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Long Noncoding RNA Loss in Immune Suppression in Cancer

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Abstract

Long noncoding RNAs (lncRNAs) have multiple functions in the regulation of cellular homeostasis. In recent years, numerous studies have shown that tumor-associated lncRNAs play key roles in promoting and maintaining tumor initiation and progression by shaping the tumor microenvironment through changing tumor cell intrinsic properties. Here, we focus on the roles of lncRN As in cancer immunology. In the first part, we provide an overview of the roles played by lncRNAs and their deregulation in cancer at the cancer cell- and tumor microenvironment-associated immune cell levels. We go on to describe preclinical strategies for targeting lncRNAs, particularly highlighting the effects on tumor microenvironments. We then discuss the possibility of combining lncRNA targeting and tumor immune checkpoint inhibitor antibodies to treat cancer.

Keywords

Long noncoding RNA; Tumor-cell-intrinsic factors; Tumor-cell-extrinsic factors; Cancer immunotherapy

1. Introduction

Long non-coding RNAs (lncRNAs) are defined as RNA transcripts that are longer than 200 nucleotides but exhibit low coding potential (Perkel, 2013). With the advancement of high-throughput technology, more and more lncRNAs have been identified. In recent years, in-

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Conflict of interest

The authors have no conflicts of interest to disclose.

depth studies of lncRNAs have identified characteristics that are distinct from protein coding RNAs (mRNAs), such as tissue specificity; 78% of lncRNAs are tissue-specific, compared to ~19% for mRNAs (Cabili, et al., 2011; Ravasi, et al., 2006). LncRNAs also show higher developmental stage specificity and cell subtype specificity (S. J. Liu, et al., 2016; Yan, et al., 2013). Due to these specific manifestations, lncRNAs have been found to be involved in the regulation of multiple physiological functions, including regulating cell cycles, cell growth, differentiation, apoptosis, motility and invasion, signal transduction, DNA damage regulation, survival, immune response, and pluripotency (Huarte, 2015; C. Lin & Yang, 2018). They also play essential roles in early embryonic development and regulating tissue homeostasis in adults (Perry & Ulitsky, 2016; Salviano-Silva, Lobo-Alves, Almeida, Malheiros, & Petzl-Erler, 2018). Recently, numerous studies demonstrated that aberrant expression of lncRNAs plays crucial roles in both the development of tumors and metastasis (Batista & Chang, 2013; Wu, et al., 2019). In addition to affecting cancer cells themselves, lncRNAs also influence the tumor microenvironment (TME) (Denaro, Merlano, & Lo Nigro, 2019). The role of lncRNAs as oncogenes or tumor suppressors at the cancer cell level is still a matter of debate due to their differential effects in different cancer types. Meanwhile, at the microenvironment level, lncRNAs contribute to mediating and controlling several immune and cancer cell interactions and important mechanisms of immune response (Y. Zhou, Zhu, Xie, & Ma, 2019). Thus, targeting lncRNAs as a cancer therapy may require more in-depth studies.

Gene alteration is considered an important cause of tumorigenesis. With the advancement of large-scale sequencing technology, numerous somatic mutations, copy number alteration, and cancer-related single-nucleotide polymorphisms (SNPs) have been discovered from clinical cancer patient samples. Interestingly, the majority of these gene alterations are in the noncoding region of the genome (Fatica & Bozzoni, 2014; Maurano, Wang, Kutyavin, & Stamatoyannopoulos, 2012; Melton, Reuter, Spacek, & Snyder, 2015; Reuter, Spacek, & Snyder, 2015). Among those non-coding genes, lncRNAs have emerged as essential new participants involved in tumorigenesis (Beroukhim, et al., 2010; Fatica & Bozzoni, 2014; Melton, et al., 2015). Dysregulation of numerous lncRNA targets has been reported to associate with the stage and prognosis of many tumor types (Jendrzejewski, et al., 2012), including breast cancer (A. Lin, et al., 2016; T. Zhang, et al., 2019), lung cancer (Loewen, Jayawickramarajah, Zhuo, & Shan, 2014; Lu, Wang, Chen, Liu, & Jiao, 2018; Tao, et al., 2016), and liver cancer (Mai, et al., 2019; Mehra & Chauhan, 2017; O'Brien, Zhou, Tan, Alpini, & Glaser, 2019), as well as linked to resistance against chemotherapy and targeted therapy (Chen & Xu, 2018; De Los Santos, Dragomir, & Calin, 2019; W. Jiang, et al., 2020; K. Liu, et al., 2020; Majidinia & Yousefi, 2016; Pan, Xie, Li, & Chen, 2015). Although much has been learned about the multiple functions of lncRNAs in tumor cell proliferation, apoptosis, migration, invasion, and maintenance of stemness during cancer development (Batista & Chang, 2013; Slack & Chinnaiyan, 2019), little is known about their potential role in regulating tumor immunity as tumor-cell-intrinsic factors or tumor-cell-extrinsic factors that affect the cancer immunotherapy.

In recent years, breakthroughs in the field of tumor immunotherapy have greatly improved the efficacy of tumor treatments. Nevertheless, only a small percentage of cancer patients benefit from tumor immunotherapy, and the majority of patients develop primary or

secondary resistance following treatment (Corrales, Matson, Flood, Spranger, & Gajewski, 2017; Cristescu, et al., 2018; Farhood, Najafi, & Mortezaee, 2019; Jia, et al., 2017; Ribas, 2012; Sharma, Hu-Lieskovan, Wargo, & Ribas, 2017; Y. Zhou, et al., 2019). Further in-depth studies suggest that both tumor-cell-intrinsic and tumor-cell-extrinsic factors may be involved in cancer immunotherapy resistance mechanisms (Fares, Van Allen, Drake, Allison, & Hu-Lieskovan, 2019; Sharma, et al., 2017). Many clinical sample-based studies have shown that the dysregulation of the antigen presentation pathway is one of the major factors in driving tumor immunotherapy resistance. For example, studies suggested that tumor cell antigen loss leads to the tumor failing to respond to immune checkpoint therapy (Gubin, et al., 2014; Iorgulescu, Braun, Oliveira, Keskin, & Wu, 2018). Alternatively, cancer cells may express tumor antigens but develop mechanisms to avoid presenting them on the surface through the major histocompatibility complex (MHC) due to alterations in antigen-presenting machinery (such as proteasome subunits or transporters associated with antigen processing), beta-2-microglobulin (B2M), or the MHC itself (Q. Hu, et al., 2019; Marincola, Jaffee, Hicklin, & Ferrone, 2000; Sucker, et al., 2014). In addition to defects in antigen processing, some new dysregulated tumor-intrinsic signaling pathways have also been shown to associate with tumor immunotherapy resistance, such as the mitogen-activated protein kinase (MAPK)-PI3K and PTEN-PI3K signaling pathways, WNT/β-catenin signaling pathway, interferon-gamma (IFNγ) signaling pathways, and a lack of the immune checkpoint Programmed death-ligand 1 (PD-L1) expression (Sharma, et al., 2017; Stutvoet, et al., 2019). Although there are many studies focusing on the causes of tumor cell resistance, the detailed mechanisms of this phenomenon are still unclear. To better understand the mechanisms of tumor immunotherapy resistance, more tumor cell intrinsic factors need to be discovered.

