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REVIEW

LncRNAs in Immune and Stromal Cells Remodel Phenotype of Cancer Cell and Tumor Microenvironment

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Abstract: Emerging studies suggest that long non-coding RNAs (lncRNAs) participate in the mutual regulation of cells in tumor microenvironment, thereby affecting the anti-tumor immune activity of immune cells. Additionally, the intracellular pathways mediated by lncRNAs can affect the expression of immune checkpoints or change the cell functions, including cytokines secretion, of immune and stromal cells in tumor microenvironment, which further influences cancer patients' prognosis and treatment response. With the in-depth research, lncRNAs have shown great potency as a new immunotherapy target and predict immunotherapy response. The research on lncRNAs provides us with a new insight into developing new immunotherapy drugs and predicting the outcome of immunotherapy. With development of RNA sequencing technology, amounts of lncRNAs were found to be dysregulated in immune and stromal cells rather than tumor cells. These lncRNAs function through ceRNA network or regulating transcript factor activity, thus leading abnormal differentiation and activation of immune and stromal cells. Here, we review the function of lncRNAs in the immune microenvironment and focus on the alteration of lncRNAs in immune and stromal cells, and discuss how these alterations affect tumor growth, metastasis and treatment response.

Keywords: lncRNA, immune and stromal cells, tumor microenvironment, differentiation, cytokine secretion

Introduction

At present, cancer poses the highest clinical, social, and economic burden in terms of cause-specific Disability-Adjusted Life Years among all human diseases.[1] The cellular environment, in which tumor cells are located, referred as tumor microenvironment (TME), steps into the limelight since its importance in cancer incidence, progress and treatment response.[2] In TME, the infiltration and function of immune and stromal cells were reprogrammed via multiple ways. The growth-promoting signals and intermediate metabolites were released to remodeling the tissue structure to build a suitable environment for tumor progression and metastasis.[3] By interacting with the microenvironment, tumor cells acquire more vigorous proliferation and metastasis capabilities.[4] Moreover, immune escape in tumor microenvironment has been indicated a treating target of cancers. For instance, immunotherapy recovers activity of exhausted CD8+ T cells to suppress tumor cells.[5] However, the pivotal elements and pathways of immune tolerance in TME were still obscure.

Long noncoding RNA (lncRNA) is a non-protein coding RNA with more than 200 nucleotides. LncRNAs were reported to regulate shearing, transposon silencing, and mRNA translation.[6] In cancer cells, several oncogenic lncRNAs were shown to promote the progression of cancer by competitively binding miRNAs. For instance, the downregulation of

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the oncogenic lncRNA MALAT-1 was shown to suppress the expression of immune-suppressive cytokines,[7,8] and the lncRNA CCAT1 and H19 were reported to target PD-L1 expression in cancer cell lines.[9,10] In TME, lncRNAs can act as intermediaries between tumor cells and other cells through exosomes and regulate immune cell function through intracellular pathways, such as PD-1/PD-L1 pathway, a major target of immunotherapy in cancers.[11,12] Previous studies have suggested that lncRNAs exhibit a non-negligible effect on the formation of immune suppression in the immune microenvironment[13] and can be used as targets to relieve immunosuppression to predict the efficacy of immunotherapy.[14]

However, previous studies mainly focused on lncRNAs or exosomes derived from tumor cell, relatively ignoring the dysregulation of lncRNAs in immune and stromal cells. Therefore, we review the effects of lncRNAs in immune and stromal cells, and discuss their effect of lncRNAs on the differentiation and function of immune and stromal cells, which remodels phenotype of cancer cell and tumor microenvironment.

LncRNAs Participate in Development and Differentiation of Lymphoid and Myeloid Cells Without Existence of Cancer

Development of immune and myeloid cells was controlled by multiple processes from hematopoietic stem cells (HSCs) to specialized cell types, and lncRNAs were involved in each stage, such as myeloid and lymphocyte commitments, in which LncHSC-1 promoted HSC to myeloid commitment, while lncHSC-2 to lymphocyte commitment.[15] Due to characteristics of lncRNAs expression, unique repertoire of their expression was observed in different cells. In the following texts, we will simply discuss the role of lncRNAs in development and differentiation of lymphoid and myeloid cells without existence of cancer.

