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Review Article

Roles of long noncoding RNAs on tumor immune escape by regulating immune cells differentiation and function

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Abstract: A long noncoding RNA (lncRNA) transcript is generally more than 200 nucleotides in length and rarely codes for any protein. Currently, many lncRNAs have been identified among mammalian genomes, and their known functions are associated with various physiological activities or pathological processes. Some lncRNAs are dysregulated in a variety of malignant tumors, while increasing evidence indicates that abnormal expression can contribute to the regulation of immune cells in tumors and to shaping the immune response. More specifically, lncRNAs participate in regulating the differentiation of immune cells, also known as myeloid and lymphoid cells, as well as recruiting various immunosuppressive factors to influence the tumor microenvironment, thereby promoting tumor cell immune escape. However, we still know very little about the specific mechanism of lncRNAs in immune escape of cancer. Nonetheless, although unprecedented achievements have allowed the development of a new generation of anti-tumor immune therapies to be applied in clinical trials, the drug resistance caused by immune escape has become a major clinical challenge. The focus of this review is to describe the relationship among lncRNAs, immune cells, and tumor immune escape, in order to identify novel diagnostic and therapeutic targets in human cancers.

Keywords: lncRNA, tumor, immune escape, immune cell

Introduction

According to accumulating research findings, long coding RNAs (lncRNAs) exert critical functions associated with the pathogenesis of different types of malignancies [1]. Moreover, the expression of lncRNAs regulate the cellular activities of the immune system, such as neutrophils, monocytes, macrophages, dendritic cells (DCs), T cells, and B cells, that are closely linked to tumor cell immune escape [2, 3]. As a property that allows tumor growth, tumor immune escape is the result of multiple activities employed by tumor cells during proliferation and metastasis, which lead to the failure of the immune system to recognize and thereby destroy abnormal cells. Thus, tumor-induced immunosuppression leading to immune escape has become one of the most pursued research topics [4]. There are two major pathways which can activate tumor-induced immunosuppression. The first pathway is initiated by the accumulation of immunosuppressive cells around the tumor, followed by the secretion of immunosuppressive factors, which inactivate cytotoxic T lymphocytes (CTLs) and inhibit the responses of immune cells, such as regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), DCs, and M2 macrophages [5-10]. The second pathway relies on inducing the expression of immunosuppressive molecules or their receptors, for example, cytotoxic T-lymphocyte associated protein 4 (CTLA4), lymphocyte activating 3 (LAG3), and programmed death-ligand 1 (PD-L1)/programmed death-1 (PD-1), which are major checkpoints for orchestrating immune responses against tumor cells, and suppressing effector T lymphocytes to achieve tumor-induced immunosuppression [4].

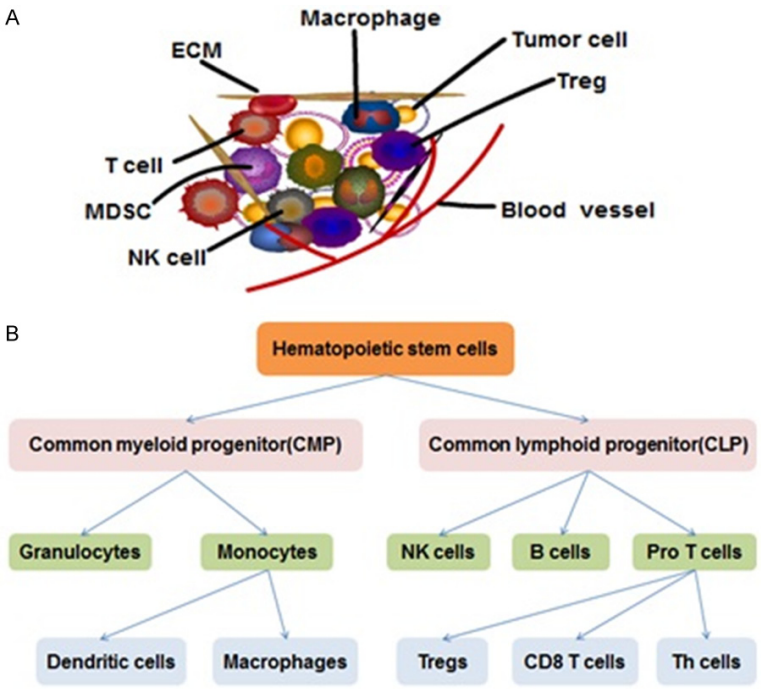

Figure 1. A. Schematic diagram of the tumor microenvironment. TME consists of cell component, the extracellular matrix (ECM) and abundant soluble signaling molecules. B. Schematic representation of the hematopoietic stem cells differentiate into various myeloid and lymphoid cells. NK cells: Natural Killer Cells. Th cells: T helper cells Tregs: regulatory T cells.

Non-communicable diseases are reported to be predominant death-causing factors around the world, and malignant tumors are especially renowned for their high fatality rate and difficulties in treatment, which are predicted to be the major problems threatening public health in the future [11]. Despite the advances achieved in anti-tumor chemotherapy and immunotherapy, treatment outcomes are still unsatisfactory to relieve the huge burden caused by malignancies [4, 11]. Thus, it is essential to investigate the mechanisms involved in tumor immune escape and to identify new diagnostic markers to reduce cancer-related mortality. In the section that follows, we will elaborate on the role and mechanisms employed by lncRNAs for inducing tumor immune escape in various immune-related cells.

Differences in tumor or immune cell-derived lncRNAs

The tumor microenvironment (TME) comprises not only tumor cells but also diverse innate and adaptive immune cells. Immune cells within the TME include immunosuppressive cells, such as tumor-associated macrophages (TAMs), MDSCs, and Tregs, as well as tumor-fighting effector cells, such as cytotoxic $CD8^+$T cells, and natural killer (NK) cells. In addition, it also includes vascular endothelial cells, fibroblast cells, and extracellular matrix (ECM) and multiple extracellular soluble molecules [12, 13] (**Figure 1A**). Together, they help tumor cells escape immunosurveillance and thus form a tumor-promoting microenvironment favoring proliferation and metastasis [14]. However, lncRNAs may be dysregulated to different degrees in both tumor and immune cells. Below, we will discuss the roles and mechanisms involving tumor or immune cell-derived lncRNAs in tumor immune escape (**Table 1**).

