosomes. In esophageal squamous cell carcinoma, the lncRNA POU3F3, which is carried by exosomes produced by cancer cells, reprograms fibroblasts into CAFs. The activated fibroblasts secrete inflammatory cytokines, among which IL-6 promotes the proliferation and cisplatin resistance of esophageal squamous cell carcinoma (ESCC) cells [50]. In melanomas, tumor-secreted exosomal lncRNA Gm26809 was found to transform NIH/3T3 fibroblasts into CAFs, as evidenced by the increase in the expression of α-smooth actin and fibroblast activation protein. Coculture of CAFs and melanoma cells revealed significantly enhanced proliferation and migration of melanoma cells [51].

Overall, the findings described in this section indicate that lncRNAs derived from tumor cells are involved in various stages of the cancer-immune cycle in several types of cancers, as well as the regulation of immune cells. Thus, the mechanisms underlying their effects on the cancer-immune cycle may be related to their effects on the expression of specific proteins by immune cells and the functions of these cells.

In addition to cancer cells, other immune cells and stromal cells may also have an influence on anti-tumor activities via their effects on events of the cancer-immune cycle. Therefore, the next two sections focus on lncRNAs associated with these cells.

Immune Cell-derived lncRNAs

Modulation of immune cell differentiation

Various studies have reported that lncRNAs serve as crucial modulators in lymphoid and myeloid differentiation and activation [52-55]. Further, bioinformatics mining analyses have indicated that T cell-derived lncRNAs could affect the differentiation and function of T cells [56-58]. Zhang and his colleagues determined that the lncRNA lnc-DC interacts with STAT3 in the cytoplasm and activates the STAT3 pathway, affecting the differentiation and maturation of DCs [59]. Further, research by Jonathan and his colleagues has revealed that the lncRNA Morrbid regulates the lifespan of myeloid cells by maintaining the pro-apoptotic gene Bcl2l11 [60]. Furthermore, long noncoding monocytic RNA (lnc-MC) was found to enhance the expression of activin A receptor type 1B, which promotes activation of the TGF-β signaling pathway, thus ultimately promoting the differentiation of monocytes and macrophages [61].

Researchers have characterized lncRNAs in immune cell differentiation and development, and recently, more studies have been exploring how these lncRNAs promote tumor progression or suppress tumor growth. In one such study, overexpression of lnc-epidermal growth factor receptor (EGFR) in Tregs was found to correlate positively with the expression of EGFR/Foxp3 in patients with HCC. lnc-EGFR

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	[70-72]
	LncRNA Pvt1	Inhibits MDSCs by upregulating HIF-1a	[74]
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]

targets EGFR and blocks its interaction and ubiquitination via c-CBL. Stabilization of EGFR enables activation of the AP-1/NF-AT1 pathway, which in turn enhances the expression of EGFR. Modulation of EGFR by lnc-EGFR results in Treg differentiation and CTL suppression, and this promotes tumor growth and immune escape [62]. It has been reported that another lncRNA, namely SNHG1, plays a vital role in modulating Treg differentiation. In breast cancer, blocking SNHG1 has been found to downregulate IDO expression and inhibit Treg differentiation, thereby suppressing tumor growth [12] (**Table 3**).

Antigen presentation

Dendritic cells are the prominent antigen-presenting cells in the TME. After phagocytosis of antigens, they mature under cytokine stimulation, express co-stimulatory molecules such as CD80/86/40, and present antigens to T cells to activate immune responses [63]. Silencing of lnc-DC has been found to suppress the expression of HLA-DR and impair the antigen uptake of DCs, thereby reducing the ability of DCs to boost T-cell proliferation. In other words, lnc-DC can enhance T-cell priming and inflammatory cytokine secretion [64].

DC trafficking is also required to initiate immune defense. Chemokine receptor type 7 (CCR7) ligands have been demonstrated to be important in the migration of DCs. CCR7 stimulation promotes lnc-Dpf3 expression by preventing its degradation, and CCR7 induces metabolic reprogramming toward glycolysis. This promotes DC migration by activating the HIF-1α pathway in DCs. However, lnc-Dpf3 can directly target HIF-1α and suppress Ldha, a glycolytic gene that is transcribed in an HIF-1α-dependent manner. This results in the constitution of a negative feedback loop that inhibits the glycolytic metabolism and migratory capacity of DCs, and causes termination of CCR7-mediated DC migration and helps to maintain immune homeostasis [65] (**Table 3**).

