Long noncoding RNA: a dazzling dancer in tumor immune microenvironment

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Abstract

Long noncoding RNAs (lncRNAs) are a class of endogenous, non-protein coding RNAs that are highly linked to various cellular functions and pathological process. Emerging evidence indicates that lncRNAs participate in crosstalk between tumor and stroma, and reprogramming of tumor immune microenvironment (TIME). TIME possesses distinct populations of myeloid cells and lymphocytes to influence the immune escape of cancer, the response to immunotherapy, and the survival of patients. However, hitherto, a comprehensive review aiming at relationship between lncRNAs and TIME is missing. In this review, we focus on the functional roles and molecular mechanisms of lncRNAs within the TIME. Furthermore, we discussed the potential immunotherapeutic strategies based on lncRNAs and their limitations.

Keywords: LncRNA, Tumor immune microenvironment, Cancer immunotherapy

Background

Cancer is not a chaotic malignant cell mass, but a delicate “hostile” organ, where many other cells are recruited and domesticated to become “accomplices”, thereby protecting themselves from recognition and attack by the immune system [1]. In addition to tumor cells, there are also important stromal components in tumor niche. The stroma is composed of substantial cells, including epithelial, fat, fibroblasts, smooth muscle, vascular, and immune cells along with the extracellular matrix (ECM) and abundant signaling molecules (Fig. 1) [2]. Together, they form the microenvironment in which the tumor is located, namely tumor microenvironment (TME). Besides, TME exhibits aberrant physiological conditions, like hypoxia, acidic extracellular pH and elevated interstitial fluid pressure, due to the malformed tumor vessels. The TME is an intricate physical and biochemical system that plays a significant role in tumor initiation, growth, distant metastasis, and affect the outcome of treatments [1, 2]. Among the components of TME, distinct populations of innate and adaptive immune cells consist of tumor immune microenvironment (TIME). TIME primarily consists of myeloid cells, lymphocytes and some other innate immune cells. Myeloid cells comprise macrophages, neutrophils, myeloid derived suppressor cells (MDSCs); lymphocytes include B cells, CD4+ T helper (Th) cells, regulatory T cells (Tregs), CD8+ cytotoxic T lymphocytes (CTLs); and the innate immune cells contain natural killer (NK) cells and dendritic cells (DCs) (Fig. 1). TIME influences the immune escape of cancer, the response to immunotherapy, and the survival rate of patients.

In the human genome, about 93% of DNA can be transcribed into RNA, of which only 2% are protein-coding mRNAs, while the remaining 98% are called non-coding RNAs (ncRNAs) (Fig. 2) [3]. Among these ‘dark matters’, linear ncRNAs lack significant protein-coding potential and can be divided into two main categories according to whether the length exceeds 200 nucleotides (nt), namely short ncRNAs and long ncRNAs (lncRNAs) [4, 5]. The detailed classification is summarized in Fig. 2. Over the past two decades, a series of significant
Advances have been achieved in exploring the biogenesis, abundance, and function of lncRNAs across different species and cell types. Unlike miRNAs whose central function is to restrain mRNA translation by inducing degradation, lncRNAs can act as numerous roles to exert their functions by directly or indirectly interacting with DNA, RNA or protein, even can encode some short peptides (Fig. 3a-d) [6]. One of the most important mechanisms is to act as miRNA sponge and sequester miRNAs from target mRNAs, that is, to competitively bind miRNAs as competing endogenous RNA (ceRNA) of mRNAs, thereby regulating the levels of intracellular target mRNAs (Fig. 3e).

In particular, an increasing number of observations have proved that lncRNAs are involved in the regulation of substantial biological functions that determine cell fate and affect a series of physiological and pathological states [7], including cell apoptosis, differentiation,
pyroptosis, autophagy and embryonic development [8]. More importantly, recent studies have also reported lncRNAs participate in cancer onset and progression via reprogramming the TIME [7, 9]. Indeed, ectopic expression of certain lncRNAs are potently associated with infiltration of immune cells and predict the prognosis of cancer patient. For instance, lncRNA-LINC00665 affects the infiltration level of macrophages and DCs, as well as suppresses Tregs and prevent T-cell exhaustion by acting as ceRNA to target FTX [10]. LncRNA-TCL6 is positively related to tumor-infiltrating lymphocytes (TILs) infiltration and immune checkpoint molecules, like PD-1, PD-L1, and CTLA-4 [11]. Oncogenic lncRNA LINK-A attenuates antigen presentation of tumor cells, which weakens immunosurveillance and facilitates cancer cells escape from immune checkpoints and survival of malignant cells [12]. Herein, we provide a general overview on the relationship between lncRNAs and TIME, and discuss immunotherapeutic potential of lncRNAs in cancer treatment.

Tumor associated macrophages (TAMs)
Immune cells account for the remarkable percentage of the whole tumor tissue. Among them, macrophages, namely TAMs, stand for one of the most plentiful stromal compositions in the TIME [13]. It is generally recognized that TAMs derive from circulating bone marrow monocytes which infiltrate the primary and metastatic tumors due to being attracted by inflammatory cytokines. Afterwards, they differentiate into TAMs under the inductions of various signaling molecules in the TME [14]. However, recent evidence demonstrates that tissue resident macrophages derived from myeloid progenitors developed in fetal liver and yolk sac at the embryonic stage, where they are maintained via self-renewal [15–17]. TAMs are a major ingredient of the
inflammatory cells infiltrate in diffusely distinct amounts in solid tumors [18]. They contribute to cancer progression through facilitating proliferation, metastasis and angiogenesis [19, 20]. Actually, TAMs are vital drivers of tumor-promoting inflammation, which recognized as the holistic factor that damps the response to antitumor immunity and prompts cancer progression [18, 21]. Mechanistically, TAMs could remodel the structure of ECM, which facilitates the migration and invasion of the tumor cells by means of the TME and communicates with cancer cells or stromal cells through the secretion of cytokines, chemokines or growth factors [21].

Resting macrophages (M0) could be generally polarized into two major phenotypes according to specific microenvironment, classical pro-inflammatory activation (M1; IFN-γ/LPS-dependent) and alternative anti-inflammatory activation (M2; IL-4/IL-10/IL-13-dependent). Traditionally, macrophages have been deemed antitumorigenic when they release plentiful iNOS, TNF or MHC class II molecules and protumorigenic when they secrete abundant IL-10, Arg1, CD163 or CD206 [22, 23]. However, accumulating evidence reveals that this kind of classification is oversimplified because the polarized macrophages can be further reprogrammed via reversing previous phenotype in respond to the alternative milieu [24]. Therefore, M1- and M2-polarized TAMs are only extremes of a continuum in a range of functional roles and the majority of the TAMs are variable stases in the continuum between M1 and M2 [25].

Increasing data suggested that lncRNAs are crucial coordinators of changes in gene expression during macrophage polarization, although studies on lncRNAs in TAMs have just started [26]. LncRNAs are potent associated with macrophage recruitment, differentiation and activation [27]. In order to acquire differentially expressed lncRNAs profiles existing in different macrophage phenotypes, Huang et al. utilized microarray and bioinformatics methods and eventually identified 9343 and 4592 lncRNAs were deregulated in M (LPS + IFN-γ) group and M (IL-4) group, respectively, in comparison to primary monocyte-derived macrophages [28]. Unsurprisingly, a recent study found that transcriptional factor STAT3 could facilitate the transcription of lncRNA RP11–389C8.2 (being named Inc-M2) and induce M2 macrophage polarization through the PKA/CREB pathway [29].

M2 polarization of macrophages is requisite for their function in immunologic tolerance, which might facilitate tumor progression. Plenty of pro-/anti-tumoral lncRNAs can help the realization of the process, that is, regulation of M1/M2 macrophage polarization via regulating the expression of downstream target proteins. LncRNA GNAS-AS1 promotes the growth and metastasis of estrogen receptor positive breast cancer through motivating M2 macrophage polarization via directly sponging miR-433-3p to target GATA3 [30]. Also, GNAS-AS1 can redirect polarization of macrophage in TME by miR-4319-mediated inhibition of NECAB3 [31]. Protein kinase C zeta (PKCζ) belongs to the PKC family and a key tumor suppressor gene. LncRNA-CCAT1 regulates macrophage polarization to prevent cell migration of prostate cancer by miR-148a/PKCζ axis [32]. Notch signaling is an important regulator in macrophage polarization [33–35]. LncRNA NIFK-AS1 could competitively bind to miR-146a to promote the expression of target gene Notch1, causing the inhibition of macrophage differentiation to M2 type in endometrial cancer [36]. LncRNA-XIST, subjected to the modulation of TCF-4, boosts M2 polarization of macrophages and is closely linked to tumor progression of lung cancer [37]. LncRNA-MM2P as a specific regulator of M2 polarization that acts by regulating phosphorylation of STAT6. Silence of LncRNA-MM2P alleviates macrophage-promoted angiogenesis and retards tumorigenesis [38]. Accumulation of LncRNA-ANCR in macrophages could fuel cancer metastasis through hindering M1 type differentiation via propelling FoxO1 ubiquitination degradation [39]. Downregulated lncRNA-p21 promotes proinflammatory M1 polarization of macrophages in the TME, driven by MDM2 causing degradation of p53 and activation of the NF-κB/STAT3 pathway. In vivo, lncRNA-p21 knockdown macrophage adoptive transfer can hinder breast cancer progression [40]. Compared with M1 macrophages, the level of LncRNA cox-2 is lower in M2 macrophages. LncRNA cox-2 suppresses the tumor growth and immune evasion of hepatocellular carcinoma (HCC) via facilitating M1 polarization and curbing M2 polarization [41].