Roles of tumor cell-derived lncRNAs

The low-expression of lncRNA BM466146 in breast cancer may allow competing endogenous RNA (ceRNA) to adsorb hsa-miR-224-3p, which in turn up-regulates the expression of CXCL-13, generating CXCL-13 proteins that activate $CD8^+$T cells to exert their cytotoxic role [15]. Overexpression of the lncRNA NNT-AS1 promotes immune escape of hepatocellular carcinoma (HCC) by enhancing the TGF-β signaling pathway and further decreasing CD4+ lymphocyte infiltration [16]. In addition, LncNATP73-AS1 and SNHG9 have been reported to be highly expressed in gliomas and prostate cancer, respectively, and their expression was positively correlated with the score of most immune cell infiltration [17, 18]. However, the effects of lncRNA TP73-AS1, SNHG9, and NNT-AS1 on the corresponding immune cells and the specific mechanism of action have not been thoroughly studied.

Interestingly, tumor cell-derived lncRNAs can also interfere with macrophage polarization in a paracrine manner [19]. LINC00662 up-regulates the expression and secretion of WNT3A by competitively binding to the miR-15a/16/107

Table 1. Examples of mechanisms through which lncRNAs are involved in tumor immune escape by regulating immune cells differentiation and function

Tumor cell-derived lncRNAs						
LncRNA	Cancer type	Expression	Related immune cell	Target gene/pathway	Immune escape-Related Mechanisms	References
BM466146	Breast cancer	Down	$CD8^+$T cells	miR-224-3p/CXCL-13	Activating $CD8^+$T cells to play their cytotoxic role	[15]
NNT-AS1	HCC	Up	CD4 lymphocyte	TGF-β signaling pathway	Reducing CD4 lymphoc-yte infiltration in HCC	[16]
LINC00662	HCC	Up	Macrophages	WNT3A/Wnt/β-catenin signaling pathway	promoting M2 macrophages polarization	[20]
HOTTIP	Ovarian	up	T cells/MDSCs	IL-6/c-Jun/PD-L1	inhibiting T cell proliferation, promoting the differentiation of MDSCs	[38]
HOTAIRM1	Lung cancer	up	MDSCs	Arg1	down-regulating Arg1 expression, delaying tumor progression and enhance the anti-tumor immune respons	[34]
LNMAT1	Bladder Cancer/*Colorectal Cancer*	up	Macrophages	CCL2/VEGFC/VEGFR3 signaling pathway	enhancing lymph angiogenesis and synergistic inhibition on antitumor immunity	[54, 64]
UCA1	Gastric cancer	up	T cells	miR-26a/b, miR-193a/miR-214	up-regulating PD-L1 expression, thus promoting immune escape of gastric cancer cells	[84, 85]
MALAT1	DLBCL	up	$CD8^+$T cells	miR-195/PD-L1	interacting with miR-195 and suppress its expression, which promoted PD-L1 expression and DLBCL tumorigenesis	[94]
SNHG1	Breast cancer/Gastric cancer	Up	Tregs	miR-448/IDO	promoting the differentiation of Tregs	[99, 100]
Immune cell-derived lncRNAs						
LncRNA	Cancer type	Expression	Related immune cell	Target gene/pathway	Immune escape-Related Mechanisms	References
Dnmt3aos	-	Up	Macrophages	Dnmt3a/IFN-γ	regulating the expression of polarization related gene IFN-γ in m-acrophages	[24, 25]
HISLA	Breast cancer	Up	Macrophages	PHD2/HIF-1α	forming a feed-forward loop between TAMs and tumor cells	[27]
AFAP1-AS1	Esophageal cancer	Up	M2 macrophages	miR-26a/ATF2	-	[21]
MM2P	-	Up/down	Macrophages	STAT6	regulating M2-induced angiogenesis and promotes tumor occurrence and growth	[48]
CCAT1	-	up	Macrophages	miR-148A/PKCζ	promoting M2 macrophages polarization	[58]
NEAT1	HCC	up	DCs/T cells	miR-3076-3p/MHCII	inducing T cell hypo-responsiveness, enhance the proliferation of Tregs, and decrease the number of Th17 cells	[72]
Lnc-SGK1	Gastric cancer	up	T cells	SGK1/JunB signaling pathway	stimulating Th2 and Th17 and suppressing Th1 differentiation	[88, 89]
lnc-TIM3	HCC	up	CD8 T cells	p53/MDM2/BCL-2	aggravating the exhaustion of $CD8^+$T cells	[93]
FLICR	-	Up	Tregs	Foxp3	regulating the expression of Foxp3 and autoimmunity	[98]
Lnc-CD56	-	Up	NK cells	CD56	-	[109]
GAS5	HCC	down	NK cells	miR544/RUNX3/NCR1/NKp46	Enhancing the killing effect of NK cell on liver cancer through regulating miR-544/RUNX3	[111]

HCC: hepatocellular carcinoma MDSCs: myeloid-derived suppressor cells DCs: dendritic cells Th cells: T helper cells DLBCL: diffuse large B cell lymphoma Tregs: regulatory T cells NKs: natural killer cells.

cluster. Secreted WNT3A activates Wnt/β-catenin signaling in HCC cells in an autocrine manner, and promotes the proliferation and invasion of HCC cells. Moreover, WNT3A also activates Wnt/β-catenin signaling in macrophages in a paracrine manner and promotes the polarization of M2 macrophages [20]. Exosomes are membrane sacs from different cells that contain many substances, such as nucleic acids, proteins, and enzymes [21, 22]. Circulating exosomes from esophageal squamous cell carcinoma (ESCC) cell lines can be endocytosed by $CD19^+$B cells, thereby inhibiting B cell proliferation and inducing differentiation. Using bioinformatics, it was determined that lncRNAs in exosomes may be involved in the regulation of B cell differentiation [23]. Thus, lncRNAs carried by exosomes of tumor cells may promote immune escape by regulating immune cell differentiation and remodeling of the immune microenvironment.