2. Roles of lncRNAs as tumor-cell-intrinsic factors

Recently, numerous tumor-associated lncRNAs have been recognized as tumor cell intrinsic factors or tumor-cell-extrinsic factors that mediate tumor cell escape of immunosurveillance (Figure 1). They are involved in cancer immunity regulation as either oncogenic genes or tumor-suppressive genes (Table 1). These tumor-associated lncRNAs may play vital roles in immunotherapy resistance (Denaro, et al., 2019; Y. Zhou, et al., 2019).

2.1 LINK-A

Long intergenic non-coding RNA for kinase activation (*LINK-A*) was first identified to predominately reside in the cytoplasm and is highly expressed in triple-negative breast cancer (TNBC). Further studies showed that *LINK-A*-dependent signaling pathway activation promotes breast cancer metabolic reprogramming and tumorigenesis. The expression of *LINK-A* is correlated with advanced lymph node metastasis stages and shorter survival time for breast cancer patients (A. Lin, et al., 2017; A. Lin, et al., 2016). Transgenic expression of *LINK-A* in mouse mammary glands results in mammary gland malignancies and lung metastasis. Mechanistically, *LINK-A* facilitates the association between phosphatidylinositol (3,4,5)-trisphosphate (PIP_3) and inhibitory G protein-coupled receptors (GPCRs), facilitating the cAMP-dependent protein kinase (PKA)-mediated phosphorylation of the E3 ligase TRIM71 (also known as LIN-41). As a consequence, TRIM71 catalyzes the

K48-linked polyubiquitination and proteasome-mediated degradation of the peptide-loading complex (PLC) upon *LINK-A* expression (Figure 2). Treatment with *LINK-A* Locked Nucleic Acids (LNAs) led to stabilization of the PLC components and improved the infiltration and cytotoxicity of tumor-resident $CD8^+$ T cells *in vivo*. Treatment with *LINK-A* LNAs in combination with immune checkpoint blockers exhibits synergistic efficacy in repressing breast tumor growth. Most importantly, human breast cancer tissues with high *LINK-A* expression are associated with decreased activated $CD8^+$ T cell and antigen-presenting cell (APCs) infiltration in tumors. *LINK-A* upregulation and the downregulation of the PLC are correlated in TNBC patients whose tumors are resistant to anti-PD-1 immunotherapy. Hence, lncRNA-directed targeted therapy using LNAs could serve as a promising strategy to improve breast tumor antigenicity and sensitize TNBC patients to immunotherapy (Q. Hu, et al., 2019).

2.2 HOTAIR

HOX transcript antisense intergenic RNA (*HOTAIR*) has been identified at the *HOXC* locus and inhibits the transcription of the *HOXD* locus. HOTAIR binds to Polycomb Repressive Complex 2 (PRC2) and plays an important role in the occupation of PRC2 at the *HOXD* locus and modulation of histone H3 lysine 27 trimethylation (Rinn, et al., 2007; Tsai, et al., 2010). It has been reported that *HOTAIR* is highly expressed in numerous cancers, providing notable prognostic value (Cai, Song, Cai, & Zhang, 2014; Gupta, et al., 2010; Hajjari & Salavaty, 2015). The role of HOTAIR in transcriptional regulation in cancer cells has been extensively reviewed (Hajjari & Salavaty, 2015; Tang & Hann, 2018). Recent advances have suggested that *HOTAIR* may play important roles in antigen presentation and immunotherapy. Song et al. reported that *HOTAIR* overexpression in gastric cancer cells might also involve tumor cell immune escape mechanisms by influencing HLA-G upregulation via inhibition of miR-152 and miR-148a (Song, et al., 2015; Sun, et al., 2016). Recent studies indicated that HOTAIR facilitates macrophage and myeloid-derived suppressor cell activity in liver cancer through transcriptional upregulation of chemokine (C-C motif) ligand 2 (Fujisaka, et al., 2018).

2.3 MALAT1

The transcript of the *MALAT1* gene, also known as *NEAT2*, represents nuclear-rich enriched transcript 2 and consists of >8000 nucleotides (Ji, et al., 2003). Although early reports provided evidence for its association with metastasis in patients with early non-small cell lung cancer (NSCLC), subsequent studies have reported that *MALAT1* is abundant and highly conserved in 33 different mammals (Eissmann, et al., 2012). Computational and biochemical studies demonstrated the interaction between *MALAT1* and the serine and arginine (SR) proteins involved in splicing regulation or interaction with spliceosome proteins (Yoshimoto, Mayeda, Yoshida, & Nakagawa, 2016). Recently, *MALAT1* have been found to positively regulate the expression of PD-L1 by sponging miR-195, thus promoting cancer cell migration and immune escape by regulating the proliferation and apoptosis of $CD8^+$ T cells (Q. M. Wang, Lian, Song, Huang, & Gong, 2019). *MALAT1* also has been showed to modulate miR-200a and the expression of PD-L1, serving as one of the mechanisms of lung cancer progression (Wei, Wang, Huang, Zhao, & Zhao, 2019). In lung cancer, the expression of *MALAT1* is correlated with infiltration of Myeloid-derived

suppressor cells (MDSCs) and possibly modulates the patient's response to immunotherapy (Q. Zhou, et al., 2018).

3. Roles of lncRNAs as tumor-cell-extrinsic factors

Recently, the functional roles of lncRNAs in innate immune response have emerged. Aberrant expression of lncRNAs has also been found to closely associate with innate and adaptive immune response regulation, which have important effects on cancer progression (Figure 1 and Table 1).