LncRNAs have the capability of regulating the protein secretion of TAMs to influence the survival and metastasis of tumor cells. In thyroid cancer, LncRNA MALA T1-mediated fibroblast growth factor-2 (FGF2) secretion from TAMs depresses release of inflammatory cytokines, induces vasculature formation and accelerates proliferation, invasion and migration of tumor cells [42]. Besides, TAMs can also influence the malignant behaviors of tumor cells by biological vectors rich in specific lncRNA. In pancreatic cancer, LncRNA SBF2-AS1 abundant in M2 macrophage-derived exosomes. Constrained SBF2-AS1 in these exosomes is beneficial to limit the tumorigenic capacity of neoplastic cells by elevating miR-122-5p expression and inhibiting expression of XIAP [43], a cytosolic suppressor of apoptosis-related protein [44].

More importantly, the polarization direction of TAMs is affected by tumor-secreted proteins, and this process is perhaps regulated by lncRNAs. A recent study indicated that upregulated LINC00662 contributed to secretion of WNT3A from cancer cells and activation of
suppressive shield and prevent the cancer from the patient’s immune system and immunotherapy. They are even vividly called the “queen bee” in the TIME [110]. As early as the late 1990s, it was found that a class of immune suppressive myeloid cells (CD11b+Gr-1+) in spleens of mice, and the phenotypically similar but functionally different from neutrophils and monocytes [111, 112]. Diverse phenotypic criteria were used to define this kind of cells in subsequent studies. Until 2007, the name MDSC, according to the origin and the functional feature, was proposed to unify various descriptions of these cells [113].

MDSCs comprise two main types of cells termed monocytic (M-MDSCs) and polymorphonuclear (PMN-MDSCs). M-MDSCs are morphologically and phenotypically like monocytes, and PMN-MDSCs are morphologically and phenotypically similar to neutrophils. Apart from above-mentioned two major cell communities, MDSCs contain a small fraction of cells with activity of myeloid colony formation such as myeloid progenitors and precursors [114]. In mice, M-MDSCs can be defined as CD11b+Ly6G−Ly6Ch+ and PMN-MDSCs are described as CD11b+Ly6G+Ly6Clo. In humans, M-MDSCs are defined as CD11b+CD14+HLA-DR−/loCD150 and PMN-MDSCs as CD11b+CD14+CD15− or CD11b+CD14+CD66b+ among peripheral blood mononuclear cells (PBMC) [115].

In the cancer setting, M-MDSCs are more dominant than PMN-MDSCs in terms of suppressive activity due to M-MDSCs could promptly mature into TAMs, despite PMN-MDSCs make up more than 80% of all MDSCs [116, 117]. More importantly, MDSCs refrain the immune response of T cells and mediate immunosuppression in tumor milieu via the expression of NOX2, NOS2 Arg-1, COX2, as well as production of NO and ROS [114]. Besides, MDSCs are able to facilitate the formation of Tregs and motivate fibroblasts differentiate into cancer-associated fibroblasts (CAFs) [118–120]. In addition to immune suppression, MDSCs also can secrete a series of cytokines, VEGF, MMP9, bFGF, etc., to influence angiogenesis and remodel the TIME [121, 122]. These result in the risk of dying from tumor is almost doubled in patients with MDSCs [123].

A number of studies have shown that IncRNAs are implicated in MDSCs differentiation and immunosuppressive function, and act as the crucial regulators. To date, the most of the experiments on MDSCs are performed on mice using murine cancer cells. In mice, transcription factors CCAAT/enhancer-binding protein (C/EBPβ) and C/EBP homologous protein (CHOP) pivotally regulate the expansion and function of MDSCs [124]. C/EBPβ has three isoforms and liver-enriched inhibitory protein (LIP) is one of the isoforms, which relies on forming heterodimers with other family members to manage gene expression due to lack of DNA activation domains [125]. There are three kinds of IncRNAs are identified in MDSCs; that is, Inc-C/EBPβ, IncRNA-RNCR3 and Inc-