Roles of immune cell-derived lncRNAs

The lncRNA Dnmt3aos (DNA methyltransferase 3A, opposite strand) is highly expressed in M (IL-4) tissue macrophages and is involved in regulating the expression of Dnmt3a, which regulates the expression of the polarization-related gene IFN-γ in macrophages by modifying DNA methylation [24, 25]. It is well known that macrophage polarization is directly associated with tumor immune escape. The extracellular vesicles (EVs) shuttle is an efficient means of transport of biomolecules across different cell types in the TME and plays a key role in regulating cancer cell biology [26]. For instance, the lncRNA HIF-1α-stabilizing long noncoding RNA (HISLA) delivered by the extracellular vesicle from TAMs enhances the aerobic glycolysis of breast cancer cells by blocking the interaction between PHD2 and HIF-1α, and inhibiting hydroxylation and degradation of HIF-1α. In turn, lactic acid released by glycolytic tumor cells upregulates HISLA in macrophages, forming a feed-forward loop between TAMs and tumor cells [27]. It has been shown that EVs released by primary tumors can be recycled to distant organs, while lncRNAs encapsulated in EVs can shuttle from inflammatory cells to reprogram tumor metabolism [27-29]. We speculate that EVs produced by immune cells may promote immune escape of cancer cells, which is worthy of future research.

Subsequent studies have found that extracellular AFAP1-AS1 can be transferred into KYSE410 cells via their incorporation into M2 macrophage-derived exosomes. M2 macrophage-derived exosomes downregulate miR-26a and promote the expression of ATF2 through the high expression of AFAP1-AS1, thereby promoting the migration, invasion, and lung metastasis of esophageal cancer (EC) [21]. These results provide further evidence that lncRNAs carried by exosomes from cancer cells or immune cells may participate in the pathogenesis and progression of tumors by regulating the microenvironment. However, some lncRNAs are dysregulated in both tumor cells and immune cells, but the source remains unclear. For example, lncRNA PCAT6 is increased in cholangiocarcinoma (CCA) and M2 macrophages. The increase of PCAT6 promotes the production of reactive oxygen Species (ROS) through miR-326 and the regulation of the RhoA/ROCK signaling pathway, and promotes the disorder of mitochondrial and metabolic functions of macrophages, which leads to the M2 polarization of macrophages, and finally leads to the immune escape of the tumor. The lncRNA MIAT has been reported to be mainly distributed in tumors and enriched in $FOXP3^+CD4^+$T cells, $PDCD1^+CD8^+$, and $GZMK^+CD8^+$T cells and participates in the immune escape process of liver cancer [30]; although, the exact molecular mechanisms involved are obscure. The material exchange between tumor cells and immune cells in the TME and the potential molecular mechanisms should be the focus of future research.

Roles of lncRNAs in myeloid cells

The involvement of lncRNAs in the regulation of the differentiation and function of various immune cells have been reported. Derived from hematopoietic progenitor cells, myeloid cells broadly include granulocytes, erythrocytes, megakaryocytes, and monocytes [2, 3] (**Figure 1B**). In mature, short-lived myeloid cells, the myeloid RNA regulator of Bim-induced death (Morrbid) is a conserved lncRNA, which is highly and selectively expressed in the nucleus. To modify the apoptotic rates of neutrophils, eosinophils, and classical monocytes, Morrbid regulates the expression of its adjacent pro-apoptotic gene Bcl2L11 (also known as Bim, located ~150 kb downstream of Morrbid). On

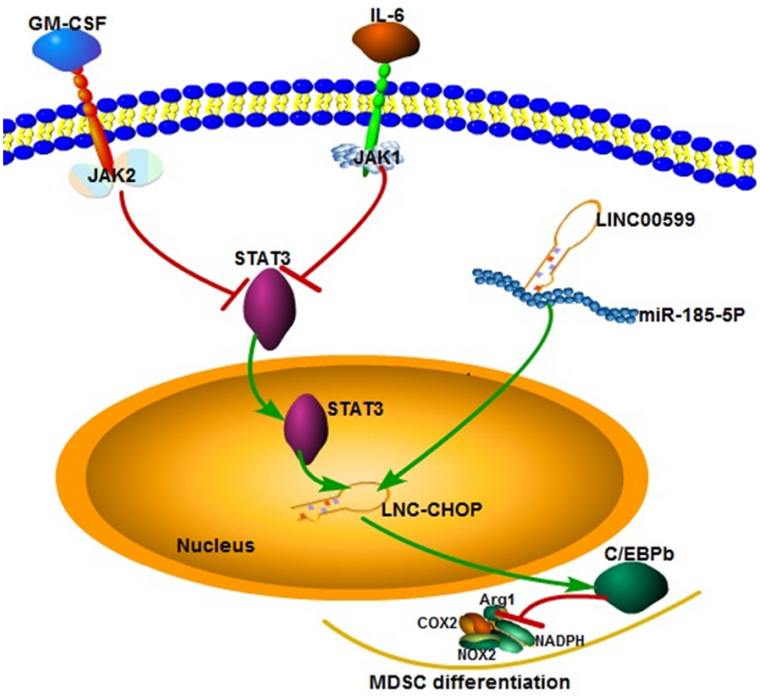

Figure 2. Schematic diagram of the mechanism of lnc-CHOP in MDSCs.

the promoter region of Bcl2L11, Morrbid enables the enrichment of the PRC2 complex to preserve its stability [31]. In the myeloid cells, the effects on Bcl2L11 expression led to precise regulation on their lifespan, which is essential for achieving an appropriate immune response and minimizing the harmful consequences of long-term inflammation, suggesting that relevant lncRNAs have diagnostic and therapeutic potential in inflammatory diseases.

Roles of myeloid-derived suppressor cells

Unlike normal immature myeloid cells, MDSCs fail to mature into macrophages, granulocytes, or DC under the typical chronic inflammatory conditions of the TME; nonetheless, MDSCs are involved in tumor-induced immunosuppression [32]. More specifically, MDSCs strongly disturb the normal cellular functions of $CD4^+$T cells, $CD8^+$T cells, and NK cells, which deactivate the corresponding anti-tumor immune responses and thereby facilitate tumor growth. MDSC-induced immunosuppression has been recognized as the main cause of tumor escape [32, 33]. MDSCs can produce inhibitory molecules, namely arginase 1 (Arg1), inducible nitric oxide synthase (INOS), and ROS, which directly inhibit the Th1/CTL pathway to deactivate the corresponding immune responses against the tumor [34]. In addition, MDSCs can also enhance the release of IL-10 which have potent anti-inflammatory properties, while they suppress the CTL functions by inducing Tregs or developing into TAMs [35]. Recent studies have shown that multiple lncRNAs are strongly linked to the function of MDSCs, including lnc-CHOP, lncRNA RNCR3, lnc-TCF7, lncRNA HOTTIP, HOTAIRM1, lncRNA MALAT1, and lncRNA RUNXOR.