3.1 lncRNA-Cox2

Inducing gene expression is an important feature of host inflammatory response (Ahmed, Williams, & Hannigan, 2015; Mathy & Chen, 2017; Smale & Natoli, 2014; J. Wang, Blanchard, & Ernst, 2001). Recently, lincRNA-*Cox2* has been found to be highly expressed in macrophages upon stimulation of Toll-like receptors (G. Hu, et al., 2016). Further studies found that it also mediates both the activation and repression of distinct classes of immune genes. Mechanistically, lincRNA-*Cox2* interacts with heterogeneous nuclear ribonucleoprotein A/B and A2/B1 to inhibit the transcription of target genes (Carpenter, et al., 2013). To evaluate the *in vivo* functions of lincRNA-*Cox2*, Elling et al. developed a variety of lincRNA-*Cox2*-deficient mouse models. They found that the loss of LincRNA-*Cox2* led to an inflammatory response in mouse macrophages and tissues (Elling, et al., 2018). In addition to interacting with heterogeneous nuclear ribonucleoprotein A/B and A2/B1, lincRNA-*Cox2* also assembles into the switch/sucrose nonfermentable (SWI/SNF) complex in cells after Lipopolysaccharides (LPS) stimulation. Consequently, SWI / SNF-related chromatin remodeling leads to the activation of inflammatory gene expression under the influence of macrophages in the presence of a microbial challenge (G. Hu, et al., 2016). This lncRNA also plays important roles in regulating the NF-κb signaling axis and inflammatory response (Bian, Yang, Zhang, Li, Wang, Jiang, Chen, & Zeng, 2019).

3.2 CASC2c

Macrophages play an important role in innate immunity and TME (Hao, et al., 2012; Noy & Pollard, 2014; Pathria, Louis, & Varner, 2019). Macrophages can transform into the M1 type or M2 type when induced by LPS and IFN-γ or IL-4 (interleukin 4) and IL-13 (interleukin 13), respectively, and the two phenotypes can mutually transform (Martinez & Gordon, 2014). Expression of the lncRNA *CASC2c* has been shown to inhibit the expression and extracellular production of coagulation factor X (FX) (Y. Zhang, et al., 2018). The reduced production of FX leads to decreased phosphorylation and the inactivation of ERK1/2 and AKT in macrophages. As a consequence, the expression of *CASC2c* contributes to repression of M2 polarization and decreased proliferation of tumor cells (Y. Zhang, et al., 2018).

3.3 TUC339

The lncRNA *TUC339* was first identified as a lncRNA that is highly-expressed in hepatocellular carcinoma (HCC) cell-derived extracellular vesicles (Kogure, Yan, Lin, & Patel, 2013). X Li et al. reported that cellular HCC-derived exosomes contain high levels of

lncRNA *TUC339*, which are subsequently taken up by macrophages (X. Li, Lei, Wu, & Li, 2018). Depletion of *TUC339* in macrophages results in increased production of pro-inflammatory cytokines, expression of costimulatory molecules, and phagocytosis. In addition, compared to M1 macrophages, elevated levels of *TUC339* in M2 macrophages were detected. Depletion of *TUC339* in the macrophages led to reduced expression of M2 markers after IL-4 treatment, while the overexpression of *TUC339* in the macrophages enhanced the expression of M2 markers after IFN-γ + LPS treatment, indicating that *TUC339* plays a key role in M1 / M2 polarization (X. Li, et al., 2018).

3.4 Morrbid

$CD8^+$ T cells are key immune cells that eliminate cancer cells with MHC class I molecules (Janeway & Bottomly, 1994; Mueller, Jenkins, & Schwartz, 1989; N. Zhang & Bevan, 2011). To achieve this, cells must first be triggered by their primary interactions with dendritic cells (DCs), natural killer (NK) cells, and $CD4^+$ T cells, with the cells themselves playing a key role in this initiation. The cells are then activated to form effector cytotoxic T lymphocytes (CTLs), which kill cancer cells by releasing particles or inducing FasL-mediated apoptosis (Farhood, et al., 2019; van der Leun, Thommen, & Schumacher, 2020). Recently, the Henao-Mejia J. group has identified a long non-coding RNA named *Morrbid*, which regulates the survival of neutrophils, eosinophils, and monocytes upon stimulation of mouse survival cytokines. To control the life span of these cells, *Morrbid* maintains gene equilibrium states by recruiting the PRC2 complex to the *Bim* promoter, thereby regulating the transcription of the neighboring pro-apoptotic gene *Bim* (Kotzin, et al., 2016). In a recent study, Kotzin JJ, et al reported that T cell receptor (TCR) and type I IFN stimulation specifically induces the transcription of lncRNA *Morrbid* during the early stages of acute and chronic lymphocytic choroidal meningitis virus (LCMV) infection. In response to type I IFN, *Morrbid* and its loci control the expansion, survival, and effector function of $CD8^+$ T cells by regulating the expression of the pro-apoptotic factor Bcl2111 and the strength of the PI3K-AKT signaling pathway (Kotzin, et al., 2019).

3.5 Lnc-CD56

Natural killer (NK) cells are innate immune lymphocytes that play critical roles in host defense against viral infection and surveillance against malignant transformation (Chiossone, Dumas, Vienne, & Vivier, 2018; Smyth, Hayakawa, Takeda, & Yagita, 2002; Vivier, et al., 2011). NK cells exhibit cytotoxicity toward adjacent cells that express oncogenic transformation-associated surface markers (Shimasaki, Jain, & Campana, 2020). In addition, NK cells also enhance the response of antibodies and the activation of T cells, which proves that NK cells have play important role in tumor immunotherapy (Souza-Fonseca-Guimaraes, Cursons, & Huntington, 2019). Recently, R. Zhang et al. determined the expression profile of lncRNAs in human primary lymphocytes. They found that innovative NK-specific lncRNAs are closely related to the differentiation and function of NK cells (R. Zhang, et al., 2016). Among them, they found that the expression of a NK-specific lncRNA, lnc-CD56, is positively correlated with the expression of NK cell surface marker CD56. Further stud ies found that lnc-CD56 may play important roles in promoting the expression of CD56 and differentiation of NK cells from human CD34 + hematopoietic progenitor cells (R. Zhang, et al., 2016). Another study indicated that lncRNAs MEG3,

GAS5, and numerous microRNAs modulate the killing efficacy of NK cells in a variety of cancer types (Fang, et al., 2019; W. Liu, et al., 2017; Yang, Shen, Feng, & Li, 2019).

3.6 Linc-MAF-4

Recently, the importance of stimulating $CD4^+$ T helper cell (Th) response in cancer immunotherapy has been increasing (Bretscher, 2019; Cohen, et al., 2000; Knutson & Disis, 2005). By activating antigen-specific effector cells and recruiting cells of the innate immune system, Th cells are essential for the development of an immune response (Dong & Flavell, 2000; Hung, et al., 1998; Walker & McKenzie, 2018). There are two main Th cell subtypes: Th1 and Th2. Th1 cells are characterized by the secretion of IFN-γ and TNF-α (Tumour Necrosis Factor alpha), which are closely associated with cytotoxic T cell activation (Kalams & Walker, 1998). Th1/Th2 cells enhance the ability of APCs to influence antigen presentation and promote the cytotoxicity of CD8+ T cells (Fallarino, et al., 2000). LncRNAs have been suggested to regulate adaptive immunity by controlling the differentiation and function of different types of T cells (Atianand, Caffrey, & Fitzgerald, 2017). Ranzani et al. reported that the expression of *linc-MAF-4* is negatively correlated with the expression of TH2-related transcription factor MAF (Ranzani, et al., 2015). The down-regulation of *linc-MAF-4* facilitates the differentiation of T cells toward the TH2 phenotype (Ranzani, et al., 2015; F. Zhang, Liu, Wei, Gao, & Hao, 2017). They also indicated that *linc-MAF-4* regulates MAF transcriptional activities by recruiting chromatin modifiers (Ranzani, et al., 2015).