**MDSCs**

The MDSCs are one of the cornerstones of the immunosuppressive shield and prevent the cancer from the patient’s immune system and immunotherapy. They are
| LncRNA | Related immune cell | Cancer type | Expression | Mediator miRNA | Target gene/pathway | Immunity-Related Mechanisms | Clinical significance | References |
|--------|---------------------|-------------|------------|----------------|---------------------|-----------------------------|-----------------------|------------|
| LINK-A | —                   | TNBC        | Upregulated in tumor cells | —              | PtdIns(3,4,5)P3, GPCR, PKA, TRIM7 | LINK-A-dependent downregulation of antigenicity and intrinsic tumor suppression by mediating the crosstalk between PtdIns(3,4,5)P3 and GPCR | Overall survival | [12]       |
| LINC00665 | —               | HGSOC       | Upregulated in tumor cells | —              | FTX                | Influencing the infiltration level of macrophages and DCs, and inhibiting Tregs and prevent T-cell exhaustion by FTX | Overall survival | [10]       |
| GNAS-AS1 | Macrophages        | ER+ Breast cancer | Upregulated in tumor cells and M2 macrophages | miR-433-3p | GATA3              | Accelerating M2 macrophage polarization | — | [30]       |
| GNAS-AS1 | Macrophages        | Non-small cell lung cancer | Upregulated in tumor cells and M2 macrophages | miR-4319 | NECA83              | Regulating macrophage polarization | Overall survival, metastasis-free survival | [31]       |
| CCAT1 | Macrophages        | Prostate cancer | Downregulated in M2 macrophages | miR-148a | PKCε             | Regulating macrophage polarization | — | [32]       |
| NIFK-AS1 | Macrophages        | Endometrial Cancer | Downregulated in M2 macrophages | miR-146a | Notch1             | Inhibiting M2 macrophage polarization | — | [36]       |
| XIST | Macrophages        | Lung cancer | Upregulated in M2 macrophages | —              | —                  | Regulating macrophage polarization | — | [37]       |
| MM2P | Macrophages        | —           | Upregulated in M2 macrophages | —              | STAT6              | Accelerating M2 macrophage polarization | — | [38]       |
| ANCR | Macrophages        | Gastric cancer | Upregulated in tumor cells | —              | FoxO1              | Promoting tumor metastasis through hindering M1 type differentiation of macrophages by facilitating FoxO1 ubiquitination degradation | — | [39]       |
| LinRNA-p21 | Macrophages      | Breast cancer | Upregulated in M2 macrophages | —              | MDM2, P53, NF-kB, STAT3 | Inhibiting macrophage polarization into pro-inflammatory M1 by promoting its interaction with p33 | — | [40]       |
| LncRNA-cox-2 | Macrophages | HCC          | Downregulated in M2 macrophages | —              | —                  | Preventing immune evasion and metastasis of cancer by altering M1/M2 macrophage polarization | — | [41]       |
| MALAT1 | Macrophages        | Thyroid cancer | Upregulated in tumor cells and M2 macrophages | —              | FGF2               | MALAT1-mediated FGF2 protein secretion from TAMs inhibits inflammatory cytokines release, promotes proliferation, migration, and invasion of tumor cells and induces vasculature formation | — | [42]       |
| SBF2-AS1 | Macrophages       | Pancreatic cancer | Upregulated in M2 macrophages | miR-122-5p | XIAP              | M2 macrophages secrete SBF2-AS1-rich exosomes to promote tumor progression. | — | [43]       |
| LINC00662 | Macrophages      | HCC          | Upregulated in tumor cells | miR-15a, miR-16, miR-107 | WNT3A, Wnt/β-catenin signaling | Increasing tumor-derived WNT3A and activating Wnt/β-catenin signaling in macrophages via paracrine manner, and promoting M2 macrophages polarization | Overall survival, differentiation, tumor size, microvascular invasion | [45]       |
| MALAT1 | Macrophages        | HCC          | Upregulated in tumor cells | miR-140 | VEGF-A              | Regulating macrophage polarization | — | [46]       |
| RPPH1 | Macrophages        | Colorectal cancer | Upregulated in tumor cells | —              | TUBB3              | Inhibiting TUBB3 ubiquitination and | Overall survival, TNM stages | [47]       |
| LncRNA      | Related immune cell | Cancer type       | Expression         | Mediator miRNA | Target gene/pathway | Immunity-Related Mechanisms                                                                 | Clinical significance | References |
|------------|---------------------|-------------------|--------------------|----------------|---------------------|--------------------------------------------------------------------------------------------|----------------------|------------|
| BCRT1      | Macrophages         | Breast cancer     | Upregulated in tumor cells and M2 macrophages | miR-1303       | PTBP3               | Enhancing exosomes-mediated macrophages M2 polarization and influences the tumor microenvironment | Overall survival     | [48]       |
| TUC339     | Macrophages         | HCC               | Upregulated in HCC-derived exosomes | —              | —                   | Regulating macrophage activation and polarization                                           | —                    | [49]       |
| CASC2c     | Macrophages         | Glioblastoma      | Downregulated in tumor cells | miR-338-3p     | FX                  | Inhibiting macrophage migration and polarization to the M2 subtype by FX                   | —                    | [50]       |
| CamK-A     | Macrophages         | Breast cancer     | Upregulated in tumor cells | —              | —                   | Promoting infiltrated macrophage recruiting, angiogenesis, tumor microenvironment remodeling, and cancer development | Overall survival, recurrence-free survival | [51]       |
| Lnc-C/EBPβ | MDSCs               | —                 | Upregulated in MDSCs                  | —              | C/EBPβ isoform LIP  | Controlling immunosuppressive function and differentiation of MDSCs by a set of target transcripts | —                    | [52]       |
| Lnc-C/EBPβ | MDSCs               | —                 | Upregulated in MDSCs                  | —              | IL4iL, C/EBPβ isoform LIP, WDR5 | Promoting PMN-MDSCs but impede differentiation of M-MDSCs | —                    | [53]       |
| RNCR3      | MDSCs               | —                 | Upregulated in MDSCs                  | miR-185-5p     | Chop                | Regulating MDSC differentiation and suppressive function to influence tumor growth by RNCR3/miR-185-5p/Chop axis | —                    | [54]       |
| Lnc-chop   | MDSCs               | —                 | Upregulated in MDSCs                  | —              | CHOP, C/EBPβ isoform LIP | Interacting with CHOP and the C/EBPβ isoform LIP to regulate immunosuppressive function of MDSCs | —                    | [55]       |
| Olfr29-ps1 | MDSCs               | —                 | Upregulated in MDSCs                  | miR-214-3p     | MyD88               | Regulating the differentiation and function of M-MDSCs by a m6A-modified Olfr29-ps1/miR-214-3p/MyD88 regulatory network | —                    | [56]       |
| Pvt1       | MDSCs               | —                 | Upregulated                        | —              | C-myc               | Regulating the immunosuppression activity of PMN-MDSCs by C-myc                             | —                    | [57]       |
| AK036396   | MDSCs               | —                 | Upregulated                        | —              | Ficolin B           | Inhibiting maturation and accelerating immunosuppression of PMN-MDSCs by Enhancing the Stability of Ficolin B | —                    | [58]       |
| MALAT1     | MDSCs               | Lung Cancer       | Downregulated                     | —              | —                   | Negatively regulating the generation of MDSCs                                            | —                    | [59]       |
| RUNXOR     | MDSCs               | Lung cancer       | Upregulated                        | —              | RUNX1               | Mediating MDSCs associated immunosuppression by targeting RUNX1                           | Smoking history, TNM stage, histological tumor type and lymph | [60]       |
| LncRNA   | Related immune cell | Cancer type      | Expression       | Mediator miRNA | Target gene/pathway | Immunity-Related Mechanisms                                                                 | Clinical significance                                      | References |
|----------|---------------------|------------------|------------------|----------------|---------------------|--------------------------------------------------------------------------------------------|------------------------------------------------------------|-------------|
| HOTAIRM1 | MDSCs               | Lung Cancer      | Downregulated    | —              | HOXA1               | Regulating MDSCs associated immunosuppression by targeting HOXA1                           | Smoking history, TNM stage, histological tumor type and lymph node metastasis | [61]        |
| HOTAIR   | MDSCs               | HCC              | Upregulated      | —              | CCL2               | Promoting proliferation of macrophages and MDSCs                                           | —                                                          | [62]        |
| Gm43181  | Neutrophils         | —                | Upregulated in neutrophils | —              | CXCR2               | Provoking inflammation by regulating the recruitment and activation of neutrophils into the specific tissues | —                                                          | [63]        |
| MALAT1   | Neutrophils         | —                | Upregulated      | p300, IL-8     |                     | Ameliorating the inflammatory injury by inhibiting chemotaxis of neutrophils through p300-mediated downregulation of IL-8 | Overall survival                                            | [64]        |
| XIST     | Neutrophils         | —                | Upregulated      | miR-21         | IL-12A              | Increasing IL-12A by binding to miR-21, thereby inducing neutrophil extracellular trap formation | —                                                          | [65]        |
| TCL6     | Neutrophils         | Breast cancer    | Downregulated in tumor cells | —              |                     | Enhancing IL-6 expression to potentiate immune escape of tumor cells by up-regulating the expression of PD-L1 in neutrophils | Overall survival                                            | [11]        |
| HOTTIP   | Neutrophils         | Ovarian cancer   | Upregulated in tumor cells | c-jun, IL-6, PD-L1 |                     | —                                                                                         | —                                                          | [66]        |
| Lnc-DC   | DCs                 | —                | Upregulated in DCs | —              | STAT3, TLR9, TIMP, MMP | Regulating the differentiation and capacity of DCs by activating the transcription factor STAT3 | —                                                          | [67–70]     |
| NEAT1    | DCs                 | —                | Upregulated in DCs | miR-3076-3p    | NLRP3               | Inducing tolerogenic phenotype in DCs by inhibiting activation of NLRP3 inflammasome        | —                                                          | [71]        |
| HOTAIRM1 | DCs                 | —                | Downregulated in DCs | miR-3960       | HOXA1               | Regulating DC differentiation by competitively binding to endogenous miR-3960              | —                                                          | [72]        |
| Lnc-Dpf3 | DCs                 | —                | Upregulated in DCs | —              | HIF-1α              | CCR7-inducible Lnc-Dpf3 restrains DC migration by inhibiting HIF-1α-mediated glycolysis     | —                                                          | [73]        |
| MALAT-1  | DCs                 | Colon cancer     | Upregulated in DCs | —              | Snail               | Blocking MALAT-1 significantly decreases the TADC-conditioned medium and CCL5-mediated migration and invasion by decreasing the Snail | —                                                          | [74]        |
| SNHG16   | B cells             | DLBCL            | Upregulated in tumor cells | miR-497-5p    | PIM1                | Promoting proliferation and inhibits apoptosis of lymphoma cells by targeting miR-497-5p/PIM1 axis | —                                                          | [75]        |
| TUG1     | B cells             | DLBCL            | Upregulated in tumor cells | —              | MET                 | Regulating tumor growth by ubiquitination of MET                                           | —                                                          | [76]        |
| SNHG14   | B cells             | DLBCL            | Upregulated in tumor cells | miR-5590-3p   | ZEB1                | SNHG14/miR-5590-3p/ZEB1 positive feedback loop promotes lymphoma                           | —                                                          | [77]        |
| LncRNA | Related immune cell | Cancer type | Expression | Mediator miRNA | Target gene/pathway | Immunity-Related Mechanisms | Clinical significance | References |
|--------|---------------------|-------------|------------|----------------|---------------------|-----------------------------|----------------------|------------|
| MALAT1 | B cells             | DLBCL       | Upregulated in tumor cells | miR-195 PD-L1 | PD-L1 | Promoting tumorigenesis and immune escape of lymphoma by sponging miR-195 | — | [78] |
| MINCR  | B cells             | BL          | Upregulated in tumor cells | —             | AURKA, AURKB, and CDT1 | Controlling cell cycle by participating in MYC transcriptional network | — | [79] |
| NEAT1  | B cells             | DLBCL       | Upregulated in tumor cells | miR-34b-5p GLI1 | GLI1 | Promoting B cell proliferation and lymphomagenesis by the miR-34b-5p-GLI1 pathway. | — | [80] |
| FIRRE  | B cells             | DLBCL       | Upregulated in tumor cells | —             | Wnt/β-catenin pathway | Promoting the development of lymphoma by Wnt/β-catenin signaling pathway | Overall survival | [81] |
| PANDA  | B cells             | DLBCL       | Downregulated in tumor cells | —             | MAPK/ERK pathway | Inhibiting the growth of lymphoma by inactivation of MAPK/ERK signaling pathway | Overall survival, recurrence-free survival, B symptoms, Ann Arbor stages, CHOP-like treatment, Rituximab and IPI | [82] |
| OR3A4  | B cells             | DLBCL       | Upregulated in tumor cells | —             | Wnt/β-catenin signaling | Promoting cell proliferation through activating Wnt/β-catenin signaling pathway | Overall survival | [83] |
| SMAD5-AS1 | B cells          | DLBCL       | Downregulated in tumor cells | miR-135b-5p APC, Wnt/β-catenin pathway | APC, Wnt/β-catenin pathway | Inhibiting proliferation of lymphoma through Wnt/β-catenin pathway via targeting miR-135b-5p to elevate expression of APC | — | [84] |
| HULC   | B cells             | DLBCL       | Upregulated in tumor cells | —             | Bcl-2, cyclin D1 | Regulating cell proliferation and inducing apoptosis by Bcl-2 and cyclin D1 | Overall survival, progression-free survival, Ann Arbor stages, B symptoms, CHOP-like treatment, Rituximab and IPI | [85] |
| HOTAIR | B cells             | DLBCL       | Upregulated in tumor cells | —             | PI3K/AKT/NF-κB pathway | Promoting cell proliferation by PI3K/AKT/NF-κB pathway | Overall survival, tumor size, clinical stage, B symptoms and IPI | [86] |
| LUNAR1 | B cells             | DLBCL       | Upregulated in tumor cells | —             | E2F1, cyclin D1 and p21 | Regulating cell proliferation by E2F1, cyclin D1 and p21 | Overall survival, progression-free survival, stage, rituximab and IPI | [87] |
| PEG10  | B cells             | DLBCL       | Upregulated in tumor cells | —             | — | — | Overall survival, B symptoms, CHOP-like treatment, Rituximab and IPI | [88] |
| MALAT-1 | B cells            | DLBCL       | Upregulated in tumor cells | —             | LC3-II/LC3-I, p62, ATG5 | Regulating autophagy-related signaling pathway on chemotherapy resistance | — | [89] |
| FAS-AS1 | B cells            | Non-Hodgkin’s lymphomas | Upregulated in tumor cells | —             | RBM5 | Regulating of the sFas expression by interacting with RBM5 to influence cell apoptosis | — | [90] |
| FENDRR | Tregs               | HCC         | Downregulated in Tregs | miR-423-5p GADD45B | GADD45B | Inhibiting the Treg-mediated immune escape of tumor cells through | — | [91] |
| LncRNA     | Related immune cell | Cancer type         | Expression          | Mediator miRNA | Target gene/pathway | Immunity-Related Mechanisms                                                                 | Clinical significance                                                                 | References |
|------------|---------------------|---------------------|---------------------|----------------|---------------------|---------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|------------|
| SNHG1      | Tregs               | Breast cancer       | Upregulated in Tregs | miR-448        | IDO                 | upregulating GADD45B by sponging miR-423-5p Accelerating the differentiation of Treg cells and promoting the immune escape of cancer by regulating miR-448/IDO axis | —                                                      | [92]       |
| POU3F3     | Tregs               | Gastric cancer      | Upregulated in Tregs | —              | TGF-β/SMAD2/3 pathway | Promote the distribution of Tregs in peripheral blood T cell, increasing cell proliferation by recruiting TGF-β as well as activating TGF-β signal pathway | Tumor size                                                                                   | [93]       |
| Lnc-EGFR   | Tregs               | HCC                 | Upregulated in Tregs | —              | EGFR, AP-I/NF-AT1 axis | Stimulating Treg differentiation, suppresses CTL activity and promoting HCC growth in an EGFR-dependent manner. | Tumor size                                                                                   | [94]       |
| RP11-323N12.5 | Tregs          | Gastric cancer      | Upregulated in tumor cells | —              | YAP1, TAZ, TEAD, Hippo signaling | Promoting Treg cell differentiation by enhancing YAP1 transcription in T cells | Disease-free survival, stage                                                                 | [95]       |
| SNHG16     | Tregs               | Breast cancer       | Upregulated in tumor cells | miR-16-5p | SMAD5 | Breast cancer-derived exosomes transmit SNHG16 to induce CD73+/y61 Treg cells by activation of the TGF-β1/SMAD5 pathway | —                                                      | [96]       |
| Lnc-sox5   | CTLs                | Colorectal cancer   | Upregulated in tumor cells | —              | IDO1 | Regulating the infiltration and cytotoxicity of CD3+/CD8+/T cells by IDO1, and unbalancing the TME | Metastasis                                                                                   | [97]       |
| NEAT1      | CTLs                | Lung cancer         | Upregulated in tumor cells | —              | DNMT1, P53, cGAS/STING | Interacting with DNMT1 to regulate malignant phenotype of cancer cell and cytotoxic T cell infiltration by epigenetic inhibition of p53, cGAS, and STING | Tumor stage, lymph node metastasis.                                                                 | [98]       |
| NEAT1      | CTLs                | HCC                 | Upregulated in CTLs   | miR-155        | Tim-3 | Regulating the antitumor activity of CD8+ T cells against HCC by miR-155/Tim-3 axis | —                                                      | [99]       |
| Lnc-Tim3   | CTLs                | HCC                 | Upregulated in CTLs   | —              | Tim-3, Bat3, Lck/NFAT1/AP-1 pathway | Exacerbating CD8+ T cell exhaustion by binding to Tim-3 and inducing nuclear translocation of Bat3 | —                                                      | [100]      |
| LINC00473  | CTLs                | Pancreatic cancer   | Upregulated in tumor cells | miR-195-5p | PD-L1 | Inhibiting activation of CD8+ T cells by sponging miR-195-5p to elevate the expression of PD-L1 | —                                                      | [101]      |
| SNHG14     | CTLs                | DLBCL               | Upregulated in tumor cells | miR-5590-3p | ZEB1, PD-1 | Promoting apoptosis of CD8+ T cells by PD-1/PD-L1 immune checkpoint, and eventually leading to the immune evasion | —                                                      | [77]       |
| MALAT1     | CTLs                | DLBCL               | Upregulated in tumor cells | miR-195      | PD-L1 | Promoting apoptosis of CD8+ T cells and immune escape of lymphoma | —                                                      | [78]       |
| GM16343    | CTLs                | —                   | Upregulated in CTLs   | —              | IFN-γ | Promoting IL-36β to regulate the TME by CD8+ T cells | Overall survival                                                                 | [102]      |
chop, which are significantly elevated in response to tumor-associated and extracellular inflammatory factors such as IL6. They are able to control function and differentiation of MDSCs in the TIME by regulating the downstream genes, C/EBPβ isoform LIP or/and CHOP (Fig. 5) [52, 54, 55]. Lnc-C/EBPβ binds the C/EBPβ isoform LIP to inhibit activation of C/EBPβ, affecting expansion of a suite of target transcripts including Arg-1, COX2, NOS2, NOX2 [52, 126]. Furthermore, lnc-C/EBPβ can facilitate differentiation of PMN-MDSCs but hinder differentiation of M-MDSCs via downregulating IL-4 induced gene 1 (IL4i1), an important gene mediating monocyte/macrophage differentiation [53, 127, 128]. Lnc-C/EBPβ also interacts with WDR5 to block the enrichment of H3K4me3 mark on the IL4i1 promoter region [53]. The conserved homo lnc-C/EBPβ has an analogous role with murine lnc-C/EBPβ. Human lnc-C/EBPβ may also exert a significant function in the differentiation and function of MDSCs in colorectal cancer patients [52, 53]. LncRNA-RNCR3 knockdown can stimulate Chop release and interrupt MDSC differentiation by binding to miR-185-5p, leading to reduction of the immunosuppressive activity of MDSCs and inhibition of tumor growth [54]. Lnc-chop directly interacts with both CHOP and the C/EBPβ isoform LIP to propel the activation of C/EBPβ and enrichment of H3K4me3, leading to expansion of a series of immunosuppression-related transcripts to govern differentiation and suppressive function of MDSCs [55].