Modulation of the cytotoxic effect of $CD8^+$ T cells

Currently, lncRNAs are considered as important regulators of $CD8^+$ T cell function. For example, Ji and his colleagues discovered that lnc-Tim3 is a pivotal regulator of $CD8^+$ T cell exhaustion and survival. lnc-Tim3 is highly expressed by $CD8^+$ T cells in HCC, and its expression correlates negatively with IFN-γ and IL-2 production. These findings suggest that lnc-Tim3 promotes $CD8^+$ T cell exhaustion. An in-depth study into this effect revealed that lnc-Tim3 could inhibit the interaction between Tim-3 and Bat3 by specifically binding to Tim-3, thus resulting in the nuclear localization of Bat3. Furthermore, lnc-Tim3 was found to enhance the transcriptional activation of p53 and RelA and induce expression of the anti-apoptotic proteins p21, MDM2, and Bcl-2, thus leading to the survival of $Tim\text{-}3^+$ exhausted $CD8^+$ T cells [66]. In another study exploring the roles of $CD8^+$ T cell-derived lncRNAs during HCC development, the lncRNA NEAT1 was found to participate in immune surveillance escape of HCC through the miR-155/Tim-3 pathway in $CD8^+$ T cells, thus promoting $CD8^+$ T-cell apoptosis and suppressing cytolysis [15] (**Table 3**).

Modulation of other immune cells

Based on the accumulating evidence for the pivotal role of lncRNAs in modulating immune cell differentiation and function, Cao and his colleagues tried to identify the lncRNAs of macrophages that modulate macrophage polarization. Using lncRNA arrays, they determined that lncRNA-MM2P serves as a modulator of macrophage M2 polarization. That is, inhibition of lncRNA-MM2P was found to inhibit macrophage polarization to M2 and reduce angiogenesis of M2 by blocking STAT6 phosphorylation [67]. On the contrary, the lncRNAs NIFK-AS1 and Cox-2 were found to suppress M2 polarization of macrophages [68,69]. In addition, knockdown of lncRNAs, such as lincRNA-p21, lncRNA TUC339, and lncRNA ANCR, could promote macrophage polarization into pro-inflammatory M1 subsets [70-72] (**Table 3**).

MDSCs, which are pathologically activated immature cells, participate in tumor-elicited immunosuppression. These cells dramatically suppress the T cell-induced anticancer response, thereby contributing to the immune escape of malignant cells [73]. The lncRNA Pvt1 has been revealed as a suppressor in the functional regulation of MDSCs. Under hypoxic stress, Pvt1 is upregulated by HIF-1a in MDSCs, and this remarkably inhibits the function of MDSCs. Accordingly, Pvt1 knockdown was found to reduce the immunosuppressive ability of MDSCs, thereby accelerating tumor progression and inhibiting anti-tumor immune responses [74]. Other studies have demonstrated that some lncRNAs, for instance, Lnc-C/EBPβ and Lnc-chop, inhibit the immune suppressive function of MDSCs by regulating target transcripts, including arginase-1, nitric oxide synthase 2, NADPH oxidase 2, and cyclooxygenase-2, all of which are closely related to the immunosuppressive function of MDSCs in the TME [75,76].

Modulation of tumor cells via extracellular vesicles

LncRNAs have been found to be transported from immune cells to tumor cells through extracellular vesicles. For example, the lncRNA HIF-1α-stabilizing long non-coding RNA (HISLA), which is transmitted by extracellular vesicles from tumor associated macrophages (TAMs) to breast cancer cells, enhances the aerobic glycolysis of cancer cells by blocking the binding of PHD2 and HIF-1α and stabilizing HIF-1α. Correspondingly, glycolytic tumor cells deliver lactic acid to further facilitate HISLA expression in TAMs, connecting TAMs and tumor cells in a feed-forward loop [77]. Another example is that of the lncRNA AFAP1-AS1 from M2 macrophage-derived exosomes, which can inhibit the expression of miR-26a and upregulate ATF2, consequently promoting the migration, invasion, and lung metastasis of esophageal cancer cells [78] (**Table 3**).