In lymphoid cells, T cell, B cell and NK cell were differentiated from their progenitors. Based on array-based expression profiling of eleven distinct flow-sorted B-cell subsets, 272 lincRNAs, 471 antisense RNAs, 376 pseudogene RNAs, and 64 lncRNAs were found to be associated with distinct stages of B-cell development, indicating involvement of lncRNAs in B cell development.[16] Differentiation of NK cell was also affected with lncRNAs, such as lnc-CD56[17] and Nest.[18] However, the specific mechanisms of these lncRNAs were not clear in B cell and NK cell. On the contrary, the researches about T cell was relatively mature, in which lncRNAs may drive the lineage commitment by selective recruitment of transcription factors. In T helper cells, LncRNA-MAF-4 participated in Th1/Th2 polarization. It was reported to interact with the MAF promoter and EZH2, thus facilitating binding of the chromatin-modifying complex and increasing H3K27 methylation at the MAF promoter.[19,20] A transcription factor in differentiation of naïve T cells, NFAT1, was demonstrated to be regulated by lncRNA NRON. This lncRNA helps in stabilizing complex of phosphorylated NFAT1, DYRK, GSK-3 and CK1, and downregulated NRON may cause disruption of this complex, further leading nuclear translocation of NFAT1 and T cell activation.[21]

In myeloid cells, monocyte-macrophage differentiation was crucial for inflammation balance. During the differentiation of THP-1 cell, lnc-MC expression was upregulated by PU.1 while miR-199a-5p was repressed. And lnc-MC may further upregulate ACVR1B expression to promote the differentiation of monocyte to macrophage.[22] Meanwhile, COX-2 expression was promoted by lncRNA PACER with LPS stimulation in PMA-induced monocyte-macrophage differentiation.[23] A more complex example was that lncRNA NTT was regulated by transcription factor C/EBPβ and further bind to the promoter of nearby gene PBOV1 via hnRNP-U, to overexpress PBOV1 and facilitate differentiation of monocyte into macrophages.[22] These findings suggested that lncRNAs exhibited important effect in differentiation and development of lymphoid and myeloid cells. However, in TME, these processes may be interrupted or overactivation. Next, we will introduce and discuss the involvement of lncRNAs in immune and stromal cells in TME, including T cell, B cell, dendritic cells (DCs), macrophage, myeloid-derived suppressor cell (MDSC), NK cell and cancer-associated cells (CAFs).

LncRNAs in Immune and Stromal Cells Were Dysregulated to Sustain Cancer Cell Viability

LncRNAs in T Cells

CD8+T Cells

The number and ratio of different types of T cells are related to the prognosis and defines immunotherapy efficacy in cancer patients, but dysregulation of lncRNAs may cause abnormal differentiation and disability of T cells.[24] $CD8^+$ T cell

was the major anti-cancer effector cell in the tumor microenvironment, which differentiated into cytotoxic T cells after activation. However, $CD8^+$ T cells will enter a state of reduced proliferation and activation and weakened anti-cancer effects during continuous stimulation of tumor antigens, termed as T cell exhaustion.[25] In CD8+ T cells, lncRNAs were involved in T cell exhaustion, immune checkpoint expression and cytokines secretion (Figure 1). Lnc-Tim3 specifically bind Tim-3 to suppress downstream Lck/NFAT1/AP-1 signaling and induced nuclear translocation of Bat3 to promote CD8+ T exhaustion.[26] Even worse, exhausted $CD8^+$ T cell can assimilate normal CD8+T cell via exosomal lncRNAs and thus expanded population of exhausted CD8+ T cell, which formed a malignant positive feedback.[27] PD1, another important immune checkpoint, were also reported to be overexpressed in CD8+ T cell by lncNDEPD. Interestingly, the effect of lncNDEPD1 may be induced by Notch signal from uncertain senders. In lung cancer xenograft mouse model, CAR-T cells expressing anti-lncNDEPD1 shRNAs to knock down lncNDEPD1 expression showed enhanced cytokine production and cytotoxic function, despite of presence of PD-L1, which suggested a promising application of targeting lncRNAs to reverse immune escape.[28] Excepting immune checkpoints, the cytokine's response and secretion of CD8+ T cell were also regulated by lncRNAs. It is found that lncRNA GM16343 can be stimulated by IL-36β and further promote secretion of IFN-γ by CD8+ T cells.[29]

A well studied lncRNA, NEAT1, was found to be up-regulated in peripheral blood mononuclear cells in hepatocellular carcinoma cancer, and slicing NEAT1 will reduce CD8+ T cell apoptosis and enhanced the cytolysis activity through miR-155/Tim-3 pathway.[30] This study suggested that the dysregulation of lncRNAs in T cell may be not only involved in TME but also altered in systemic immunity.