In MDSCs, lnc-chop is mainly located in the nucleus and its expression can be induced in inflammatory and tumor environments. By direct binding with both CHOP and the C/EBPb isoform liver-enriched inhibitory protein, lnc-CHOP can promote C/EBPb isomer LAP activation and up-regulate Arg-1, NOX2, NADPH2 and COX2 expression, thereby regulating a series of target transcripts in MDSCs to promote MDSC differentiation, which is closely associated with MDSC-induced immunosuppression during the anti-tumor inflammatory responses [36]. Interestingly, retinal non-coding RNA3 (RNCR3), also called LINC00599 in the human lncRNA database, acts as a ceRNA by sponging miR-185-5p, thereby promoting CHOP expression during MDSC differentiation [37] (**Figure 2**).

The two lncRNAs, HOTTIP and lncTCF7, are expressed in ovarian and liver cancer cells, respectively [38, 39]. HOTTIP can up-regulate the secretion of IL-6 by targeting c-Jun and then up-regulates neutrophil PD-L1 expression by promoting the phosphorylation of STAT3, which inhibits T cell proliferation, promotes the differentiation of MDSCs, and ultimately enhances ovarian cancer escape [38]. The pro-inflammatory cytokine IL-6 is considered an effective activator of STAT3. Induced by transactivation of IL-6/STAT3, the lncRNA TCF7 has been reported to be involved in epithelial-mesenchymal transition (EMT), invasion, and migration of malignant cells in liver cancer [39].

HOTAIRM1, MALAT1, and RUNXOR are lncRNAs commonly expressed in lung cancer tissues [40-42]. The MALAT1 gene is located on chromosome 11q13, and the transcript has negative regulatory effects on MDSCs and facilitates the tumor growth of lung cancer, and especially promotes NSCLC cells to proliferate, invade, and migrate by sequestering endogenous miR-200a-3p [41, 42]. For kidney cancer, the transcription of MALAT1 is activated by c-Fos, thereby interacting with EZH2 and miR-205, to promote the development of invasive kidney cancer [40]. HOTAIRM1 is an intergenic lncRNA, as its gene locates between human HOXA1 and HOXA2 genes. HOTAIRM1 expression is specifically detected in the myeloid lineage, and the highest expression is detected in the terminal stage of monocyte differentiation [34, 43]. Overexpression of HOTAIRM1 can down-regulate Arg1 expression, as well as immunosuppression of MDSCs, to delay tumor progression and enhance the anti-tumor immune response [34]. LncRNA RUNXOR regulates MDSC-induced immunosuppression by targeting RUNX1 in lung cancer, while RUNXOR recruits EZH2 and RUNX1 to allow epigenetic regulation of the RUNX1 gene in acute monocyte leukemia (AML). In addition, miR-9 regulates MDSC growth and functions by targeting RUNX1 [35, 44]. Therefore, it has been hypothesized that RUNXOR and miR-9 might synergistically regulate RUNX1 expression at both the transcriptional and post-transcriptional levels [44]. However, the specific regulatory mechanisms of HOTAIRM1 and RUNXOR in tumor conditions, especially the factors causing the down-regulation of MDSC functions via HOTAIRM1 expression, remain to be resolved.

Roles in macrophages

Macrophages are key cells in the innate immune system, as they have key functions in normal and pathological tissue remodeling, including angiogenesis, basement membrane rupture, leukocyte infiltration, and immunosuppression [45-47]. According to their different activation modes and functions, macrophages are destined for polarization and become one of two phenotypes: M1 (classically activated macrophages) and M2 (alternatively activated macrophages). It is noteworthy that macrophage polarization is an important component of cancer pathogenesis. Although both M1 and M2 macrophages have been detected in malignant tissues, the presence of M2 is predominant and tends to promote tumor progression and angiogenesis [48]. Normally, M1 macrophages exert critical functions to enable host defense and inflammation, while M2 macrophages are involved in tissue repair [49]. Further, the M1 and M2 phenotypes can convert to the phenotype of the other under the stimulation of some chemokines [50, 51]. LncRNAs are associated with the modification of macrophage gene expression, which contributes to regulating the response of macrophage gene expression to polarizing environmental conditions [52]. In addition, lncRNAs can promote the metastasis of malignant tumors by affecting the expression of chemokines [53-55]. Below, the section focuses on how the molecular mechanisms of diverse lncRNAs promote tumor immune escape by affecting the polarization and function of macrophages.

M2-polarization of macrophages is essential to tumor immune tolerance [56]. Recent studies have shown that M2-TAM (infiltrating macrophages in tumors) could drive the development of primary and metastatic tumors through their effects on the decomposition and deposition of the basement membrane, angiogenesis, leukocyte recruitment, and immunosuppression [56, 57]. Both lncRNA-MM2P and CCAT1 promote the occurrence and migration of tumors by regulating M2 polarization of macrophages [48, 58]. However, their specific mechanisms differ to a large extent. It has been reported that CCAT1 knockdown promoted M2 macrophages polarization and tumor cells migration by up-regulating miR-148A to down-regulate the expression of PKCζ [58]. In comparison, lncRNA-MM2P has been recognized as the only lncRNA which is up-regulated in M2 macrophages and down-regulated in M1 macrophages during the polarization of macrophages. Mechanistically, lncRNA-MM2P can alter the phosphorylation of STAT6 to regulate M2 gene expression in macrophages, which regulates M2-induced angiogenesis and promotes tumor occurrence and growth [48]. Although no evidence has revealed the molecular pathways involved in lncRNA-MM2P regulation of STAT6 activation, the cytoplasmic localization of lncRNA-MM2P suggests that subsequent research should probe into the interactions between phosphatases (namely SHP1 or SHP2)