3.7 Lnc-DC

Dendritic cells (DCs) are a special class of antigen-presenting cells that play a key role in the initiation and regulation of innate and adaptive immune response. Therefore, there is currently great interest in regulating DC function to improve the effectiveness of cancer immunotherapy (Bottcher & Reis, 2018; Demoulin, Herfs, Delvenne, & Hubert, 2013; Wculek, et al., 2020). In one pioneering study, the Cao group identified a new lncRNA named *lnc-DC*, which is expressed only in human conventional dendritic cells (DC) (P. Wang, et al., 2014). Knocking down *lnc-DC* impairs the DC differentiation of human monocytes and mouse bone marrow cells *in vitro* and reduces the ability of DCs to stimulate T cell activation (P. Wang, et al., 2014). *lnc*-DC mediates these effects by activating the transcription factor STAT3 (signal transducer and transcriptional activator 3) (P. Wang, et al., 2014). Recently, *lnc*-DC has been shown to regulate the immune response of dendritic cells upon hepatitis B virus (HBV) infection through a Toll-like receptor 9 (TLR9) and STAT3-mediated signaling axis (Zhuang, Tian, Zhang, Wang, & Huang, 2018).

3.8 Flatr

Regulatory T cells (Tregs) are a specialized subpopulation of $CD4^+$ T cells and are essential for maintaining self-tolerance (Benoist & Mathis, 2012; Corthay, 2009; Vignali, Collison, & Workman, 2008). Treg dysfunctions are associated with severe autoimmune diseases such as inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, colitis, and type 1 diabetes (Alroqi & Chatila, 2016; Buckner, 2010). However, excessive activation of these cells is also harmful because it inhibits beneficial anti-pathogens and anti-tumor immunity (Dannull, et al., 2005; Franceschini, et al., 2009). Recently, the Adrian Liston group

identified a new lncRNA named *Flatr* (Foxp3-specific lncRNA of Treg expected), which is highly conserved and enriched in activated Treg cells (Brajic, et al., 2018). Jiang et al. found that Treg cells in HCC tumor areas specifically express *lnc-EGFR*, and further research found that *lnc-EGFR* stimulates the differentiation of Treg cells, thereby inhibiting CTL activity in the tumor area and enhancing the growth of HCC. (R. Jiang, et al., 2017). Furthermore, the lncRNA *Flicr* has been shown to negatively regulate the expression of *FoxP3*, which is a master regulator of Treg (Rudensky, 2011). *Flicr* modulates chromatin accessibility of the *FoxP3* gene loci, leading to impaired Treg activity and autoimmunity (Zemmour, Pratama, Loughhead, Mathis, & Benoist, 2017).

3.9 Lnc-CHOP

Myeloid suppressor cells (MDSCs) produced from bone marrow-like progenitor cells in the bone marrow are one of the major components of the tumor microenvironment (Bronte, et al., 2016; Gabrilovich, 2017; Talmadge & Gabrilovich, 2013). These cells have become key regulators of immune response in cancer and other pathological conditions (Bronte, et al., 2016; Kumar, Patel, Tcyganov, & Gabrilovich, 2016; Talmadge & Gabrilovich, 2013; Ugel, De Sanctis, Mandruzzato, & Bronte, 2015). Gao et. al identified an uncharacterized lncRNA named *lnc-CHOP*. They found that *lnc-CHOP* may interact with CHOP and C / EBPβ isoforms to encourage C / EBPβ activation and regulate a large number of target transcripts in MDSC to control immunosuppressive function and MDSC differentiation in inflammatory and tumor environments (Gao, Wang, Li, Zhang, & Yang, 2018). MicroRNAs and other lncRNAs, including *lnc-C/EBPbeta*, *Olfr29-ps1*, *Pvt1, MALAT1*, and *HOXA* regulate the immunosuppressive activity of MDSC (Gao, Sun, et al., 2018; Shang, Gao, Tang, Zhang, & Yang, 2019; Shang, et al., 2017; Tian, et al., 2018; Zheng, et al., 2019; Q. Zhou, et al., 2018).

4. LncRNAs as Potential Targets for Immunotherapies

The tumor-specific upregulation and important functional roles of lncRNAs as oncogenes brings attention to considering lncRNAs as promising therapeutic targets in cancer (Arun, Diermeier, & Spector, 2018; M. C. Jiang, Ni, Cui, Wang, & Zhuo, 2019; Lavorgna, et al., 2016). Moreover, as previously mentioned, lncRNAs also act as tumor suppresser genes that regulate immune cell function and immune response in the TME. With this in mind, there are several strategies currently available in preclinical studies to assess the role of lncRNAs as targets of immunotherapy, including downregulating the oncogenic role of lncRNAs through ASO-based strategies, siRNAs, small molecule inhibitors, and CRISPR inhibition (CRISPRi) strategies, and upregulating the tumor suppresser role of lncRNAs via CRISPR activation (CRISPRa) strategies. We also proposed a combinatorial therapy with immune checkpoint antibodies treatments, which need to be evaluated for their effects on cancer immunotherapy (Figure 3).

4.1 ASO-based strategies

Anti-sense oligonucleotides (ASO), including ASO gapmers (Kole, Krainer, & Altman, 2012), duplex RNA (Williams & Fried, 1986), and locked nucleic acids (LNAs) (Vester & Wengel, 2004) bind to lncRNA transcripts via base-pairing. The RNA-DNA duplexes trigger

RNase-H-dependent cleavage (Chan, Lim, & Wong, 2006). The new generation of ASOs utilizes chemical modification of the sugar backbone to improve binding affinity and stability *in vivo* (Geary, Norris, Yu, & Bennett, 2015), and ASOs have advanced to clinical trials (Hong, et al., 2015). The mixed LNA-DNA-LNA gapmers are base-paired to RNA targets and can be used to silence RNA targets in cell line-based experiments and animal models. The application of ASO to knock down lncRNAs *in vivo* has been investigated in a variety of cancer models and has been shown to have significant inhibitory effects on tumor growth and progression. For example, LNAs targeting *PVT1* have been shown to significantly reduce cell proliferation, migration, and invasion (Iden, et al., 2016). A study found that *lncARSR* promotes the resistance of cancer cells to sunitinib and that administration of LNAs targeting *lncARSR* enhances the sensitivity of cancer cells to sunitinib (Qu, et al., 2016). Therapeutic delivery of locked nucleic acids (LNAs) targeting *BCAR4, LINK-A*, and *MAYA* strongly suppresses breast cancer growth and metastasis in mouse models (C. Li, et al., 2017; A. Lin, et al., 2016; Xing, et al., 2014). Systematic knockout of *Malat1* using antisense oligonucleotides (ASO) in a MMTV (mouse mammary tumor virus) -PyMT mouse breast cancer model resulted in inhibited tumor growth with significantly increased cystic tumor differentiation and reduced metastasis (Arun, et al., 2016). In addition to its use in cancer, it has also been suggested that ASO could benefit patients with neuronal diseases and other human pathological conditions (Khorkova & Wahlestedt, 2017).