Overall, the findings so far demonstrate that several lncRNAs derived from immune cells are closely involved in the modulation of tumor cells and various types of immune cells. LncRNAs expressed in the immune cells, such as $CD8^+$ T cells and MDSCs, participate in regulating their functions, such as differentiation, antigen presentation, and cytotoxic effects. Yet, more research is need to further illustrate how immune cell-derived lncRNAs affect another type of immune cell.

Stromal Cell-derived lncRNAs

Stromal CAFs are the most important stromal components in the TME [79]. Ding and his colleagues uncovered a so-far uncharacterized lncRNA, FLJ22447, which is remarkably upregulated during the transformation of normal fibroblasts to CAFs, and they named it lnc-CAF. With regard to its mechanism of action, lnc-CAF maintains the proliferative effect of IL-33 on tumor cells by directly upregulating IL-33 and preventing degradation of IL-33 by p62-dependent autophagy-lysosome. In turn, tumor cells further induce an increase in lnc-CAF levels in stromal fibroblasts via exosomal lnc-CAF [80] (**Table 4**).

Exosomes from CAFs, carrying lncRNAs, can participate in tumor pathogenesis and progression by modulating the behavior of tumor cells. In colorectal cancer, the lncRNA H19 and colorectal cancer-associated lncRNA (CCAL) are more abundant in the stroma than in the tumor nests. They are transported to cancer cells from CAF-secreted exosomes. Both lncRNA H19 and CCAL can promote aggressiveness and chemoresistance by activating the β-catenin pathway [81,82]. Similarly, lncRNA TIRY-overexpressing CAF-derived exosomes

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	[81,82]
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]

deliver miR-14 to oral squamous cell carcinoma (OSCC) cells, and this promotes cancer cell invasion and metastasis [83].

In addition to enhancing aggressiveness, lncRNAs from CAF-derived exosomes were also able to reprogram the metabolic pathways of cancer cells. For example, a CAF-specific lncRNA, LINC01614, was found to strengthen glutamine uptake in lung adenocarcinoma (LUAD) cells [84]. In addition, the lncRNA SNHG3 can inhibit mitochondrial oxidative phosphorylation and increase glycolysis and carboxylation after uptake of exosomes by tumor cells, and this leads to enhanced tumor cell proliferation [85] (**Table 4**). Thus, CAFs seem to be the prominent source of lncRNAs derived from the stroma that are associated with cancer proliferation and metastasis.

Other than fibroblasts, lncRNAs also have impact on the function of endothelial cells. Researchers have discovered lncRNA n342419, which they termed it MANTIS, serves as an endothelial angiogenic facilitator [86]. Moreover, lncRNA-MIAT can ameliorate diabetes mellitus-induced retinal microvascular dysfunction by forming a feedback loop with vascular endothelial growth factor and miR-150-5p [87]. However, more efforts to demonstrate how lncRNAs function in cancer associated endothelial cells are still in urgent need.

The Clinical Implication of Immune-related lncRNAs

Therapeutic potential of immune-related lncRNAs

From a clinical perspective, lncRNAs may serve as promising targets for tumor therapy since they extensively mediate tumor progression. Currently, there have been significant advances in technologies targeting lncRNAs [88], including techniques to modulate nuclear and cytoplasmic lncRNA expression: (1) Blocking lncRNA transcription through the integration of RNA destabilizing elements (RDE) into the genomic locus [89]. (2) Destabilizing lncRNA transcript by siRNA [3], antisense oligonucleotides (ASO) [90] and locked nucleic acid (LNA) GapmeRs [91]. (3) Inhibiting interactions of lncRNAs with others by small molecules and aptamer [92]. (4) Gene editing for lncRNAs using CRISPR [93].