CD4+ T Cells

Previous studies have demonstrated the vital role of T cell differentiation in anti-cancer immunity. In helper T cells, lncRNAs affect the polarization direction of them. The expression of chromatin-associated lncRNA Linc-MAF-4 of specific T helper 1 (Th1) cell subsets is negatively correlated with the expression of T helper 2(Th2) cell-related transcription factor MAF. Down-regulation of Linc-MAF-4 makes T cell differentiation bias towards Th2 phenotype.[19] LncRNA SATB2-AS1 can inhibit the expression of Th1 cells chemokines induced by IFN-γ, thereby affecting the tumor immune microenvironment.[31] In addition to cell polarization, lncRNA NKILA is overexpressed in Th1 cells and interacts

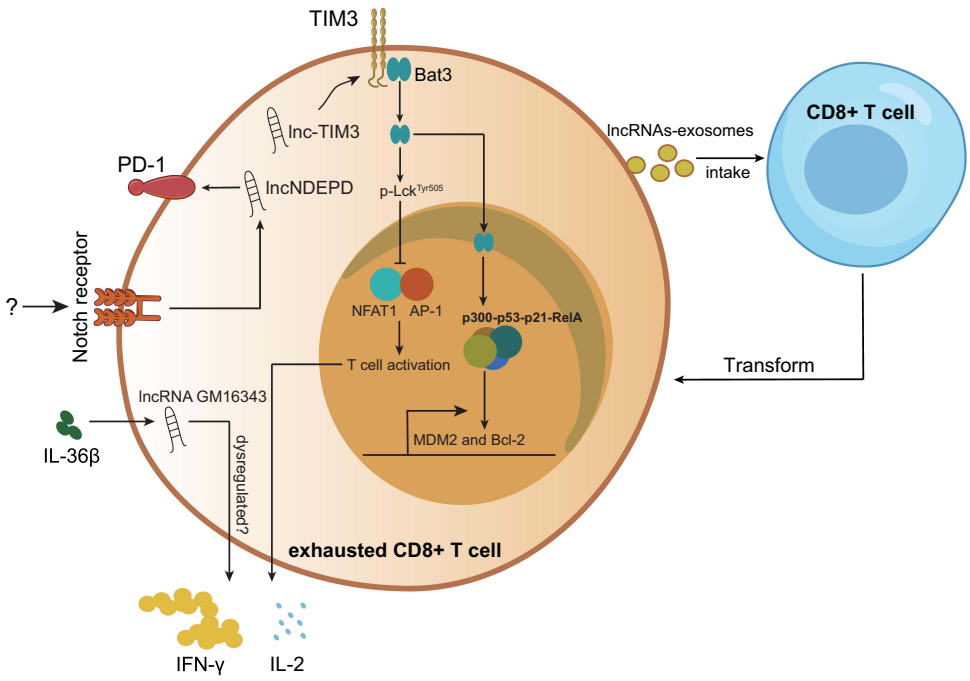

Figure 1 LncRNAs were involved in CD8+ T cell exhaustion. LncRNAs can be regulated by cytokines and Notch signals, further dysregulating immune checkpoint pathways and cytokine secretion.

with NF-κB to inhibit NF-κB activity, thereby regulating T cell sensitivity to activation-induced cell death (AICD). Next, NKILA promotes tumor immune evasion by sensitizing T cells to AICD.[32] LncRNA can also establish histone H3K4Me markers on the IL-4, IL-5, and IL-13 promoters of Th2 cells, and these markers can recruit alternative splicing enzymes to promote Th2 cells to express IL-4, IL-5, and IL-13, stimulating the proliferation and survival of B cells.[33]