4.2 siRNAs

Using siRNAs targeting lncRNAs to inhibit the expression of these targets is a strategy that has been successfully applied to various preclinical models (Ozpolat, Sood, & Lopez-Berestein, 2010, 2014; Rupaimoole, et al., 2015). Recently, nanoliposomes based on oleylphosphatidylcholine (DOPC) have been developed for use with nucleotide-based therapeutics (siRNA, microRNA, lncRNA, antisense oligonucleotides, etc.) *in vivo* and clinical delivery (Ozpolat, et al., 2014). Studies have shown that DOPC-nanoliposomal siRNAs effectively inhibit the expression of target proteins in mouse tumors for about 3–5 days (Aslan, et al., 2015). DOPC nanoliposomes with an average size of 50 nm can be administered by a single intravenous or intraperitoneal injection to deliver the selected siRNA and anti-miR to tumor cells *in vivo*. This single administration significantly inhibits gene expression levels and reduces tumor size in both mouse models and preclinical models of human cancer, including subcutaneous xenografts and orthotopic tumor models (C. Lin & Yang, 2018; Ozpolat, et al., 2010, 2014). Other research has indicated that nanoparticle-encapsulated siRNAs deplete brain metastasis-associated lncRNAs in preclinical mouse models (S. Wang, et al., 2017).

4.3 Small Molecule Inhibitors

LncRNAs form complex tertiary structures (Jones & Sattler, 2019; Zampetaki, Albrecht, & Steinhofel, 2018). Whether the secondary or three-dimensional structure of lncRNAs is conserved among different species remains unclear (Rivas, Clements, & Eddy, 2017). RNA molecules are potential targets for small molecule inhibitors (Connelly, Moon, & Schneekloth, 2016). High-throughput screening has been used to identify small molecule compounds that may inhibit RNAs (Brustikova, et al., 2018; Lucas-Hourani, et al., 2014).

For example, Howe et al. reported the discovery and characterization of riboprotein, which is a highly selective chemical regulator of bacterial riboflavin riboswitches and was identified in phenotypic screening as a natural ligand for Flavin single core. Structurally unique nucleotide mimics have been screened and characterized to inhibit bacterial growth and riboswitch-mediated *ribB* gene expression (Howe, et al., 2015). A platform has been established to screen and identify small molecule inhibitors that target non-coding RNAs; this platform will help with large-scale screening of drugs that target lncRNAs (Velagapudi, et al., 2017).

4.4 Gene editing to target lncRNAs

In recent years, with major breakthroughs in gene editing technology like CRISPR-Cas9, gene therapy has reignited people's interest. New technologies continue to be used to treat animal models of disease, cell editing, and *in vivo* gene repair (Bortesi & Fischer, 2015; Nelson & Gersbach, 2016; H. Wang, La Russa, & Qi, 2016). In order to better utilize gene editing technology to treat human diseases, new delivery technologies are constantly being developed, such as liposomes, protein delivery, nanoparticles, adeno-associated virus delivery vectors, adenovirus delivery vectors, and lentivirus delivery vectors (Khan, 2019; Nelson & Gersbach, 2016). However, direct insertion / deletion terminated by a single double-strand break is unlikely to cause functional ablation of non-coding genes. Therefore, in terms of lncRNA function, a more comprehensive approach must be considered (Zhen & Li, 2019). Currently, nuclease-inactivated Cas9-based technologies have been reported to target the promoter sequence of a target gene to apply RNA-directed transcriptional regulation without the need to permanently modify the genome. Therefore, through activation (CRISPRa) or inhibition (CRISPRi), it could be possible to control lncRNA expression transiently or stably without altering the genomic sequence (Kampmann, 2018). For example, the CRISPRa-based method has been developed to screen important lncRNAs related to drug resistance. Through this method, it was found that a lncRNA named GAS6-AS2 promotes the activation of the GAS6/TAM pathway, which is a drug resistance mechanism for a variety of cancers, including AML (Bester, et al., 2018). To explore the function of lncRNAs in humans, a CRISPR interference (CRISPRi) platform has been developed to screen growth-regulating lncRNA genes in seven cell types (S. J. Liu, et al., 2017).

4.5 Combinational treatment

As previously mentioned, there is strong evidence that lncRNAs play an important role in cancer drug resistance and cancer immunotherapy resistance. Therefore, the use of targeted lncRNA drugs in combination with chemotherapeutic drugs or immunotherapy antibodies could be an effective strategy for treating cancer (Y. Zhou, et al., 2019). In recent years, breakthroughs in the field of tumor immunotherapy (mainly in the form of immune checkpoint drugs such as PD-1, PD-L1 and CTLA-4 antibodies) have greatly improved the effectiveness of tumor treatments. Nevertheless, only a small percentage of people benefit from tumor immunotherapy, and the majority of patients develop primary or secondary resistance following treatment. Recent studies suggest that many factors affect the efficiency of immune checkpoint therapy, including antigen presentation, tumor mutational burden, and T cell infiltration (Sharma, et al., 2017). Recently, some tumor-associated lncRNAs have

been found to mediate tumor cell immune system evasion by inhibiting antigen presentation and T cell infiltration. For example, LINK-A affects breast cancer cell MHC-1 stability, and NKILA affects CTL infiltration (Huang, et al., 2018). Therefore, we believe that some lncRNAs that lead to immune checkpoint antibody therapy resistance can be effectively utilized in combinatorial therapies by utilizing drugs targeting the lncRNAs together with immune checkpoint drugs (particularly PD1, PD-L1, and CTLA-4 antibodies). For example, treatment with *LINK-A* LNAs in combination with immune checkpoint blockers exhibited synergistic efficacy in repressing breast tumor growth (Q. Hu, et al., 2019). It is possible that a combinatorial treatment that considers lncRNA ASOs or LNAs together with immune checkpoint inhibitors could exhibit synergistic effects on anti-tumor immunity.