The roles of Olfr29-ps1 depends on IL6-mediated N6-methyladenosine (m6A) modification, which not only increases Olfr29-ps1 expression, but also provokes the interaction between Olfr29-ps1 and miR-214-3p. miR-214-3p targets MyD88, which is crucial for the direct suppressive function of M-MDSCs [129, 130], to regulate the differentiation and development of M-MDSCs [56]. Apart from being related to M-MDSCs, lncRNAs are also involved in regulating the immunosuppressive activity of PMN-MDSCs. Under hypoxia environment, lncRNA plasmacytoma variant translocation 1 (Pvt1) could be enhanced by

Table 1 LncRNAs involved in TIME (Continued)

| LncRNA          | Related immune cell | Cancer type   | Expression   | Mediator miRNA | Target gene/pathway | Immunity-Related Mechanisms                                                                 | Clinical significance                  | References |
|-----------------|---------------------|---------------|--------------|----------------|---------------------|---------------------------------------------------------------------------------------------|----------------------------------------|------------|
| NKILA           | CTLs                | breast and lung cancer | Upregulated in CTLs | —              | NF-xB               | Regulating T cell sensitivity to AICD by inhibiting NF-xB activity                           | Overall survival                        | [103]      |
| INCR1           | CTLs                | —             | Upregulated in CTLs | —              | PD-L1, JAK2, STAT1, and IDO1, HNRNPH1 | Regulating tumor IFNγ signaling and CTL-mediated killing                                     | —                                      | [104]      |
| Lnc-CD56        | NK cells            | —             | Upregulated in NK cells | —              | CD56                | Serving as a positive regulator of CD56 in primary human NK cells and differentiated NK cells from human CD3+ hematopoietic progenitor cells. | —                                      | [105]      |
| IFNG-AS1        | NK cells            | —             | Upregulated in NK cells | —              | IFNG                | Triggering of the natural cytotoxicity receptors induces lncRNA IFNG-AS1 expression, and IFNG-AS1 increases IFN-γ secretion | —                                      | [106]      |
| GASS            | NK cells            | Gastric cancer | Downregulated in NK cells | miR-18a        | —                   | Promoting NK cell cytotoxicity against gastric cancer by regulating miR-18a                 | —                                      | [107]      |
| GASS            | NK cells            | HCC           | Downregulated in NK cells | miR-544        | RUNX3               | Enhancing the killing effect of NK cell on liver cancer by regulating miR-544/RUNX3       | —                                      | [108]      |
| linc-EPHA6-1    | NK cells            | Lung cancer   | —             | miR-4485-5p    | NKp46               | IFNβ-induced exosomal linc-EPHA6-1 promotes cytotoxicity of NK cells by miR-4485-5p to increase NKp46 expression | —                                      | [109]      |

Abbreviations: AICD Activation-induced cell death, BL Burkitt lymphoma, CTLs Cytotoxic T lymphocytes, DCs Dendritic cells, DLBCL Diffuse large B cell lymphoma, HCC Hepatocellular carcinoma, HGSOC High-grade serous ovarian cancer, IPI International prognostic index scores, NK Natural killer, TNBC Triple-negative breast cancer, Tregs Regulatory T cells
HIF-1α in PMN-MDSCs. Pvt1 silence can weaken PMN-MDSCs-mediated immunosuppression and recover anti-tumor T-cell responses, and accordingly retard tumor progression potentially targeting downstream c-myc [57].

The expression of Ficolin B could be considered as an indicator for PMN-MDSCs differentiation [131]. Through potentiating the stability of Ficolin B in a manner dependent on the ubiquitin-proteasome system, lncRNA-AK036396 dampens maturation and fosters immunosuppression of PMN-MDSCs [58].

In human lung cancer, lncRNA-MALAT1 is reduced in PBMCs from patients and negatively regulates the amount and proportion of MDSCs [59]. More importantly, both lncRNA-HOTAIRM1 and lncRNA-RUNXOR are tightly linked to the immunosuppression of MDSCs, but they have the opposite effect. Through analyzing the

**Fig. 4** Role of lncRNAs in crosstalk between macrophages and tumor. a LncRNAs regulate M1/M2 macrophage polarization through miRNA-mediated alterations in the expression of downstream target proteins. b LncRNAs modulate the protein secretion of TAMs and affect the survival and metastasis of tumor cells. c TAMs can also influence the malignant behaviors of tumor cells by exosomes rich in specific lncRNA. d Macrophages phagocytose and internalize tumor-secreted proteins or tumor-derived exosomes rich in lncRNAs with regulatory function and thus induce macrophage polarization. e LncRNAs are involved in macrophage recruitment from circulating monocytes by regulating the production of secreted proteins, and in turn induce the polarization of macrophages into TAMs in the TME.