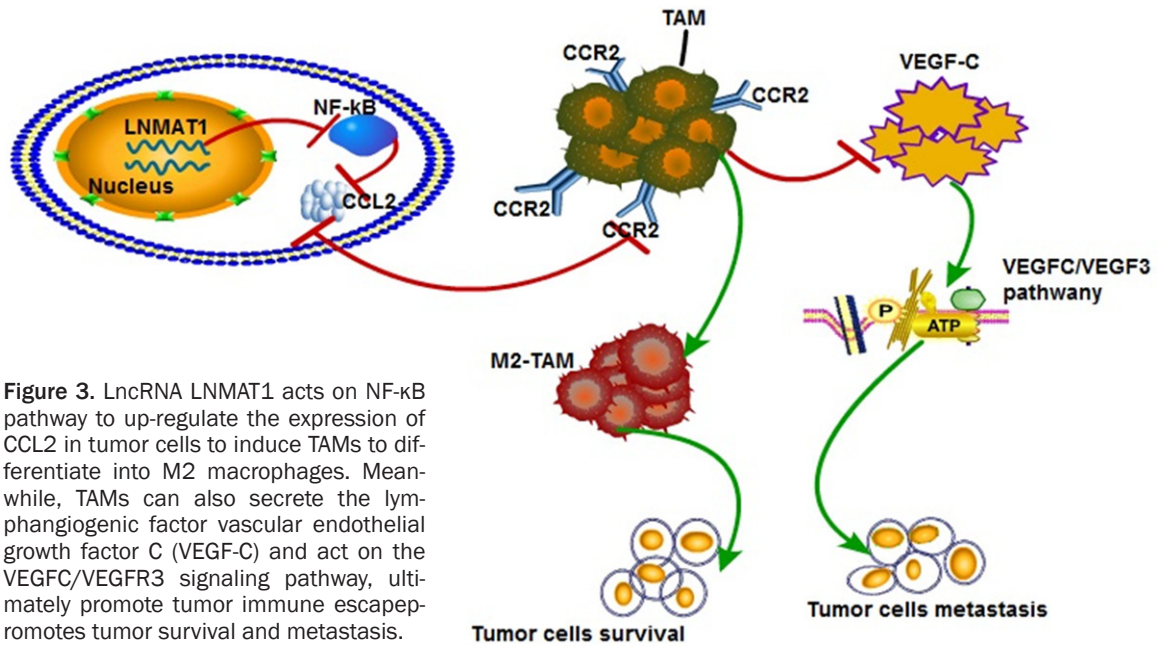

Figure 3. LncRNA LNMAT1 acts on NF-κB pathway to up-regulate the expression of CCL2 in tumor cells to induce TAMs to differentiate into M2 macrophages. Meanwhile, TAMs can also secrete the lymphangiogenic factor vascular endothelial growth factor C (VEGF-C) and act on the VEGFC/VEGFR3 signaling pathway, ultimately promote tumor immune escapepromotes tumor survival and metastasis.

and STAT6. But this hypothesis needs to be further confirmed.

Macrophage-associated receptor CCR2 is an activated receptor that performs key roles in anti-tumor immune responses, while the CCL2-CCR2 axis can induce TAM to differentiate into M2 with immunosuppressive effects, thus promoting tumor development and metastasis [59-62]. Blocking CCL2/CCR2 can eliminate the communication between tumor cells and macrophages, remodel the microenvironment of tumor education, and inhibit the M2 polarization of TAMS [54]. When CCL2 and CCR2 are unregulated in tumor tissues, the tumor infiltrating $CD68^{+}$TAMs are increased and the intratumoral $CD8^{+}$TIL is decreased, which directly affects EMT, extracellular matrix remodeling, and angiogenesis, thereby modifying the inflammatory microenvironment of the tumor and ultimately promoting immune response escape [54, 59, 63]. Interestingly, recent studies have found that lncRNAs are closely associated with CCL2. For example, the lncRNA LNMAT1 gene is located on human chromosome 14q11.2 and can up-regulate the expression of CCL2 in tumor cells, and then recruit TAMs, which secrete the lymphatic factor vascular endothelial growth factor C (VEGF-C) to enhance lymph angiogenesis and synergistic inhibition on antitumor immunity through the VEGFC/VEGFR3 signaling pathway ultimately contributing to tumor growth and lymphatic metastasis [54, 64]. Moreover, recent studies have also reported that the activation of the NF-κB pathway could up-regulate CCL2 expression to induce TAM differentiation and promote tumor metastasis [65, 66] (**Figure 3**). According to the prior studies, lncRNAs can promote tumor immune escape by modulating the differentiation and functions of macrophages. Therefore, they are promising candidates for further studies as new diagnostic and therapeutic targets for tumor immunotherapy.

Roles of dendritic cells

Among mammalian immune cells, DCs have the most remarkable antigen-presenting potency, which allow DCs to serve as a bridge between the innate and adaptive immune system. The initiation of antigen-specific immune responses relies on the normal functions of DCs [67]. Apart from managing antigen presentation, DCs are responsible for generating appropriate amounts of T cells in response to specific pathogens [43]. Accordingly, DCs hold a vital importance in the immune balance in determining pathogen clearance or escape. The maturation of DC is the key to immune activation, and DC dysfunction is a critical mechanisms used by tumors to evade the control of the immune system [43, 67]. LncRNA regulation is of great significance in the process of DC

differentiation and maturation. Recently, several individual research teams have demonstrated that lncRNAs promote tumor immune escape by regulating DCs functions and immune tolerance. The list of the concerned lncRNAs includes lnc-DC, lnc-MC, HOTAIRM1, and NEAT1.

Lnc-DC is exclusively expressed on human DCs. The lncRNA transcripts directly bind to STAT3 in the cytoplasm to promote STAT3 phosphorylation on tyrosine-705 by preventing the binding and dephosphorylation of STAT3 and SHP1, thereby promoting STAT3 signal transduction and DC differentiation. STAT3 activation is the key factor involved in the formation of the immune-suppressive TME [68]. In addition, the transcription factor PU.1 has been found to have a typical binding motif (+44 to +50 nt relative to the TSS) in the lnc-DC promoter region, while PU.1 performs a crucial function in DC differentiation [68, 69]. Interestingly, based on PU.1 regulation, it has been reported that another lncRNA, namely lnc-MC, can interact with miR-199a-5p directly and release the expression of ACVR1B. ACVR1B can promote the activation of the TGF-β signaling pathway by increasing the levels of phosphorylated Smad2 and Smad3, thus increasing C/EBPα expression, and ultimately promoting the differentiation of monocytes and macrophages [69].