Regulatory T (Treg) Cells

By detecting the lncRNAs' expression profile of peripheral Treg cells, linc-POU3F3 was identified as top upregulated lncRNA in gastric cancer. Further study demonstrated that upregulated linc-POU3F3 promoted T-reg differentiation by activating TGF-β signal.[34] Similarly, using bioinformatic analysis, researchers found a NF-AT1–lnc-EGFR–EGFR feed-forward loop in Treg of liver cancer patients. In Treg cells, lnc-EGFR binds to EGFR, stabilizes it and sustains activation of its downstream RAS/ERK/AP1 signalling, leading to Treg differentiation.[35] Another strategy to pivotal lncRNAs in CD4+T cell was to compare expression profile between CD4+ T cells purified from tumor tissues and healthy donor blood. Pei et al found that SNHG1 upregulated in tumor-infiltrating CD4+ T cells of breast cancer patients. And, SNHG1 could promote the differentiation of Treg cells by reducing miR-448 expression and increasing IDO level.[36]

In summary, lncRNAs have a non-negligible regulatory effect on various T cells through intracellular pathways. These studies suggested a potency of using lncRNAs as targets to improve immunotherapy efficacy. However, there's still an unopened question about the driving force altering the expression of lncRNAs.

LncRNAs in Dendritic Cells

DCs are the most potent antigen-presenting cells in the immune system. They function as ingesting, processing and presenting tumor antigens and activating T cells.[37] Nevertheless, TME-mediated suppression of tumor-infiltrating DC (TIDC) weakens the ability of DC cells to initiate effective anti-tumor immunity and promotes tumor progression in the tumor immune microenvironment.[38]

DC cells are composed of many different subgroups, among which classic DCs (cDCs) can present antigens in tissues and migrate to lymph nodes to induce antigen-specific T cell immunity or tolerance.[39] Lnc-DC was a stably and specifically expressed lncRNA in human cDCs, which prevented the dephosphorylation of STAT3 Y705 by SHP1 by interacting with the C-terminus of STAT3. This effect can promote STAT3 signal transduction and then promote DC cell differentiation. Lnc-DC knockdown will not only damage DC cell antigen uptake, but also weaken its ability to induce the CD4+ T cell proliferation and cytokine production. It can be seen from the above that as a specific regulator of DC differentiation and function, lnc-DC can be used as a tumor immunotherapy target to relieve the inhibition of DCs in the TME environment.[40]

Contrary to the above regulation, specific lncRNAs can also induce the tolerogenic dendritic cells (tDCs). For example, lncRNA NEAT1 can promote the expression of tDCs and induce immune tolerance by shaping T-cell responses.[41] LncRNA MALAT1 overexpression favored a switch in DCs toward a tolerant phenotype.[42] These studies highlight that the lncRNAs can become novel tolerance regulators in DCs-related immunity, but there is still a lack of research on DCs in TME.

LncRNAs in B Cells

B cells are the main effector cells of humoral immunity, which can inhibit tumor progression by secreting immunoglobulins, promoting T cell response to kill the tumor cells. B cells and B cell-related pathways activate immune response and local immune activation by forming a tertiary lymphoid structure.[43] In B cells, lncRNAs expressed across multiple stages of B-cell development and activation. These lncRNAs can be divided into enhancer-associated RNA and promoter-associated RNA.[44] Different lncRNAs expressed at different developmental stages of B cells, among which lncRNAs CTC-436K13.6, LEF1-AS1, SMAD1-AS1 and MYB-AS1 were related to the early B-cell development, while lncRNA CRNDE was associated with the proliferative stages of B-cell development.[16]

In TME, B cells are highly enriched but reported to illustrate carcinogenic effects, which may be related to the inhibition of T cells.[45,46] The local expression of lymphoid chemokines, such as CCL19, CCL21, and CXCL13 trigger the recruitment of B cells.[45] LncRNA Linc00961, BCAR4, and PART1 may influence expression of the above lymphoid chemokines.[47–49] A large number of animal models have proved that B cell infiltration has a profound impact on anti-

tumor immunity. B cells can release immunosuppressive cytokines such as IL-10, IL-35, TGFβ, which can promote the immunosuppressive phenotype in bone marrow cells, promote the development of regulatory T cells, and in turn support the formation of immunosuppressive B cells. Immunosuppressive B cells presented tumor-derived antigens and suppressor or misdirect effector T cell responses.[50,51]

In short, the specific role of cellular lncRNAs in B cells with TME is still unclear. On the other hand, the current bioinformatics studies can speculate the influence of lncRNAs in B cells. For example, Zhou et al used a machine learning-based computational framework to identify lncRNAs related to tumor-infiltrating B cells and developed a signature based on candidate lncRNAs, named as TILBlncSig.[52] Although this signature can predict prognosis and therapy efficacy of bladder cancer, the detailed regulation mechanism of these lncRNAs on B cell still needs to be further explored.