Concluding Remarks and Future Perspectives

Ultimately, the role of lncRNAs as therapeutic targets against cancer requires further study. Although emerging evidence has indicated the importance of lncRNAs in regulating the immune escape of tumor cells, this is only the tip of the iceberg. How lncRNAs affect the tumor microenvironment and regulate the function of tumor immune cells needs more research. In terms of clinical application prospects, lncRNAs with tissue-specific expression features are potential targets for cancer immunotherapy.

Future studies of the regulatory roles of lncRNAs in cancer immunotherapy will define the future of the field. Although numerous lncRNAs have been identified so far, it has been challenging to demonstrate the functional relevance of lncRNAs in cancer immunotherapy. To answer this problem, single cell sequencing, CyToF, and cellular and xenograft models have been the commonly used to study the roles that lncRNAs play in cancer and are useful tools in cursory evaluations of their functions. However, conclusions that are more definitive will require representative *in vivo* models of cancer, such as genetic models and patient-Derived xenograft (PDX) models using humanized mice that better characterize the tumor microenvironment. It is critical to determine whether tissue-specific expression of lncRNAs modulates the immune microenvironment and whether organ-specific delivery of ASOs targeting lncRNAs demonstrates effective anti-tumor immunity.

We believe that with the rise of single-cell sequencing technology and the large number of clinical trials involving cancer immunotherapy, numerous lncRNAs with tissue- and cell-type specificities will be identified. Therefore, a clear understanding of the mechanisms of lncRNAs as tumor-cell-intrinsic and tumor-cell-extrinsic factors will be greatly beneficial to expanding current cancer therapy strategies. How to develop safe and effective targeted therapies against tumor-associated lncRNAs and effectively deliver these drugs to tumors will be the primary tasks of this field.

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Abbreviations

LncRNAs	Long noncoding RNAs
TME	tumor microenvironment
SNPs	single-nucleotide polymorphisms
MHC	major histocompatibility complex
B2M	beta-2-microglobulin
MAPK	mitogen-activated protein kinase
IFNγ	interferon-gamma
PD-L1	Programmed death-ligand 1
LINK-A	Long intergenic non-coding RNA for kinase activation
GPCRs	G protein-coupled receptors
PLC	peptide-loading complex
LNAs	Locked Nucleic Acids
APCs	antigen-presenting cell
TNBC	Triple-negative breast cancer
HOTAIR	HOX transcript antisense intergenic RNA
PRC2	Polycomb Repressive Complex 2
MALAT1	Metastasis Associated Lung Adenocarcinoma Transcript 1
MDSCs	Myeloid-derived suppressor cells
SWI/SNF	switch/sucrose nonfermentable
LPS	Lipopolysaccharides
IL-4	interleukin 4
IL-13	interleukin 13
HCC	hepatocellular carcinoma
DCs	dendritic cells
NK	natural killer
CTLs	cytotoxic T lymphocytes
Morrbid	myeloid RNA repressor of BCL2L11 induced death
Th	T helper cell

STAT3	signal transducer and transcriptional activator 3
Tregs	Regulatory T cells
Flatr	Foxp3-specific lncRNA of Treg expected
ASO	Anti-sense oligonucleotides
DOPC	nanoliposomes based on oleylphosphatidylcholine
PDX	patient-Derived xenograft.

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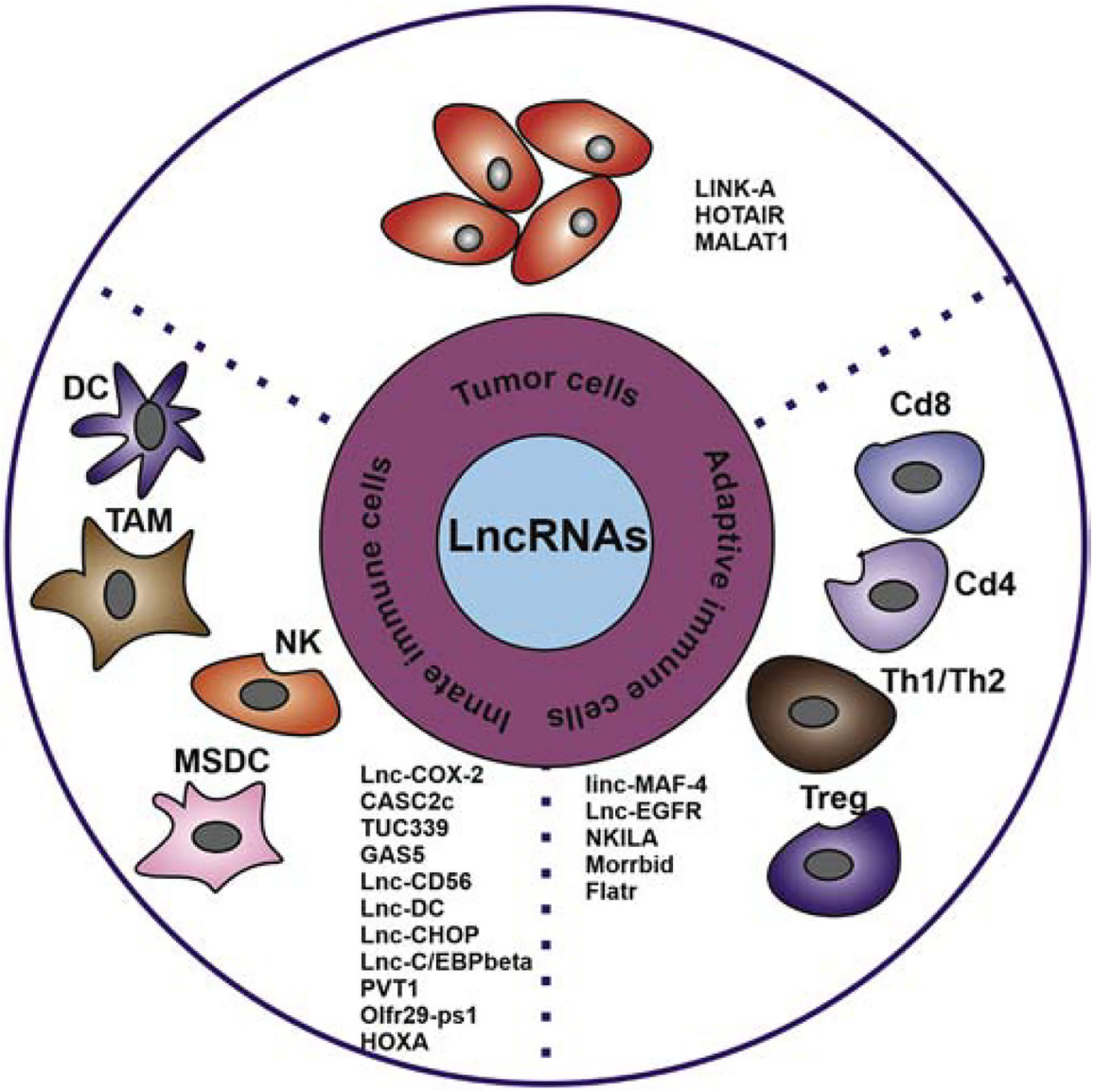

Figure 1. Tumor-cell-intrinsic and tumor-cell-extrinsic roles of lncRNAs.