To exert an inhibitory effect on DC differentiation, HOTAIRM1 can form a ceRNA network with miR-3960 and HOXA1. Furthermore, during DC differentiation, HOTAIRM1 expression is strictly regulated by epigenetic factors, for instance, histone modifiers H3K4me3 and H3K27me3 [43]. These results suggest that lncRNAs may be involved in post-translational modification and the establishment of cancer epigenetic activities.

NEAT1 is predominantly localized in the nucleus. The up-regulation of NEAT is closely related to a variety of immune-mediated disorders, neurodegenerative disorders, and cancers, especially to the immune responses and regulatory mechanisms of cancers [70, 71]. NEAT1 expression in LPS-induced DC maturation is significantly up-regulated. The lncRNA can enable the interaction between NLRP3 inflammasome bodies and miR-3076-3p to induce tolerogenic DCs. NEAT1 knockdown can inhibit the expression of co-stimulatory molecules (CD80, CD86, and MHCII), induce T cell hyporesponsiveness, enhance the proliferation of Tregs, and decrease the number of Th17 cells [72]. However, the epigenetic regulatory mechanism of NEAT1 remains largely undetermined. To date, it has been recognized that multiple lncRNAs can significantly affect human DC differentiation to determine tumor immune escape. But their exact mechanism in modulating DC function has not been well understood, and this field deserves further exploration.

Roles of lncRNAs in lymphoid cells

Lymphoid cells are important cellular components of the human immune response and are the main executors of most immune functions conducted by the lymphatic system. Lymphocytes are classified into T cells, B cells, and NKs according to their migration patterns, expression of cell-surface molecules, and functions [2, 3]. In addition, recent reports have shown that the development and function of lymphocytes are regulated by lncRNAs, and thus affect the immune escape of tumors.

Roles in T cells

In healthy individuals, the immune system recognizes and destroys tumor cells. This immune surveillance mechanism is the body's main defense against cancer. In this context, T lymphocytes are the main players in recognizing and destroying cancer cells [73, 74]. However, when the number of tumor-specific T cells is low, suppression of T cell infiltration into TMEs and T cell dysfunction/failure occurs, and the immune system is unable to destroy tumor cells, leading to tumor immune escape [75]. Nonetheless, most studies on the potential interaction between lncRNA, T cells, and tumor immune escape have focused on the PD-1/PD-L1 pathway, and rarely involve other immune checkpoints. Only a few studies have shown that some microRNAs play a role in mediating immune escape induced by T cells. For example, overexpression of miR-138 and miR-28 in T cells can lead to decreased expression of CTLA-4 and TIM-3, respectively [76, 77]. It has been suggested that lncRNAs may lead to T cell-induced immune escape through ceRNA. However, other immune checkpoint molecules such as LAG3 and BTLA have received less attention. Thus, the following discussions on T cell-mediated tumor immune escape will main-

ly focus on the PD-1/PD-L1 pathway. PD1/PDL1 inhibitors have made breakthrough achievements in clinical practice, and their mechanisms of action are closely related to the activity and function of T cells [78-80].

T cells can express PD-1, also known as CD279, which is the receptor for PD-L1 ligand. PD-1 can also be expressed by activated NK cells, DCs, B cells and some non-hematopoietic cells. PD-L1 is up-regulated in specific tumor cells. T cells expressing PD-1 can bind to tumor cells expressing PD-L1, and thus result in a T cell exhaustion phenotype and induce tumor immune escape [4, 81, 82]. The relevant lncRNAs are dynamically regulated during the life cycle of T cells, and the lncRNA expression pattern relies on PD-L1 expression levels [83].

The lncRNA UCA1 is an independent prognostic biomarker of gastric cancer patients, and its high expression is positively correlated with the malignant pathological features of gastric cancer, such as high and low differentiation [84]. UCA1 inhibits the expression of miR-26a/b, miR-193a, and miR-214 through direct interaction, and then up-regulates PD-L1 expression, thus promoting the proliferation, migration, and immune escape of gastric cancer cells [84, 85]. Additionally, EBV-associated gastric cancer (EBVaGC) can evade T cell immunity and strongly inhibit T cell proliferation through PD-1/PD-L1 interaction [86]. Interestingly, insulin can promote the production and expression of PD-L1 protein through the PI3K/Akt/mTOR pathway, while epidermal growth factor (EGF) promotes the production and transport of PD-L1 in colon cancer stem cell (CSCs), suggesting that high levels of insulin and EGF in the TME may be risk factors for tumor escape [86, 87]. Below, we will discuss how lncRNAs promote tumor immune escape in three types of T cells: T helper cells, $CD8^+$T cells, and regulatory T cells.

Roles of lncRNAs in T helper (Th) cells: Lnc-SGK1 expression has been detected in T cells of gastric cancer and in peripheral tissue, following *Helicobacter pylori* infection and high-salt diets (HSD) [88]. Lnc-SGK1 stimulates Th2 and Th17, while suppressing Th1 differentiation through the SGK1/JunB signaling pathway, and has been related to poor prognosis of GC patients [88, 89]. In addition, the expression of PD-1, CTLA4, and hepatitis A virus cell receptor 2 (also known as TIM3) can be significantly increased by tumor infiltrating Th cells in HCC. Specific ligands expressed by tumor cells bind to inhibitory receptors on immune cells, to down-regulate the immune response mediated by $CD4^+$Th cells and $CD8^+$CTL through inhibitory pathways involving receptors PD-1, TIM3, LAG3, and CTLA4, ultimately resulting in tumor immune escape [90].

Roles of lncRNAs in $CD8^+$T cells: In the immune system, $CD8^+$T cells are among the most active warriors against viral infection and cancer. In general, antigens expressed by most tumor cells can be recognized by $CD8^+$T cells to trigger anti-tumor immune responses. However, the role of lncRNAs in $CD8^+$T cell differentiation and function are still recognized as relatively limited [91, 92]. Only a handful of lncRNAs have been identified in different subsets of $CD8^+$T cells, and the functions of most are unclear. For example, lnc-TIM3 can aggravate the exhaustion of $CD8^+$T cells by enhancing the relative transcriptional activation of p300-dependent p53 and anti-apoptotic genes (including MDM2 and BCL-2) [93]. LncRNA MALAT1 can regulate PD-L1 expression by sponging miR-195, thus regulating the proliferation, apoptosis, migration, and anti-cytotoxicity of $CD8^+$T cells, and ultimately regulating the onset, migration, and immune escape of diffuse large B cell lymphoma (DLBCL) [94]. The lncRNA NEAT1 may participate in the immune escape of HCC by down-regulating the miR-155/TIM-3 pathway, inhibiting the apoptosis of $CD8^+$T cells, and enhancing its anti-tumor activity [95].