LncRNAs in Tumor-Associated Macrophages

Tumor-associated macrophages (TAMs) are important tumorigenesis regulators in TME, which can secrete various cytokines and chemokines to recruit regulatory T cells into TME, directly and indirectly inhibiting CD4+ and CD8+ T cell function.[53] According to the polarization state of macrophages, it can be divided into multiple subsets, including two major subtypes: classically activated macrophage (M1) and activated macrophage (M2) phenotypes. Current options supported that M1 macrophages promote the Th1-type inflammatory response and exerted anti-tumor activity, while M2 macrophages was essential for immunologic tolerance and might promote tumorigenesis.[54,55]

There are amounts of lncRNAs involved in TAMs polarization regulation (Figure 2A). LncRNA Xist down-regulation inhibits IL-4 induced M2 polarization, and the promotion of Xist expression in M1 macrophages might play a part in inhibiting breast and ovarian tumor proliferation and migration abilities.[56] Cao et al utilized the lncRNA microarray-based profiling assays to identified lncRNA-MM2P as a lncRNA upregulated during IL-4 induced M2 polarization but downregulated in M1 macrophages. LncRNA-MM2P was further demonstrated required in angiogenic features of M2 macrophages and promote K7M2 cells proliferation and metastasis.[57] LncRNA RP11-389C8.2 was another lncRNA identified in M2 macrophages by microarray-based profiling assays. This lncRNA was further named as lnc-M2 since it was reported to promote the differentiation of M2 macrophages through the PKA/CREB pathway, and its expression was regulated by STAT3.[58] LncRNAs were also involved in M1 polarization, such as LncRNA CCAT1 which was normally highly expressed in M1. Knockdown of CCAT1 can up-regulate miR-148a and then down-regulate the expression of a PKC isoenzyme. In prostate cancer, this process promoted the macrophages polarizing towards M2.[59]

Another effect of lncRNAs in macrophage was the participation in the interaction between TAMs and tumor cells by regulating the expression of cytokines and releasing exosomes (Figure 2B). In glioma, TAMs secrete exosomal LINC01232, which could directly bind E2F2, promote E2F2 entry into the nucleus, and promote the transcription of NBR1 in cancer cells. The increase in binding between NBR1 binding and the ubiquitinating MHC-I protein to decrease the expression of MHC-I on the surface of tumor cells, which in turn led to tumor cell escape from CD8+ CTL immune attack.[60] In breast cancer, IFN induced lncRNA IRENA in macrophages could trigger NF-κB signals and increase production of protumor inflammatory cytokines. Moreover, IRENA can be upregulated after chemotherapy, suggesting that it may be involved in chemotherapy resistance.[61] In liver cancer, knockdown of lncRNA Cox-2 decreased the expression levels of IL-12, iNOS, and TNF-α in M1 macrophages, while increased the expression levels of IL-10, Arg-1, and Fizz-1 in M2 macrophages, which promoted the immune evasion of HCC cells.[62] Additionally, TAMs can release exosomes containing HIF-1α-stabilizing long noncoding RNA (HISLA) to enhance aerobic glycolysis of breast cancer cells, and reciprocally, lactate released from cancer cells upregulated HISLA in macrophages, constituting a feed-forward loop.[63] Through exosomes derived from macrophage, lncRNAs can exert ceRNA effect to promote cancer proliferation and metastasis, including that lncRNA LIFR-AS1 can sponge miR-29a to upregulate NFIA and promote osteosarcoma cell proliferation,[64] lncRNA AFAP1-AS1 acted as a ceRNA to repress miR-26a and upregulated ATF2 to promote metastasis of esophageal cancer cell,[65] and lncRNA CRNDE elevated NEDD4-1-mediated PTEN ubiquitination to increase cisplatin resistance in gastric cancer.[66]

At present, researches have demonstrated interactions between macrophage and cancer cell via lncRNAs. It may be an interesting topic that how these interactions affect treatment efficacy, especially in immunotherapy.