These approaches have been validated in patient-derived tumor xenograft (PDX) models. Researchers have demonstrated that siRNA targeting lnc-BM can inhibit brain metastasis of breast cancer. Lnc-BM induces the expression of ICAM1 and CCL2, resulting in macrophage chemotaxis into the brain, and eventually assists brain metastasis. To explore a potential therapeutic strategy against the disease, researchers developed brain metastasis-bearing mice models and delivered nanoparticle-conjugated siRNAs for lnc-BM. *In vivo* experiments confirmed that depletion of lnc-BM by siRNAs effectively suppressed brain metastasis [41]. In addition, targeting lncRNA may also improve the effectiveness of immunotherapy. The increasing level of LIMIT by CRISPR activation can promote antigen presentation by boosting MHC-I expression, thereby exhibiting a synergistic anti-tumor effect with immune checkpoint blockade (ICB) [22]. In immunocompromised mice, NKILA silencing in T cells restrains them from immunological elimination, which enhances the efficacy of adoptive T cell therapy [18]. These findings suggest the therapeutic potential of lncRNAs in preclinical models.

LncRNA-related therapeutic strategies have several advantages. First, considering some dysregulated lncRNAs are cancer-specific, these lncRNAs are critical for the development of personalized therapy. Also, lncRNAs interact with other molecules on multiple regulatory sites, providing more opportunities for novel structure-based drug development [94].

Although targeting lncRNAs displays therapeutic potential, some issues in translating into the clinic including delivery, immunogenicity and specificity, are similar to all RNA-based treatments [95]. In terms of delivery and immunogenicity, one solution is to encapsulate lncRNAs or lncRNA-targeting molecules with extracellular vesicles [96], which are immune tolerant and tissue penetrating. An alternative is to use artificial carriers, for example, synthetic nanoparticles [41]. To improve the specificity, modification of the RNAs or nanoparticles may strengthen the on-target specificity. However, it remains uncertain whether any deviation from the target would pose a safety risk. To date, several mRNA-based therapeutics, either siRNAs or ASOs, have gained FDA approval, but no lncRNA-based ones have been applied in the clinic [95]. The research of lncRNAs on tumor therapy is mostly based on mice models, and there is still a long way to go before lncRNAs or lncRNA-targeted molecules can be used in tumor treatment.

The prognostic value of immune-related lncRNAs

LncRNAs regulate crucial mechanisms of cancer immunity, and this might imply that they have prognostic potential [5,36,41,48,50,80]. In addition to individual lncRNAs, a panel of lncRNAs can also be used for prognosis prediction in cancer patients. Inspired by studies on the metastasis-promoting roles of lncRNAs in nasopharyngeal carcinoma (NPC) patients [97-100], we conducted a retrospective multicohort study with the aim of developing an lncRNA signature for NPC metastasis prediction and exploring its potential function [101]. We employed a three-step strategy to develop a lncRNA signature to predict metastasis, including screening of lncRNAs by microarrays in matched samples in a discovery cohort, model training with a larger sample size in the training cohort, and validation in two independent cohorts. The nine-lncRNA signature (comprising lnc-TRAPPC6B-2, lnc-DRD5-10, NR2F2-AS1, lnc-CETP-1, lnc-CDK1-1, LINC02065, lnc-POTEH-7, lnc-STX6-2, and lnc-C11orf91-2) could be used to reliably classify NPC patients according to the risk of distant metastasis. Surprisingly, we discovered that the lncRNAs included in our signature were associated with immune features. In addition, digital pathology studies also confirmed the difference in the degree of immune infiltration between high-risk and low-risk groups, as the low-risk population was found to have a higher population of $CD8^+$ T cells and B cells in both tumor nests

and stroma. Overall, our results suggest that immune-related lncRNAs play an essential role in the metastasis of NPC [101].

Unlike our previous study, other studies start with the identification of immune-related lncRNAs, either by correlation analysis between lncRNAs and corresponding mRNAs [102-104] or by recognition of specific immune cell-derived lncRNAs [105,106], and then explore their potential prognostic value. Immune-related lncRNA signatures identified in such studies have been found to be robust for survival prediction in HCC, bladder cancer, and colorectal cancer [103,104,107]. In addition, a pan-cancer analysis has also characterized immune-related lncRNAs as oncogenic biomarkers [102].