Roles of lncRNAs in regulatory T cells: As the basic factor maintaining the dynamic balance of immunity, Tregs are a class of lymphocytes that negatively regulate the immune response of the body, and they are also involved in the escape of tumor cells from immune surveillance and in chronic infections [96, 97]. Foxp3 is a specific biomarker of Tregs. Treg-induced immunosuppression is now considered to be a key factor enabling tumors to escape immune-mediated destruction [96]. Overexpression of Treg cells can down-regulate CTL in tumor patients and reduce their cytotoxic activity against tumor cells, thus inducing the immune escape of tumor cells [97]. LncRNAs, such as lncRNA FLICR, lncRNA-SNHG1, and lnc-EGFR, are closely associated with the differentiation and function of Tregs.

LncRNA FLICR is specifically expressed in Tregs, regulating the expression of Foxp3 and autoimmunity, which results in the two fold- to five fold-decrease in levels of FoxP3 protein in a subset of Tregs. The stabilization of Foxp3 is essential for maintaining the dynamic balance of Tregs and in preventing autoimmunity [98]. LncRNA-SNHG1 can promote the proliferation of gastric cancer cells by regulating DNMT1 [99]. Interestingly, it can also promote the differentiation of Tregs by down-regulating the expression of miR-448 and up-regulating the levels of indoleamine-2-dioxygenase (IDO), which ultimately results in immune escape from breast cancer [100]. Lnc-EGFR specifically binds to EGFR through its R1 domain, to block the interaction and ubiquitination of c-CBL and stabilizes its auto-activation and the activation of the downstream AP-1/NF-AT1 axis. Therefore, EGFR expression leads to Treg differentiation and CTL inhibition, thus promoting immune escape and growth of HCC [101]. In conclusion, lncRNAs regulate the differentiation and function of various T cells through different mechanisms to promote tumor immune escape, and these activities have the potential to be targeted by therapeutic agents.

Roles of lncRNAs in natural killer cells

NK cells are considered to be the first line of defense against infection and cancer due to their ability to eliminate viral infection or transformed cells [102]. Defects in human NK cells can lead to severe immunodeficiency [103]. Natural-killer group 2 member D (NKG2D) on the surface of NK cells is an activated receptor that plays a key role in anti-tumor immune response. Its major ligands are UL-16 binding protein (ULBP) and MHC class I chain-related antigen A/B (MICA/B) expressed on the surface of tumor cells [104, 105]. These NKG2D ligands can bind to NKG2D and induce NK cells to exert cytotoxic effects [104, 106]. Tumor cells and the tumor-induced microenvironment can alter the expression of receptors on the surface of NK cells, block NKG2D-activated signaling, or down-regulate the expression of tumor cell surface ligands MIC A/B and ULBP, ultimately resulting in tumor immune escape [107, 108]. LncRNAs can play key roles in NK cell activities.

CD56 is an important immune marker of NK cells that participates in the differentiation and development of NK cells. Lnc-CD56 is highly expressed in human NK cells and has a positive regulatory effect on gene expression of CD56 [109]. LncIFNG-AS1 is relatively abundant in NK cells and can promote the secretion of IFN-γ by human NK cells [110]. LncRNA GAS5 is involved in regulating the tumoricidal effect of NK cells on liver cancer cells through the miR544/RUNX3//NCR1/NKp46 pathway [111] (**Figure 4**). However, the detailed molecular mechanism of the interaction between lncRNAs and NK cells to promote tumor immune escape deserves further study. It is suggested that the studies focusing on NK cells may represent a new direction for identifying novel approaches to tumor therapy.

Conclusion

Following the significant advances in the field of cancer immunity during the last decade, there is an increasing interest in lncRNAs which mechanistically interact with immune cells to promote immune escape from tumors. Despite the many important achievements in research on the tumor immune escape response and immunotherapy, there are still some processes that need to be explored, such as the underlying mechanisms of immune escape, as well as the constraints of tumor antigens and tumor immune tolerance, which severely limit the outcomes of tumor immunotherapy [112, 113]. Throughout this review, we have provided the latest findings relevant to the mechanisms involving lncRNAs on immune cell regulation and the resulting tumor immune escape (**Figure 5**). The potential of lncRNA and its corresponding regulation of immune checkpoints as novel diagnostic biomarkers and therapeutic targets in the treatment of malignant tumors has been emphasized. Although the current immunotherapy strategies mainly focus on T-cell-mediated immunity, an increasing number of studies in recent years have determined that B cells can also act as important immune regulators of cancer progression [114]. However, the interaction between lncRNAs and B cell-mediated immune escape is still poorly studied.

Tumor or immune cell-derived lncRNAs can regulate immune cells to shape the tumor suppressive microenvironment, which further introduces broad prospects for their application in clinical diagnosis and immunotherapy. It is pos-