Intrinsic factor roles of lncRNAs regulate antigen processing machinery and constitutive PD-L1 expression in cancer cells; Extrinsic factors roles of lncRNAs regulate the activity of tumor microenvironment immune cells, such as TAM, CD8+, NK cells, Th1/Th2, DC, and MDSC.

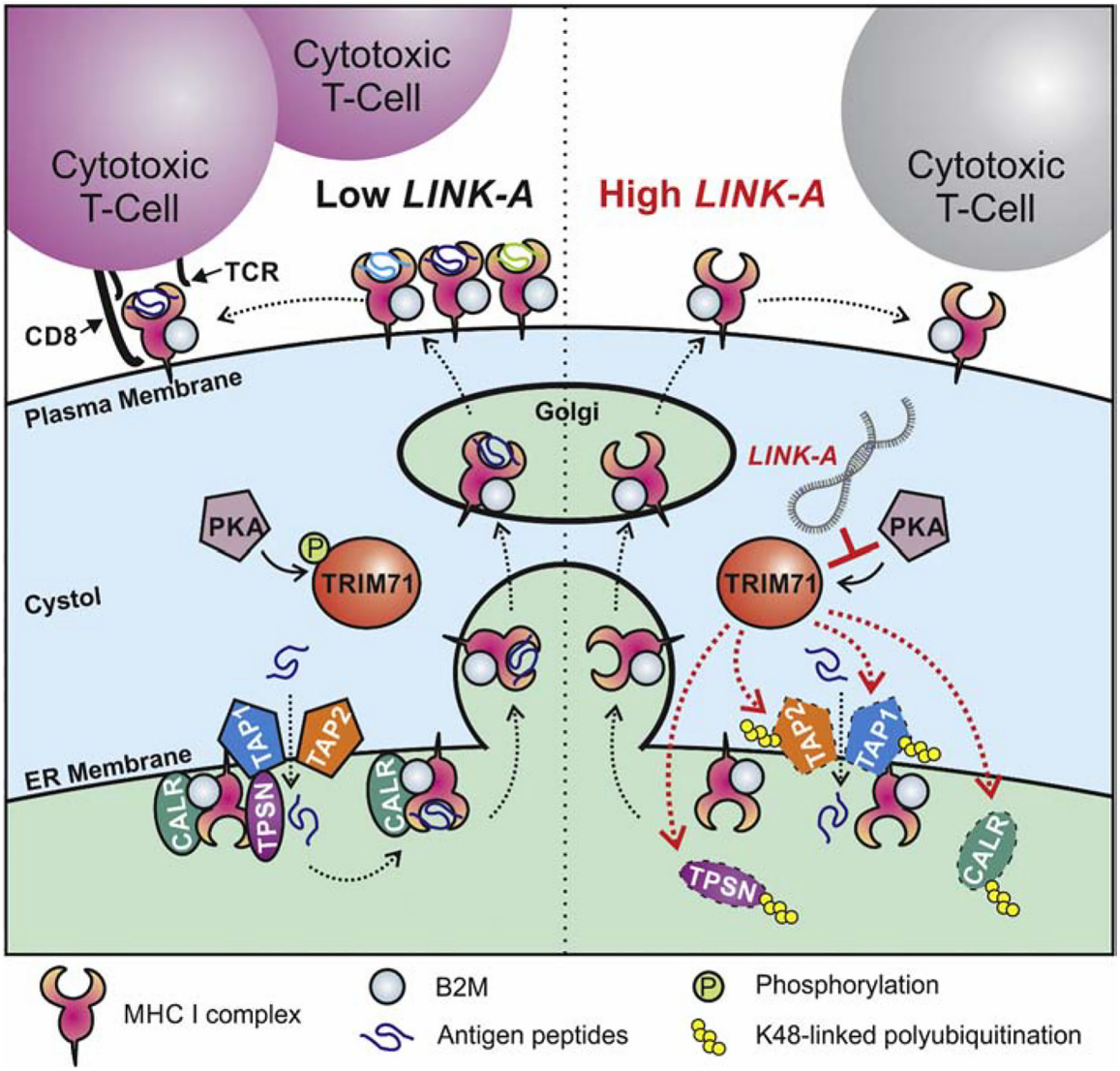

Figure 2. The mechanisms of how *LINK-A* regulates antigen processing machinery.

LINK-A-facilitated, TRIM71-mediated downregulation of antigen presentation machinery impairs antigen presentation during tumor initiation.