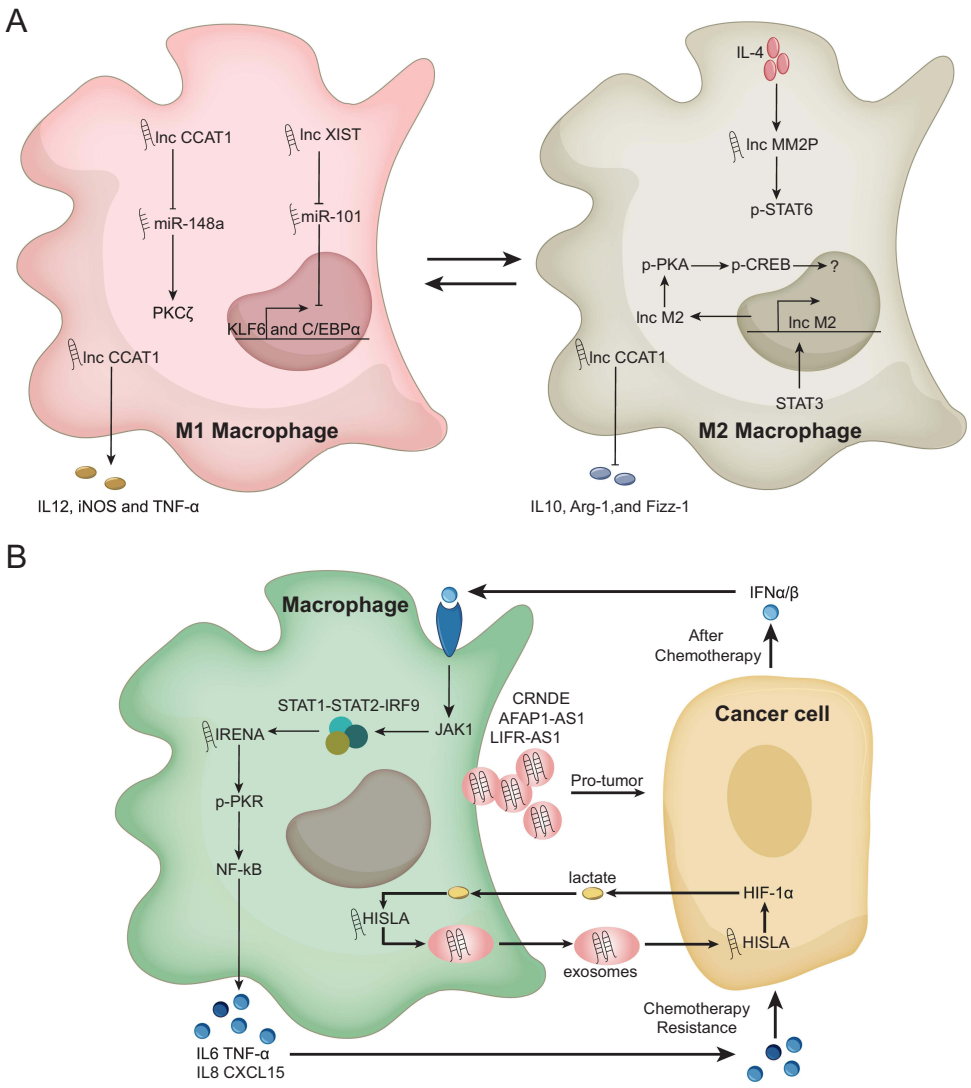

Figure 2 LncRNAs regulate polarization of macrophage (**A**) and affect cancer growth and therapy efficacy via exosome and cytokines (**B**).

LncRNAs in Myeloid-Derived Suppressor Cells

MDSC supported cancer cell survival, angiogenesis, T cell tolerance and metastasis in TME.[67] MDSC expressed multiple checkpoints, including PD-L1, to induce T cell anergy and apoptosis.[68] Both C/EBP homologous protein (CHOP) and C/EBPβ play a critical role in regulating the immunosuppressive function of MDSC. Lnc-CHOP binds to CHOP and C/EBPβ isoform liver-enriched inhibitory protein to promote the activation of C/EBPβ, and regulate a large set of target transcripts in MDSC, such as arginase-1 (Arg1), NO synthase 2, NADPH oxidase 2 and cyclooxygenase-2, so that lnc-CHOP can control MDSC's immunosuppressive function and differentiation in TME.[69] In lung cancer tissue, the expression of lncRNA RUNXOR in MDSC was found to be upregulated. Moreover, RUNXOR expression was positively correlated with Arg1 level, which was the primary suppressive molecule of MDSC.[70] In mouse model, it was also found that knocking down lncRNA Pvt1 can significantly inhibit the immunosuppressive function of granulocytic MDSC in vitro, and delay the tumor progression in tumor-bearing mice in vivo.[71] On the contrary, there is a moderately negative correlation between the expression of MALAT1 and the proportion of MDSC from patients with lung cancer. Inhibiting the expression of MALAT1 by MALAT1-siRNA can increase the proportion of MDSC in vitro. These results indicated that MALAT1 negatively regulated MDSC.[72]

To sum up, lncRNAs can be used as the target to relieve the inhibitory function of MDSC and reduce the immunosuppression of immune cells in the tumor microenvironment.