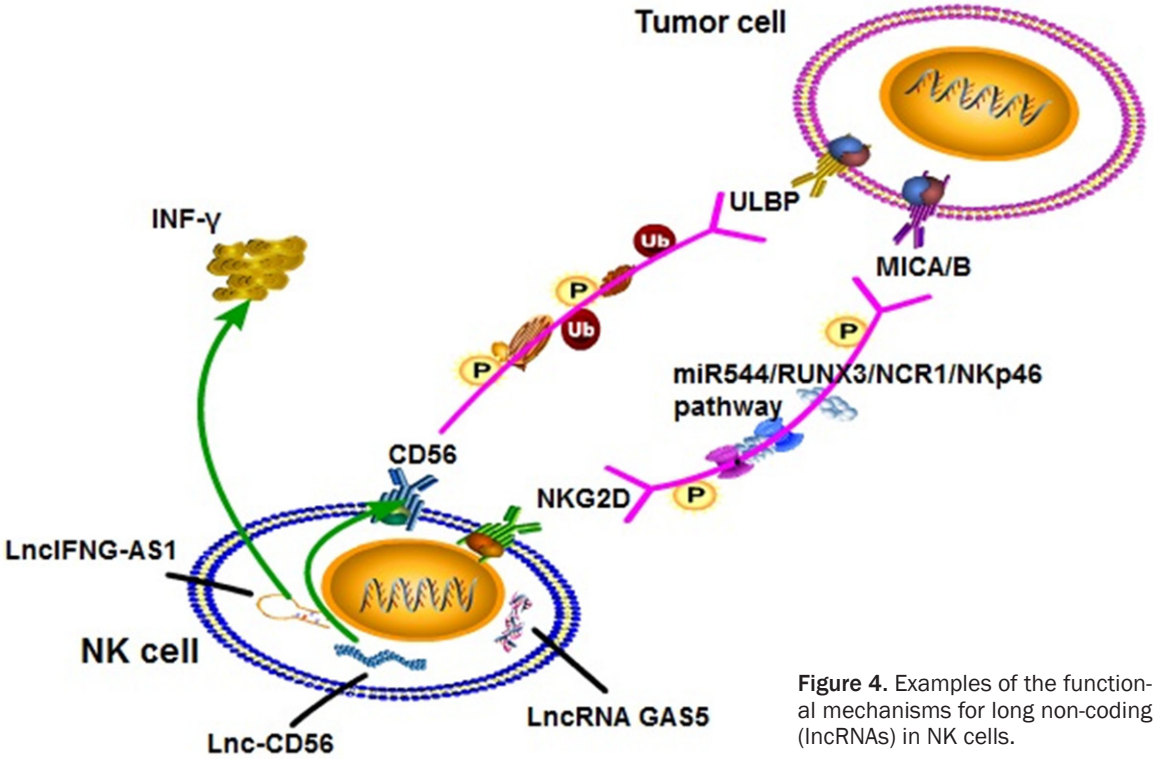

Figure 4. Examples of the functional mechanisms for long non-coding (lncRNAs) in NK cells.

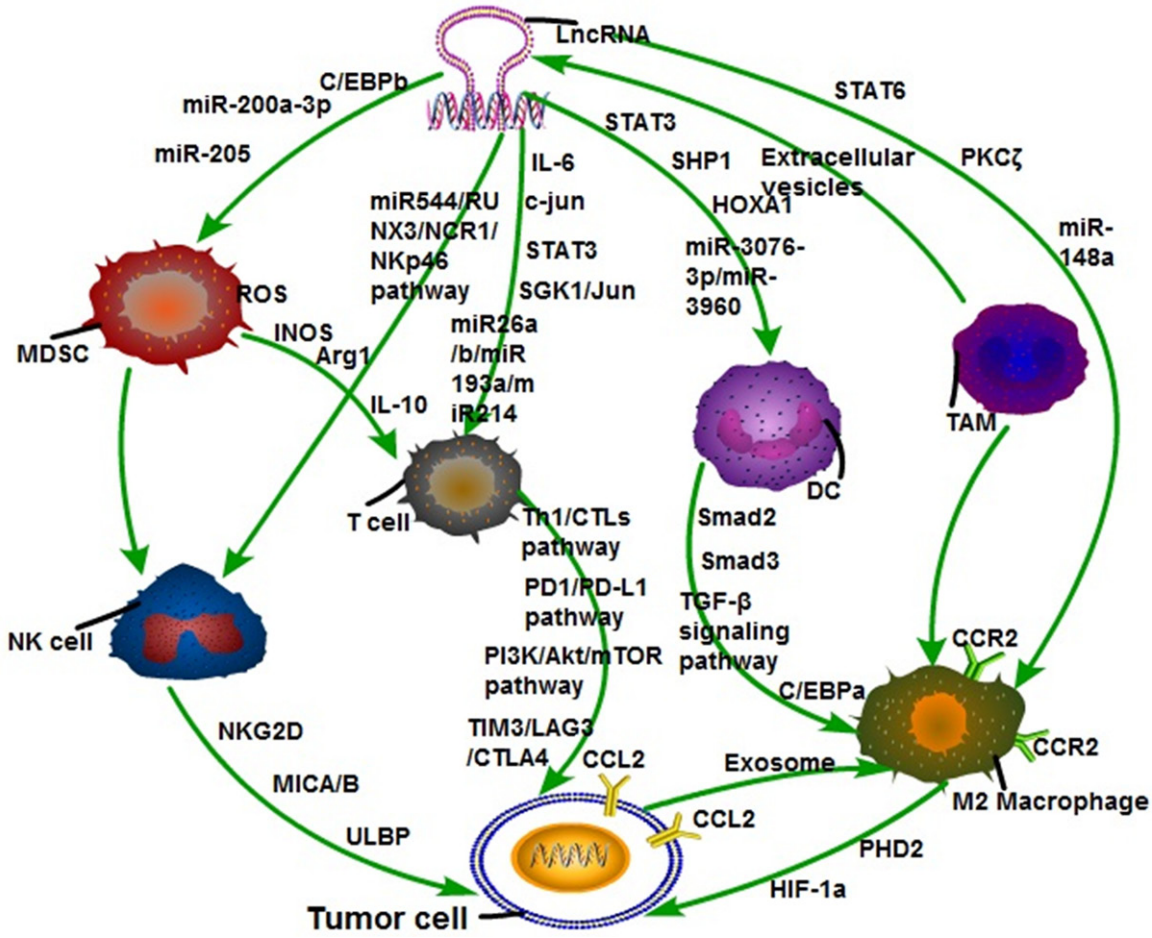

Figure 5. Schematic diagram of the mechanisms involving lncRNAs on immune cell regulation and the resulting tumor immune escape.

sible to inhibit or restore the expression of lncRNAs to achieve tailor-made therapeutic applications in a manner that is specific to cancer.

Despite the diversity in approaches and therapeutic strategies of lncRNA-related immunotherapy, there are still many limitations. The main challenge is how to deliver the individual molecules specifically to the target cell [115]. Due to the complexity of the immune system, research on the function of lncRNAs in cancer immunity has just begun. Currently, to our knowledge, there are no clinical trials in which lncRNAs are used alone or in combination with other agents to treat cancer. The research of lncRNA in cancer therapy is still focused on investigations at the molecular cytological level, using zebrafish and mouse tumor models. Therefore, our understanding of lncRNAs is only at the beginning of its journey, and their role as biomarkers and targets for cancer immune escape needs to be further explored.

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Disclosure of conflict of interest

None.

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