The tumor-infiltrating immune-related lncRNA signature (TILSig) is a collection of seven lncRNAs that are specifically expressed in immune cell lines rather than NSCLC cell lines: HCG26, PSMB8-AS1, TNRC6C-AS1, CARD8-AS1, HCP5, LOC286437, and LINC02256. Expression of the seven lncRNAs individually is associated with the overall survival of NSCLC patients. Further, the combination of the seven lncRNAs weighted by their coefficients according to multivariate Cox analysis can be used to categorize NSCLC patients into high-risk and low-risk subsets with significantly different clinical outcomes. The low-risk patients have a higher degree of immune cell infiltration: that is, the tumors in these patients are characterized by a higher number of activated $CD8^+$ T cells and activated DCs. In contrast, the high-risk patients have a higher degree of infiltration of activated $CD4^+$ T cells. TILSig is also an independent prognostic factor for overall survival prediction and serves as an indicator of immunotherapy response [105]. Similarly, TILBlncSig is an eight-lncRNA panel (comprising TNRC6C-AS1, WASIR2, GUSBP11, OGFRP1, AC090515.2, PART1, MAFG-DT and LINC01184) that represents infiltration of B lymphocytes in bladder cancer; it is comprised of lncRNAs exclusively expressed in B cells and can be used to discriminate between patients with disparate clinical outcomes in multicohort studies [106].

Prospective

As research on lncRNAs has become more intensive, an increasing number of novel lncRNAs are being discovered. In the future, more investigations are required to determine the functions of these novel lncRNAs. To date, studies on lncRNAs have relied heavily on microarray detection or bulk RNA sequencing, which limits the exploration of cell-type specific lncRNA functions in the TME. Some investigators have conducted studies on specific isolated cell types or cell lines, with the aim of determining the role and prognostic value of lncRNAs in specific immune cells [64,66,105,106,108]. Although these studies have yielded some remarkable findings, the contributions of individual cell types to the expression of these lncRNAs still need to be investigated. Single-cell RNA sequencing (scRNA-seq) serves as a powerful solution to analyze the expression of lncRNAs in a single cell. It may contribute to the discovery of new cell subtypes defined by lncRNA.

Recently, single-cell analyses have allowed for further discovery of new lncRNA markers and their functions in embryo and stem cell development [109-111], as well as viral infectious diseases [112-115]. Furthermore, studies on lncRNAs at the single-cell level have been started in the field of cancer research. For example, data on scRNA-seq of clear cell renal cell carcinoma (ccRCC) have revealed 173 ccRCC metastasis-associated lncRNAs that contribute to cell adhesion, proliferation, and immune response [116]. In addition, an M2 macrophage polarization-associated lncRNA was screened out by scRNA-seq in HCC, and found to promote glucose metabolism and cell proliferation by acting as miRNA sponge [117]. However, the number of studies on lncRNAs using single-cell analyses are still limited, partly due to the lack of annotations for new lncRNAs and failure to detect low-abundance transcripts.

Sequencing technologies have led to an "omics" revolution, with large information datasets. However, how to interpret these data to further help us understand the role of immune-related lncRNAs remains a considerable challenge. Artificial intelligence (AI) can serve as an ideal tool by accurately interpreting omics data using machine learning and deep learning, as well as integrating data from medical and pathological images [118]. Liu and his colleagues develop a machine learning-based integrative procedure for constructing a consensus immune-related lncRNA signature (IRLS), which has robust predictive value for colorectal cancer [107]. In our previous study, a machine learning-based LASSO algorithm [119] was used to develop a lncRNA-based prognostic signature, and digital pathology consisting of region annotation [120], image segmentation [121-123] and positively-staining cell identification [124] was used to evaluate immune infiltration in the sub-groups divided according to the signature [101].

Conclusion

This review summarizes the roles of lncRNAs expressed by various cells that regulate cancer immunity in the TME. Immune-related RNAs are involved in immunoregulatory processes and can be expressed by immune cells, tumor cells, or stromal cells. lncRNAs of different origins can affect the behavior of other cell types through the paracrine system or extracellular vesicles, and this implies that regulation of the TME is not an isolated intracellular process, but rather, it involves subtle interactions among various cell types. Yet, how lncRNAs interact with other noncoding RNAs in regulating the TME is not discussed here in detail. Instead, we also discussed potential therapeutic strategies based on lncRNAs and their drawbacks. Although investigations into the expression and characterization of lncRNAs currently rely on bulk RNA

sequencing, we believe that rapid advances in single-cell methods and bioinformatics analytical tools will tremendously help to further illustrate the regulatory roles and clinical value of immune-related lncRNAs [125].

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; 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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