**Fig. 5** Schematic representation about the mechanisms of lnc-C/EBPβ, lnc-chop and RNCR3. BMC, bone marrow cell; MDSC, myeloid-derived suppressor cells; M-MDSC, monocytic MDSC; PMN-MDSC, polymorphonuclear MDSC; C/EBPβ-LIP, C/EBPβ isoform liver-enriched inhibitory protein (LIP); IL4I1, interleukin 4 induced gene-1
tumor tissues isolated from patients with lung cancer, it was found that HOTAIRM1 was negatively related to the level of Arg-1 and the proportion of MDSCs, while positively related to the ratio of Th1/CTL cells [61]. In contrast, IncRNA-RUNXOR level was positively linked to the level of Arg-1 and the proportion of MDSCs, whereas a negative linked to the ratio of Th1/CTL cells [60]. In addition, HOTAIRM1 could enhance HOXA1 level to abate the immunosuppression of MDSCs and reinforce the antitumor immune response [61], while RUNXOR facilitates the generation and suppressive activity of MDSCs by targeting RUNX [60]. In HCC, IncRNA-HOTAIR is probably implicated in the recruitment of MDSCs by targeting RUNX [60]. In HCC, IncRNA-HOTAIR is probably implicated in the recruitment of MDSCs by targeting RUNX [60]. In HCC, IncRNA-HOTAIR is probably implicated in the recruitment of MDSCs by targeting RUNX [60]. In HCC, IncRNA-HOTAIR is probably implicated in the recruitment of MDSCs by targeting RUNX [60]. In HCC, IncRNA-HOTAIR is probably implicated in the recruitment of MDSCs by targeting RUNX [60]. In HCC, IncRNA-HOTAIR is probably implicated in the recruitment of MDSCs by targeting RUNX [60]. In HCC, IncRNA-HOTAIR is probably implicated in the recruitment of MDSCs by targeting RUNX [60]. In HCC, IncRNA-HOTAIR is probably implicated in the recruitment of MDSCs by targeting RUNX [60]. In HCC, IncRNA-HOTAIR is probably implicated in the recruitment of MDSCs by targeting RUNX [60]. In HCC, IncRNA-HOTAIR is probably implicated in the recruitment of MDSCs by targeting RUNX [60]. In HCC, IncRNA-HOTAIR is probably implicated in the recruitment of MDSCs by targeting RUNX [60]. In HCC, IncRNA-HOTAIR is probably implicated in the recruitment of MDSCs by targeting RUNX [60]. In HCC, IncRNA-HOTAIR is probably implicated in the recruitment of MDSCs by targeting RUNX [60]. In HCC, IncRNA-HOTAIR is probably implicated in the recruitment of MDSCs by targeting RUNX [60]. In HCC, IncRNA-HOTAIR is probably implicated in the recruitment of MDSCs by targeting RUNX [60]. In HCC, IncRNA-HOTAIR is probably implicated in the recruitment of MDSCs by targeting RUNX [60]. In HCC, IncRNA-HOTAIR is probably implicated in the recruitment of MDSCs by targeting RUNX [60]. In HCC, IncRNA-HOTAIR is probably implicated in the recruitment of MDSCs by targeting RUNX [60].

**Tumor associated neutrophils (TANs)**

Accumulating evidence indicates TANs are involved in the pathogenesis of numerous cancers [132]. It has been reported that TANs possess diverse antitumor roles, including direct cytotoxicity towards cancer cells and repression of metastasis [132, 133]. On the contrary, another part of the studies indicated that TANs can fuel tumor growth and progression through stimulating the angiogenic switch, promoting neoplastic cell motility and invasion, and regulating other immune cells [134, 135]. TANs exhibit multifaceted and even opposing properties during tumor initiation and progression due to their heterogeneity and plasticity in the TIME [136]. In response to cytokines and inflammatory mediators released by neoplastic cells and cancer-associated cells, TANs can be polarized into divergent functional phenotypes to exert various pro- or antitumoral effects and alter cancer behavior [136].

The activation states of TANs polarization have been classified into an antitumorigenic phenotype N1 and a pro-tumorigenic phenotype N2 to mirror M1/M2 paradigm of macrophages [137]. Nevertheless, the classification of TANs in tumor has long been a matter of disputation because no specific surface marker has been identified to differentiate them, the most of data were obtained only from murine models and the lack of definite evidence in humans [135, 138]. With regard to TANs polarization, the binary N1/N2 classification is probably simplistic out of the analogous reasons that have been given against adopting M1 and M2 to sort TAMs [18, 139]. Similarly, TANs polarization might exist as a variable spectrum of phenotypes, instead of only two extremes.

The short lifespan of neutrophils brings the technical difficulties to culture and handle these cells. As a consequence, there is a paucity in the literature hitherto studying the relationship between IncRNAs and neutrophils in the TME. Nevertheless, we still viewed the looming picture from the limited studies where IncRNA exerts a critical function in the pathogenesis of neutrophil-related diseases including inflammatory damage, transplantation and cancer, through affecting its quantities, phenotypes, expression and secretion of regulatory proteins. The C-X-C motif chemokine receptor 2 (CXCR2) belongs to the CXCR chemokine family and is expressed on the surface of neutrophils, where its activation could motivate neutrophil recruitment [140]. Resorting to reinforcing CXCR2 expression, IncRNA-Gm43181 can provoke inflammation through controlling the recruitment and activation of neutrophils into the specific tissues [63]. Quiescence of IncRNA-MALAT1 can ameliorate the inflammatory injury after lung transplant ischemia-reperfusion (LTR) through depressing infiltration and activation of neutrophils and downregulating IL-8 [64]. LncRNA-XIST downregulation potentiates the apoptosis of polymorphonuclear neutrophils (PMNs) and dampens the formation of neutrophil extracellular trap (NET) by inhibition of IL-12A in rat model of lung transplantation [65]. In breast cancer, IncRNA-TCL6 correlates with neutrophils infiltration and manifests poor survival of cancer patients [11]. In ovarian cancer, upregulated IncRNA-HOTTIP can stimulate the production and secretion of IL-6 by regulating transcription factor c-jun, and increase the level of PD-L1 in TANs, and in turn repriming the activity of T cells, and ultimately facilitating immune escape of cancer cells (Fig. 6a) [66]. The evidence above indicates that IncRNAs may be able to influence tumor occurrence and development through regulating the function of neutrophils, and the regulatory relationship between IncRNAs and TANs remains a virgin place worth exploring (Table 1).

**DCs**

Tumor-associated conventional DCs (cDCs) are considered to phagocytose debris from apoptotic cancer cells and transport cancer-related antigens to the draining lymph node where these antigens are presented to naïve CD4+ or CD8+ T cells and induce T cell priming and activation [141]. Although DCs equip with robust potential in anticancer immunity, the TME poses substantial challenges that often disturb normal DC functions to evade immune surveillance, and thus hinder the formation of protective immune responses [142]. Neoplastic cells can evolve a variety of mechanisms that allow them to thrive under adverse circumstance. Notably, multiple cytokines within the tumor milieu can directly influence the activity of infiltrating DCs to foster malignant progression. For example, IL-6, IL-10 and VEGF, generally
overexpressed in the TIME can stimulate STAT3-related pathway to induce an immature and tolerogenic phenotype in tumor-associated dendritic cells (TADCs), thereby boosting cancer progression [143]. In fact, DC populations exhibiting immunosuppressive and tolerogenic properties are commonly found in the TIME of aggressive malignancies.

LncRNAs influence cellular function and differentiation via interacting with signaling molecules in the cytoplasm and modulating post-translational modification [67]. LncRNA Inc-DC (Gene symbol LOC645638) is exclusively expressed in human Lin^- MHC-II^CD11c^ conventional DCs. Silence of Inc-DC refrains DC differentiation in vitro and in vivo, and decreases ability of DCs to stimulate T cell activation. Inc-DC directly binds to STAT3 in the cytoplasm, stimulating STAT3 phosphorylation on tyrosine-705 via protecting STAT3 from binding to SHP1 and dephosphorylating it (Fig. 6b) [67]. On the basis of the similar mechanisms, some research groups reveal that Inc-DC motivates DC maturation and impedes trophoblast invasion without the involvement of CD4^+ T cell, and the p-STAT3 inhibitor can restore the Inc-DC function by mediating the expression of MMP and TIMP [68]. Inc-DC induces the excessive maturation of decidual DCs and the increase of Th1 cells in preeclampsia [69]. Also, Inc-DC modulates the HBV-induced immune response and cellular turnover via TLR9/STAT3 pathway in DCs [70].

Emerging evidence has indicated that LncRNAs are capable of regulating the infiltration, differentiation, metabolism of DCs, and affecting other immune cells including T cells to fine-tune the local immune milieu. LncRNA-NEAT1 induces tolerogenic phenotype in DCs by using the NLRP3 inflammasome as a molecular decoy for miR-3076-3p [71]. In the nucleus, miRNA let-7i regulates the expression of NEAT1 via interacting with transcription factor E2F1, which influences the distribution of H3K27ac in the promoter of NEAT1. In the mouse models, infusion with NEAT1-downregulated DCs reduce the infiltration of inflammatory cells, increase the quantities of Tregs, curb the proliferation of T cells [71]. These alterations inevitably induce immune tolerance. LncRNA-HOTAIRM1 plays a key role in myeloid development. HOTAIRM1 expression is decreased when monocytes differentiated into DCs [72]. Knockdown of HOTAIRM1 alters the level of some monocyte differentiation markers, like B7H2 and CD14. Besides, miR-3960 acts as competing endogenous RNA to
regulate DC differentiate by targeting HOTAIRM1 and HOXA1, a repression gene of DC differentiation [72]. Lnc-Dpf3, induced by CCR7 chemokine receptor, inhibits DC migration via refraining HIF-1α-mediated glycolysis [73]. Concretely, CCR7 stimulation elevated Lnc-Dpf3 by eliminating m6A modification to restrain RNA degradation. Lnc-Dpf3 knockdown facilitates CCR7-mediated DC migration, aggravating inflammatory degree and adaptive immune responses. Lnc-Dpf3 directly precludes HIF-1α-dependent transcription of the glycolytic gene LDHA, thereby retarding DC glycolytic metabolism and migration ability (Fig. 6c) [73]. Therefore, we speculate that Lnc-Dpf3 reduction in DCs may be able to promote DC recruitment into the hypoxic TME through a similar mechanism, which in turn strengthens adaptive immune responses and improves the TIME. Tumor-infiltrating DCs secretes a large amount of CCL5 in human colon cancer specimens. Blocking CCL5 alleviates the promotion of tumor progression by TADCs [74]. Deficiency of lncRNA MALAT-1 strongly reduces CCL5-mediated invasion and migration via reducing Snail level [74]. These findings reveal that the MALAT-1/Snail signaling is essential for TADC-mediated tumor progression.