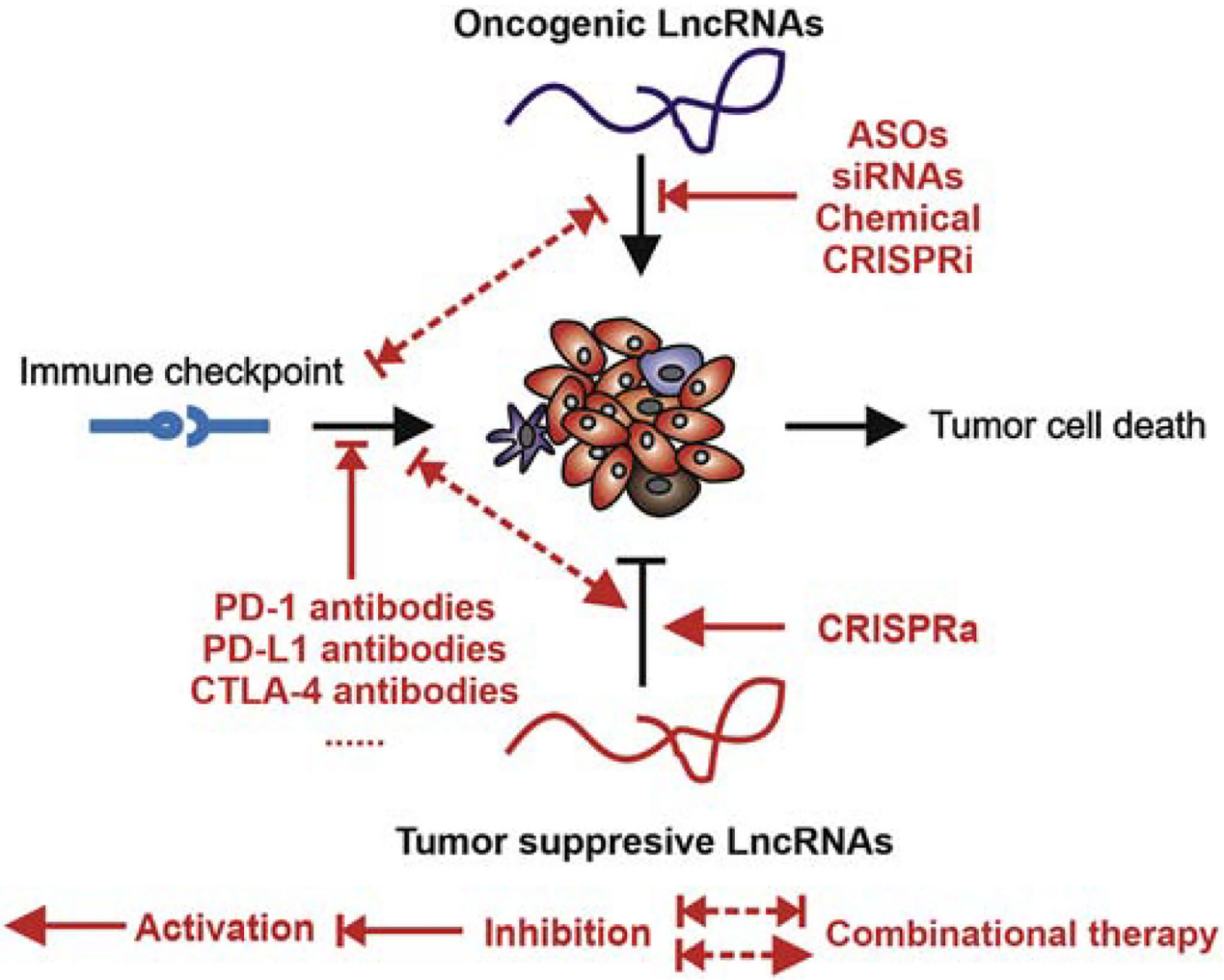

Figure 3. Targeting lncRNAs as a cancer therapy.

Targeting tumor-associated lncRNAs using ASO, siRNA, small molecular inhibitors, and gene editing methods.

Table 1

Oncogenic or Tumor-Suppressive Long Non-coding RNAs involved in cancer immunity regulation

LncRNA	O/T	Cell type	Localization	Immunity-Related Mechanisms	Reference
LINK-A	O	Tumor cell	Cytoplasm	Inhibits breast cancer cell antigen presentation and decrease CTL cells infiltration	(Q. Hu, et al., 2019)
HOTAIR	O	Tumor cell, macroph age and MDSC	Nuclear	Promotes gastric cancer cell (HLA)-G expression via inhibiting miR-152 and miR-148a, also facilitates macrophage and MDSC activity in liver cancer through transcriptional upregulation of chemokine (C-C motif) ligand 2	(Fujisaka, et al., 2018; Song, et al., 2015)
MALAT1	O	Tumor cell and MDSC	Nuclear	Increase the expression of PD-L1 by sponging miR-195 and modulating miR-200a, promotes infiltration of MDSC in lung cancer	(Q. M. Wang, et al., 2019; Wei, et al., 2019; Q. Zhou, et al., 2018)
LncRNA-C ox2	O	Macrop hages	Nuclear	Regulates the inflammatory gene expression in the macrophages via interacts with heterogeneous nuclear ribonucleoprotein A/B and A2/B1, assembles into the switch/sucrose nonfermentable (SWI/SNF) complex and regulating the NF-κb signaling axis	(Bian, Yang, Zhang, Li, Wang, Jiang, Chen, Li, et al., 2019; Carpenter, et al., 2013; Elling, et al., 2018)
CASC2c	T	Macrop hages	Nuclear	Inhibits of M2 polarization and decreased proliferation of tumor cells via downregulating the expression and extracellular production of coagulation factor X (FX)	(Y. Zhang, et al., 2018)
TUC339	O	Macrop hagy	Nuclear	Upregulates the expression of M2 markers after IFN-γ + LPS treatment	(X. Li, et al., 2018)
Morrbid	T	T cell	Nuclear	Controls the expansion, survival, and effector function of CD8+ T cells by regulating the expression of the pro-apoptotic factor Bcl2111 and the strength of the PI3K-AKT signaling pathway	(Kotzin, et al., 2019)
Lnc-CD56	T	NK Cell	Nuclear	Promotes the expression of CD56 and differentiation of NK cells from human CD34 + hematopoietic progenitor cells	(R. Zhang, et al., 2016)
GAS5	T	NK Cell	Nuclear	Enhances the killing effect of NK cell on liver cancer through regulating miR-544/RUNX3	(Fang, et al., 2019)
Linc-MAF-4	T	T Cell	Nuclear	Facilitates the differentiation of T cells toward the TH2 phenotype through regulating MAF transcriptional activities by recruiting chromatin modifiers	(Ranzani, et al., 2015)
Lnc-DC	T	DC Cell	Cytoplasm	Promotes the DC differentiation by activating the transcription factor STAT3 and increase the ability of DCs to stimulate T cell activation	(P. Wang, et al., 2014)
Flatr	O	T Cell	Nuclear	Modulates chromatin accessibility of the FoxP3 gene loci, leading to impaired Treg activity and autoimmunity	(Brajic, et al., 2018)
NKILA	T	T Cell		Regulates T cell sensitivity to AICD by inhibiting NF-κB activity	(Huang, et al., 2018)
Lnc-EGFR	O	T Cell	Cytoplasm	Stimulates the differentiation of Treg cells, thereby inhibiting CTL activity in the tumor area and enhancing the growth of HCC	(R. Jiang, et al., 2017)
Lnc-CHOP	O	MDSC	Nuclear	Promotes MDSC differentiation by interacting with CHOP and C / EBPβ isoforms to encourage C / EBPβ activation and regulate a large number of target transcripts in MDSC	(Gao, Wang, et al., 2018)
Lnc-C/EBP beta	O	MDSC	Nuclear	Controls immune-suppressive function and differentiation of MDSCs by regulating a set of target transcripts, such as Arg-1, NOS2, NOX2, and COX2	(Gao, Sun, et al., 2018)
PVT1	O	MDSC	Nuclear	Promotes the immunosuppressive function of G-MDSCs in vitro and in vivo	(Zheng, et al., 2019)
Olfr29-ps1	O	MDSC	Nuclear	Regulates the differentiation and function of MDSCs through a m6A-modified Olfr29-ps1/miR-214–3p/MyD88 regulatory network	(Shang, et al., 2019)

LncRNA	O/T	Cell type	Localization	Immunity-Related Mechanisms	Reference
HOXA	T	MDSC	Nuclear	delay tumor progression and enhance the antitumor immune response by downregulating the immunosuppression of MDSCs	(Tian, et al., 2018)

O/**T** represents the role of lncRNA as Oncogenic or Tumor-Suppressive Long Non-coding RNAs regulating cancer immunity, respectively.