B cells

Tumor-infiltrating B cells (TIBs) are present at all stages of tumor and exert crucial functions in shaping cancer advancement [144]. TIBs have been reported to the inconsistent roles in tumor immunity. On the one hand, it has been documented that B cells infiltrating plenty of cancers to generate class-switched affinity-matured antitumor antibodies in situ [145–147]. More than that, TIBs also promote T cell-mediated immune responses by acting as antigen-presenting cells to reinforce antitumor immunity [148]. On the other hand, TIBs also have been found to propel cancer progression, which have been designated as regulatory B cells (Bregs). In mouse and human studies, Bregs exhibit their immunosuppressive property by means of death ligands (TRAIL, FasL) or/and the secretion of anti-inflammatory factors (IL-10, TGFβ), which can impair NK and T cell responses and boost the pro-tumoral effects of Tregs, MDSCs, and TAMs, accordingly alleviating antitumor immune responses [148–150]. The homeostasis of B cells largely dependent on a range of factors with the TIME, such as intra-tumoral vascularity, inflammatory degree, cytokines, hypoxia, and cellular infiltration. Once that balance is broken, B cells might be polarized towards pro- or anti-tumor orientation.

Unfortunately, there are few studies concerning lncRNAs and B cells in the tumor milieu to date, and the majority of studies focus on B-cell related lymphomas triggered by dysfunction of lncRNAs during B cell development and maturation, including Burkitt lymphoma (BL), classical Hodgkin lymphoma (cHL) and diffuse large B cell lymphoma (DLBCL). Verma et al. identified 2632 novel lncRNAs in DLBCL by a systematic analysis from the poly-adenylated transcriptome of 116 primary DLBCL specimens, which expands the lymphoma transcriptome [151]. This indicating lncRNAs possibly participate in lymphoma regulation. LncRNA-SNHG16 facilitates proliferation and restrains apoptosis of lymphoma cells through regulating miR-497-5p-mediated expression of target gene PIM1 [75]. Depletion of LncRNA-TUG1 inhibits tumor growth through provoking ubiquitination of MET and subsequent degradation of MET in vitro and in vivo [76]. Several lncRNAs are capable of promoting immune evasion to alter tumor progression. LncRNA-SNHG14/miR-5590-3p/ZEB1 forms the positive feedback loop to foster immune escape and lymphoma progression via modulating PD-1/PD-L1 checkpoint [77]. LncRNA-MALAT1 fuels immune evasion of lymphoma by targeting mir-195 [78]. MALAT1 silence facilitates proliferation of CD8+ T cells and hinders EMT-like process by Ras/ERK signaling pathway [78].

More importantly, some of them are induced and regulated by MYC, a well-known transcription factor and is considered to be the major driving force in lymphoma development [152]. For example, LncRNA-MINCR acts as a regulator of the MYC transcriptional process to govern the expression of cell cycle genes, including AURKA, AURKB, and CDT1 [79]. MYC-induced LncRNA-NEAT1 facilitates lymphomagenesis and B cell proliferation by the miR-34b-5p/GLI1 axis [80]. MYC-activated LncRNA-FIRRE facilitates lymphoma progression through regulation of the nuclear translocation of β-catenin to activate Wnt/β-catenin pathway [81]. MYC is not the only modulator that interacts with the promoter region of lncRNA to promote its expression. P53-induced LncRNA-PANDA exerts the tumor-suppressive function in human lymphoma by inactivation of MAPK/ERK signaling pathway [82]. FoxM1-regulated upregulation of LncRNA-OR3A4 modulates cell apoptosis and proliferation through activating Wnt/β-catenin signaling pathway [83]. Apart from OR3A4 and FIRRE, LncRNA SMAD5-AS1 suppresses lymphoma growth also through the classic Wnt/β-catenin pathway, but dependent on the expression of APC [84].

In clinical terms, a variety of lncRNAs are associated with prognosis and affect clinical treatment in patients with B-cell related lymphoma. LncRNA HULC, HOTAIR, LUNAR1 and PEG10 can predict a poor clinical outcome, represent oncogenic activity, and the latter three lncRNAs have potential diagnostic value in DLBCL [85–88]. LncRNA MALAT-1 regulates the chemotherapy sensitivity of DLBCL by modulating autophagy-
related proteins, including LC3-II/LC3-I, p62 and ATG5 [89]. Intriguingly, Su et al. [153] reported an artificially-designed i-lncRNA, targeting 13 oncogenic microRNAs according to complementarily sequences. The i-lncRNA curbed tumor growth in vitro and in vivo through effectively consuming a large number of oncogenic microRNAs mainly targeting a series of regulatory genes, such as PTEN, TIMP3, p38/MAPK, c-myc. In addition, soluble decoy receptor of Fas (sFas) can prevents Fas-ligand induced apoptosis. LncRNA FAS-AS1, regulated by EZH2-mediated histone methylation, is a novel regulator of the sFas expression through acting as a decoy for RBM5, to influence cell apoptosis in non-Hodgkin’s lymphomas (Table 1) [90].

Tregs
At least two Treg subgroups have been generally identified in humans: those naturally developed within the thymus (natural; nTregs), and adaptive Tregs undergoing peripheral differentiation accommodate the environmental signals (induced; iTregs), such the gut, colon or placenta. The nTregs mediate suppression by cell contact-dependent mechanisms, including the Fas/FasL pathways and granzyme B/perforin, forming a major Treg subset for maintenance of peripheral immune tolerance [154]. The iTregs mediate suppression through contact-independent mechanisms resorting to the expression of immunosuppressive factors, such as TGF-β, IL-10, CTLA-4 and adenosine [155]. Understandably, tumor-infiltrating Tregs suppress the tumor-specific immune effector cells such as CD4+ T cells, cytotoxic CD8+ T cells, NK cells and DCs [156], and thus perturb the anti-tumor response of host. Besides, Tregs have been shown to stimulate angiogenesis and boost cancer aggressiveness [157, 158]. Clinically, Tregs dysfunction can evoke severe autoimmune diseases [159], but a hyperactive function of Tregs is also detrimental, because it dampens beneficial antipathogen and antitumor immunity [160]. Elevated Treg proportions of TILs, in particular decreased effector T cells, are strongly linked to poor prognosis in multiple cancers [161–163].

LncRNAs play a part in epigenetic control of Tregs fate. For example, lncRNA-Smad3 coordinate Smad3 locus accessibility to regulate iTreg polarization [164]. LncRNA-Flicr, a negative modulator of Foxp3, is specifically expressed in mature Tregs, and acts only in cis. It modifies chromatin accessibility in the CNS3/AR5 region of Foxp3 [165]. Hence, Flicr can significantly refrain antiviral responses and exacerbate autoimmune diseases via abating Treg activity [165]. Besides, foxp3 directly shapes the lncRNA transcriptome causing lncRNA transcriptome of Treg largely distinctive from that of non-regulatory CD4+ T cells [166]. Under normal physiological conditions, lncRNA-Flatr, a core member of the Treg lncRNA transcriptome, anticipates Foxp3 expression during Treg differentiation, indicating Flatr as part of the upstream cascade resulting in Treg differentiation [166].

Under the induction of cytokines or antigens in the local microenvironment, regulatory lncRNAs inside Tregs also show corresponding variation, promoting adaptive conversion of Tregs. LncRNA-FENDRR suppresses the Treg-mediated immune evasion of tumor cells by competitively binding to miR-423-5p, which specifically targets DNA damage-related protein GADD45B. As a consequence, it potentiates tumorigenicity and cell growth in HCC [91]. Interference lncRNA-SNHG1 could repress Treg differentiation and in turn preclude the immune evasion of breast cancer by targeting miR-448 expression and diminishing IDO level [92]. Among aberrant expression profiling of lncRNAs in Tregs, lncRNA-POU3F3 possesses highest fold change and the most stable expression level. POU3F3 boosts the distribution of Tregs in peripheral blood T cell, resulting in the enhancement of proliferation in gastric cancer through recruiting TGF-β and activating TGF-β/SMAD2/3 pathway [93]. In HCC, lnc-EGFR promotes Treg differentiation, CTL inhibition and cancer progression in an EGFR-dependent manner. Functionally, lnc-EGFR specifically binds to EGFR to stabilize it by blocking c-CBL-mediated ubiquitination, resulting in downstream cascade activation [94].

Additionally, TILs can take up lncRNA-rich exosomes produced by neoplastic cells, prompting changes in lncRNAs within TILs, stimulating Tregs differentiation, and triggering immunosuppression and immune escape. Tumor cell secreting exosome containing abundant lncRNA RP11-323N12.5 acting on TILs to stimulate Treg cell differentiation dependent on YAP1 activation, an important factor in Hippo signaling pathways, ultimately promoting immunosuppression and tumor growth (Fig. 7a) [95]. Infiltrating CD73+γδ Tregs exert a key immunosuppressive effect via adenosine generation in the breast TME [96]. Breast cancer-derived exosomal lncRNA SNHG16 stimulates the activation of the TGF-β1/SMAD5 pathway via mediating miR-16-5p and drives the conversion of γδT Tregs into the CD73+ immunosuppressive subtype (Fig. 7a; Table 1) [96].

CTLs
A large number of lncRNA expression profiles have changed in mouse and human CD8+ T cells in response to viral infection [167]; of note, the most of lncRNAs expressed in CD8+ T cells harbor signatures of regulated promoters, secondary structures, and evolutionary conservation, indicating many of them are likely to play a part in fate decisions during adaptive immunity of antigen-driven differentiation [168]. Saádi et al.[169] adopted PMA/ionomycin to stimulate the P5424 cells,
which partially simulated the β-selection process from pro-T cells like thymocytes, that was the CD4⁻CD8⁻ double negative (DN) to double positive (DP) transition, as well as aspects of succeeding T cell activation and maturation. Their research group uncovered a remarkable correlation between the dynamic expression of lncRNAs and neighbor coding genes including substantial new-found transcripts, thus revealing latent co-regulation. Furthermore, lncRNA Robnr displayed a significant role in terms of Bcl-2 induction, an important anti-apoptotic gene, and the concrete influence of the Robnr locus to leukemia progression and CTLs function [169].

The mechanism of lncRNAs in CD8⁺ T cells responding to antiviral processes may provide implications for the study of lncRNAs in the cancer setting. During the early stages of choriomeningitis virus infection, the transcription of the lncRNA-Morrbid is specifically induced by type I IFN stimulation and T cell receptor (TCR). As a response, the Morrbid and its locus govern the survival, proliferation and effector function of CD8⁺ T cell through controlling the pro-apoptotic factor, Bcl2l11, and activating the PI3K/Akt pathway [170]. LncRNA-CD160 eliminates the immune activity of CD8⁺ T cells via epigenetic mechanisms in hepatitis B virus infection. It can impair the secretion of TNF-α and IFN-γ in CD8⁺ T cells by recruiting histone-modification-related gene, HDAC11, to form a complex. This complex reinforces H3K9Me1 methylation and turns chromatin into the heterochromatin, thus the transcription of TNF-α and IFN-γ is retarded, inhibiting the immune response of CD8⁺ T cells [171].

Increasing studies have shown that lncRNA is the critical player for apoptosis, expansion, and cytotoxicity of CD8⁺ T cells in the TIME. To some extent, they determine the immune orientation by regulating CD8⁺ CLTs in the tumor milieu, whether it is anti-cancer or cancer-promoting. Lnc-sox5 regulates the infiltration and cytotoxicity of CD8⁺ T cells by indoleamine 2,3-dioxygenase 1 (IDO1), and unbalancing the TIME to affect tumorigenesis and advancement [97]. Reduction of lncRNA-NEAT1 can curb CD8⁺ T cell apoptosis and augment its cytosis activity against cancer by binding to miR-155 targeting Tim-3, a key regulatory factor potentiating...
CD8⁺ T cell exhaustion [99]; moreover, through epigenetic suppression of p53/cGAS/STING pathway, NEAT1 directly interacting with DNMT1 to tune CD8⁺ T cells infiltration and T cell tumor-specific immune response, regulating malignant behavior of cancer cells [98]. Apart from NEAT1, Inc-Tim3 also can affect CTLs activity by Tim-3. Lnc-Tim3 aggravates CD8⁺ T cell exhaustion, a phenotype related to diminished antimflammatory function, through interacting with Tim-3 and inducing nuclear translocation of Bat3, and further enforcing p300-dependent p53 and RelA transcriptional activation of anti-apoptotic genes, like Bcl-2 and MDM2 [100]. Several studies have revealed that IncRNAs are able to regulate the apoptosis and expansion of CD8⁺ T cells through controlling the expression of PD-L1, and in turn escaping immune surveillance in the TIME. LINCO0473 competitively binds to miR-195-5p to increase the expression of PD-1 and PD-L1 in cancer, thereby suppressing activation of CD8⁺ T cells and accelerating progression of pancreatic cancer [101]. Besides, above-mentioned SNHG14 also can induce interaction of tumor cells with CD8⁺ T cells by mediating miR-5590-3p, and causing apoptosis of CD8⁺ T cells via PD-1/PD-L1 immune checkpoint, and eventually contributing to the immune evasion of cancer cells [77]. LncRNA MALAT1 sponges miR-195 to regulate proliferation and apoptosis of CD8⁺ T cells by PD-L1, and in turn adjust immune escape abilities [78].

The research on mice found that difference of lncRNA-GM16343 was the most obvious between the two groups by taking advantage of gene chip technology in mouse CD8⁺ T cells stimulated by IL-36β [102]. GM16343 stimulated the secretion of IFN-γ in CD8⁺ T cells, markedly reduced tumor volume of mice, and potentially prolonged the survival time. It was indicated GM16343 profoundly dampened tumor growth through affecting antitumor immune function of CD8⁺ T cells (Table 1) [102]. Intriguingly, a recent study conducted by Wang et al. demonstrated that exosomes originated from exhausted CD8⁺ T cells could be internalized by non-exhausted CD8⁺ T cells, and impeding proliferation capacity and the secretion of cytokines, i.e. IFN-γ and IL-2, and thus attenuating the anticancer effect of normal CD8⁺ T cells (Fig. 7b) [172]. Importantly, they identified 257 candidate IncRNAs with different expression in exosomes of both. These IncRNAs actively implicated in tuning various biological processes of CD8⁺ T cell activity [172].

NK cells

Through utilizing a suite of germline-encoded inhibitory and activating receptors, NK cells harbor the innate ability to rapidly recognize abnormal cells and respond to changes in ligand expression of tumor cells, that is, a tumor-associated profile stimulates activation of NK cells and triggers target cell killing [173]. Granzyme B and perforin, which can cause target cell apoptosis and osmotic lysis, are the key factors required for NK cell-mediated tumor killing via forming a synapse. The process can be marked by LAMP1 (also known as CD107a) expressed on the cell surface. Direct killing mode also occurs through death-receptor pathways such as FasL and TRAIL. In addition to cytotoxicity, NK cells also secrete pro-inflammatory cytokines, chemokines, e.g. IL-6, IL-13, IFN-γ, TNF, G-CSF and CCL5, which might exert direct antitumor activity [174]. It should be noted that NK cells are not only killers but also immunoregulatory cells that positive or negative effects against tumor responses through regulating T cells and DCs in multiple manner [175]. For example, NK cells are usually not a dominant lymphoid group in the TIME, but they can attract T cell infiltration and trigger immune responses by chemokine and cytokine secretion [175]. Clinically, emerging evidence suggests that NK cell activity has been negatively related to tumor incidence [176], and the mitigate NK cell function is potently correlated with worse prognosis [177].

During the differentiation of NK cells, a number of IncRNAs are involved in this process. One study of NK-specific IncRNAs found that IncRNAs offer specific signatures to diverse NK populations, which may beneficial to different functions and phenotypes for NK cells from distinct cell compartments [105]. Among them, the expression of Inc-CD56, also called AB128931, is significantly upregulated in human NK cells and tightly associated with that of CD56, a canonical surface marker of NK cells and participates in NK cell development [178]. Lnc-CD56 serves as a positive modulator of CD56 in primary and differentiated NK cells from human CD34⁺ hematopoietic progenitor cells [105]. Triggering of the natural cytotoxicity receptors induces IncRNA IFNG-AS1 expression, and that IFNG-AS1 increases IFN-γ secretion in human NK cells [106]. Therefore, IFNG-AS1 is a general modulator of the type I immune response.

LncRNA expression is intrinsically linked to NK-related cancer progression. LncRNA-GAS5 level is decreased in NK cells of cancer patients. The expression of GAS5 augment NK cell cytotoxicity, IFN-γ secretion, and the proportion of CD107a⁺ NK cells by sponging miR-544 to target RUNX3, and thus strengthening the killing effect of NK cells [108]. Furthermore, IncRNA GAS5 also potentiates the secretion of IFN-γ, TNF-α, as well as cytotoxicity of NK cells against gastric cancer via modulating miR-18a [107]. Notably, tumor-derived exosomes contain functional IncRNAs can be taken in NK cells for intercellular communication. IFNβ-induced exosomal linc-EPHA6-1 reinforces NK cell cytotoxicity against tumor cells and Zika virus infected tumor cells.
through miR-4485-5p-mediated the increase of NKp46, a vital natural cytotoxicity receptor [109]. Therefore, these data from aforementioned studies suggest that the considerable role of lncRNAs in regulation of NK cells infiltrating the tumor milieu is nonnegligible (Table 1).

**Immunotherapeutic potential of lncRNAs in the TIME**

Plenty of lncRNAs or their fragments are stable and detectable in body fluids of patients with tumor, including the plasma, saliva and urine, as a non-invasion method [179]. They can predict cancer metastasis and the survival of patients, even the risk of recurrence. Therefore, lncRNAs may be the effective biomarkers for diagnosis and prognosis of cancer patients. The related content has been well-summarized and comprehensively discussed elsewhere [179–181]. Herein, we focus on the immunotherapeutic potential of lncRNAs in the TIME.

There are numerous advantages for lncRNA-related immunotherapy. Multiple regulatory sites of lncRNAs can interact with other molecules, which provides a broader prospect for the development of new structure-based anticancer drugs. As regulators, lncRNAs regulate an array of downstream target genes and participate in diverse cell signaling pathways, which makes lncRNAs own more powerful effectiveness in cancer therapy. Besides, a number of lncRNAs dysregulated in various tumors and possess cancer specificity. Subtype- or tissue-specific lncRNA expression is critical for development of new personalized treatments. The tumor-specific dysregulation and pivotal role of lncRNAs as oncogenes or tumor suppressor genes in regulating immune cell functions within the TIME has attracted increasing attention, arguing that lncRNAs are promising targets for immunotherapy in tumor. Restoration of aberrantly expressed vital lncRNAs by technical means fully mobilizes immune cell function, as well as evokes and enhances antitumor immune responses in vivo is an effective immunotherapeutic strategy.

**Available methods**

There are some approaches that may target lncRNA to regulate its expression in immune cells or tumors (Fig. 8) [4, 179]: (1) Integrating RNA destabilizing elements (RDEs) into the genome, a way to restrain lncRNAs via targeting specific genomic loci, produce an effect similar to knockout on gene expression, such as poly(A) signals that silence downstream sequences [182]. (2) Regulating lncRNA transcription via affecting the promoter activity of encoding lncRNA, such as inhibition of transcription factor binding to corresponding promoter. (3) LncRNA transcript destabilization or degradation, including lncRNA-specific siRNAs, antisense oligonucleotide (ASO), locked nucleic acid (LNA) GapmeRs, and ribozymes/deoxyribozymes. Similar to other genes, specific siRNAs form RNA-induced silencing complex (RISC) with related protein and bind to specific target sequence based on complementarity, causing degradation of target lncRNA [183]. ASOs are single stranded oligonucleotides with specific complementarity that can mediate the degradation of target lncRNAs using RNase H [184]. In terms of LNA GapmeRs, multiple single-stranded oligonucleotides consist of a DNA stretch flanked by LNA nucleotides and induce degradation of target lncRNA by RNase H-dependent mechanism. Catalytic degradation is another effective way. Some enzymes, like ‘Hammerhead’-ribozymes, can target lncRNA and cleave it based on specific site in a protein-independent manner [185]. (4) Small molecule inhibitors that block interactions between lncRNAs and regulatory factors, i.e. DNA, RNA, protein or other interacting complexes, via specific binding site. (5) Aptamers can specifically bind to the structural regions of the target lncRNA and prevent it from binding to original partner, eliciting functional disruption of lncRNAs. (6) Gene editing to target lncRNAs, like CRISPR-Cas9, a major breakthrough in gene editing technology. Through inhibition (CRISPRi) or activation (CRISPRa), it is feasible to govern lncRNA expression in

![Fig. 8 Schematic representation of available methods for regulating lncRNA levels in TIME](image-url)
a transient or stable manner without altering the genomic sequence [186, 187]. (7) Synthetic IncRNA mimics. It is introduced into cells to increase the level of key IncRNAs [188].

**Strategies in combinational therapy**

Over the past few years, several drugs, like PD-1, PDL-1 and CTLA-4 antibodies, have been developed for tumor immunotherapy with gratifying results. Nevertheless, the diverse resistance mechanisms of immunotherapy largely limit its effectiveness. Recently, an increasing number of studies suggested that IncRNAs play a vital role in drug resistance and immunotherapy resistance for cancers [12, 103, 104]. Accordingly, combining targeted IncRNA drugs with immunotherapy antibodies or chemotherapeutic medicine to maximize the efficacy of anticancer therapeutics may be the most effective strategy for cancer treatment.

Immunotherapy has revolutionized the treatment of malignancies especially through like immune checkpoint blockade (ICB) and chimeric antigen receptor T cell therapy (CAR-T) targeting distinct aspects of the immune-oncology cycle. The efficiency of ICB treatment primarily depends on T cell-recognized neoantigens exhibited by MHCs on cancer cells. It has been found that tumor-related IncRNAs mediates immune escape of tumor cells by suppressing antigen presentation. For instance, IncRNA LINK-A can influence MHC-1 stability of neoplastic cells. Treatment with LINK-A LNAs in combination with ICB can potently restrain tumor growth and increase the survival of the tumor-bearing mice, displaying synergistic efficacy between them [12]. The rationale for this therapeutic strategy is that inhibition of LINK-A expression by LINK-A LNAs restores the antigen presentation pathway of cancer cells, thereby improving the sensitivity of cancer to ICB treatment. Of note, treatment with LNA does not influence the distribution of immune cells, such as macrophages, MDSCs and CTLs [12]. It is, therefore, conceivable that combinatorial therapies concerning IncRNA ASOs or LNAs together with ICBs may show synergistic effects on anti-tumor immunity in humans.

Adaptive T cell therapies, especially CAR-T therapy, have achieved significant clinical effects in the treatment of hematological malignancies [189, 190]. Nevertheless, the efficacy of CAR-T therapy in solid malignant tumors is still limited. Recently, several studies have shown that IncRNAs acted as the auxiliary targets of CAR-T treatment. IncRNA-NKILA was reported to strongly increase T cell sensitivity to activation-induced cell death (AICD) by inhibiting NF-κB activity, and thus facilitating cancer cell immune evasion [103]. In the patient-derived xenograft (PDX) model, CD8+ T cells transfected with NKILA shRNA were implanted into immunocompromised mice, which effectively inhibited the tumor growth and overcame tumor immune evasion by increasing infiltration and cytotoxicity of CLTs and decreasing the AICDs [103]. These finding illuminating that engineering IncRNAs are able to improve the efficacy of adoptive T cell therapy for cancer. Analogously, Mineo et al. found that knockdown of IncRNA-INCR1 increased susceptibility of cancer cells to T cell-mediated killing in vitro and improved CAR-T cell efficacy in vivo via controlling tumor IFN-γ signaling [104]. Taken together, engineering IncRNAs in combination with CAR-T cells therapy may be a promising immunotherapeutic strategy.

On the other hand, the ideal combination immunotherapy should enhance effector cell function and reduce protector cell function [110]. Accordingly, simultaneously application of multiple IncRNAs for comprehensive treatment might be another sort of effective strategy, that is, elevation of antitumorigenic IncRNAs and reduction of pro-tumorigenic IncRNAs. We conceive that multi-method combination therapy and combined regulation of multiple immune cells (i.e., inhibition of infiltration and effects of MDSCs and enhancement of infiltration and cytotoxicity of CTLs) not only reduce the dose and side effects of each drug, but also increase the overall efficacy of immunotherapy.

**Current limitations of IncRNA immunotherapy**

Although there are a variety of available methods and therapeutic strategies for IncRNA-related immunotherapy, there are still multiple limitations. Firstly, a major challenge is how to specifically deliver the respective molecules into targeted cells. To date, there are two main solutions for specific-target delivery. One of them is the utilization of artificial carriers, such as synthetic nanoparticles, to deliver biologically active constructs and IncRNAs [191]. Another is extracellular vesicles such as exosomes that mediate cell-to-cell communication and encapsulate a large number of key IncRNAs for successful targeted therapy [192]. The greatest advantage of using extracellular vesicles as delivery vehicles for transporting IncRNAs is that immune tolerance with the use of autologous vesicles and more effective tissue penetration into target tumor mass [4]. Components modified-nanoparticles and exosomes, based on the principle of ligand binding to receptor or antibody binding to ligand may improve the specificity of the delivery of IncRNAs into targeting immune cells. However, there are still some uncertainties, including whether they affect the other cellular components in TIME and cause safety problems after off-target. Secondly, IncRNAs are not simply single-stranded structures, and they also have secondary and even tertiary structures. This may result in the inability to intervene effectively, such as frequent disruption of efficient binding of these molecules to
specific targets and difficulty in forming base pairs to induce their degradation as expected. Thirdly, unlike protein-coding genes, IncRNAs are poorly conserved among distinct species; thus, effective therapies developed through in vitro experiments and animal models may be difficult for human applications. Fourthly, there are still some other issues such as how to choose the proper IncRNA as drugs and how to ensure that IncRNAs can not cause unexpected side effects under the complex regulatory network.

So far, to our best knowledge, there are no clinical trials of IncRNAs for cancer treatment independently or in combination with other drugs. Studies on IncRNAs in cancer therapy still focus on the levels of molecular cytology and mouse tumor models. Therefore, our hitherto understanding of IncRNA mechanisms in TIME is only the tip of the iceberg. A series of intriguing questions remain unanswered.

Conclusions
Collectively, we have summarized recent advancement involving of IncRNAs within the TIME, and their functions in the crosstalk between neoplastic cells and infiltrated immune cells, and the underlying molecular mechanisms. As well, we discussed potential immunotherapy strategies based on IncRNAs and their limitations. Undeniably, IncRNA molecules exert remarkable functions in remodeling TIME and regulating the immune escape of tumor cells. LncRNA-based targeted cancer immunotherapy is promising.

Abbreviations
AKT1: Activation-induced cell death; Arg-1: Arginase-1; ASO: Antisense oligonucleotide; BL: Burkitt lymphoma; Bregs: Regulatory B cells; C/EBPP: CCAAT/enhancer-binding protein; CAFs: Cancer-associated fibroblasts; CAR-T: Chimeric antigen receptor T cell therapy; CCL2: Secretion of chemokine (C-C motif) ligand 2; cDCs: Conventional dendritic cells; cERNA: Competing endogenous RNA; cHLA: Classical Hodgkin lymphoma; CHOP: C/EBP homologous protein; COX2: Cyclooxygenase-2; CTLA-4: Cytotoxic T lymphocyte antigen 4; CXCR2: C-X-C motif chemokine receptor 2; DCs: Dendritic cells; DLBCL: Diffuse large B cell lymphoma; ECM: Extracellular matrix; FGFR2: Fibroblast growth factor-2; FX: Coagulation factor X; GADD45B: Growth arrest and DNA-damage-inducible beta protein; HCC: Hepatocellular carcinoma; HDAC11: Histone-modification enzyme gene histone deacetylase 11; ICB: Immune checkpoint blockade; IDO1: Indoleamine 2,3-dioxygenase 1; LAMP1: Lysosomal-associated membrane protein 1; LCMV: Lymphocytic choriomeningitis virus; LIP: Liver-enriched inhibitory protein; LNA: Locked nucleic acid; LncRNAs: Long noncoding RNAs; MDSCs: Myeloid derived suppressor cells; M-MDSCs: Monocytic MDSCs; NECAB3: N-terminal EF-hand calcium binding protein 3; NET: Neutrophil extracellular trap; NK cells: Natural killer cells; NOX: Nitric oxide; NOX2: Nitric oxide synthase 2; NOS2: Nitric oxide synthase; NETs: Tumor-infiltrating B cells; TILs: Tumor infiltrating lymphocytes; TIME: Tumor immune microenvironment; TME: Tumor microenvironment; TRAIL: TNF-related apoptosis-inducing ligand; Tregs: Regulatory T cells; XIAP: X-linked inhibitor of apoptosis protein

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Authors’ contributions
ZYL collected literatures, prepared figures and tables, and drafted the manuscript. LQF conceived the idea and edited the manuscript. LQ reviewed the manuscript. All authors read and approved the final manuscript.

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