LncRNAs in Natural Killer Cells

NK cell was one of the major types in innate immune cells, which can recruit DCs, mediate target cell lysis, immune monitoring, and directly eliminate tumor cells.[73] However, the function of NK cells in the tumor immune microenvironment was usually inhibited, and the ligands of the NK cell receptor on the tumor surface were dysregulated, which allowed immune escape of cancer cell from NK cell-mediated cytotoxicity.[74–76]

Feng et al determined four lncRNAs, RP11-222K16.2, G005087, G044640, and ANKRD36BP2 may be candidate biomarkers of immunotherapy. With GO annotations, these lncRNAs was found to be correlated with immune system. Based on the above findings, they further analyzed the pan-cancer data from the chip library, which indicated that eomesodermin was the most correlated mRNA with RP11-222K16.2 and related to the blocking of NK cell differentiation. For this reason, they proposed that lncRNA-mediated eomesodermin dysregulation could prevent NKs differentiation, thereby promoting the immune escape of malignant cells.[77]

LncRNAs can also regulate the cytokine secreted by NK cell. In NK cell, lncRNA IFNG-AS1 was rapidly upregulated within 1 hour after activating natural cytotoxic receptors. When using target-mediated activation (721.221 cells, which express high levels of CD48) or stimulatory cytokines (IL-2 and IL-15) to activate NK cells, they overexpressed IFNG-AS1 to produced more IFN-γ. This finding indicated that overexpression of lncRNA IFNG-AS1 enhances the production of IFN-γ in NK cells.[18] IFN-γ was engaged in cytostatic, pro-apoptotic and immune-provoking effects.[78] In the tumor microenvironment, cancer cells decreased IFN-γ to reduce inflammation and remodel a "cold tumor" phenotype.[79] Some lncRNAs was proved to enhance cytotoxicity of NK cells, such as NK cell activity-associated lncRNA 1 (NCAL1) which targeted Gab2-PI3K-AKT pathway. Interestingly, NCAL1 upregulated Gab2 epigenetically by binding to the Gab2 promoter, and further decreased methylation, recruited the transcription factor Sp1, and increased H3K4me3 and H3K27ac levels in the Gab2 promoter, rather than function via ceRNA network.[80] Another lncRNA was also reported to enhances the IFN-γ secretion and killing effect of NK cells simultaneously through miR-544/RUNX3 axis, which was called GAS5.[81]

Above findings indicated that lncRNAs were closely related to the differentiation and cytokines secretion of NK cells, but the specific mechanism still needs to be further explored.

LncRNAs in Cancer-Associated Fibroblasts

CAFs were the primary type of stromal cells in the tumor microenvironment. They play an active role in shaping the tumor microenvironment with supporting tumor cell survival, proliferation, angiogenesis, immunosuppression, and treatment resistance.[82]

LncRNA lnc-CAF was differentially expressed in normal fibroblasts (NFs) and CAFs. In CAFs, the expression of α-SMA, vimentin, and N-cadherin will be inhibited by knock down lnc-CAF expression through siRNA. These proteins enhance the mesenchymal phenotype of CAFs. Nevertheless, IL-33 knockdown reversed the stromal phenotype regulated by lnc-CAF, suggesting that lnc-CAF maintains the stromal phenotype of CAFs via IL-33. Then, researchers overexpressed lnc-CAF and used siRNA-IL-33 in cultured NFs, which was then directly co-cultured with the human OSCC cell line (HSC-3) cells. NFs overexpressing lnc-CAF enhanced the proliferation of HSC3 cells when compared with normal NFs, but this effect was attenuated by IL-33 knockdown. In short, these findings suggested that up-regulated lnc-CAF/IL-33 signaling in stromal fibroblasts enhanced the proliferation of HSC3 cells, and this cancer-promoting effect was related to the CAF phenotype. In the detection of the HSC3 cell-derived exosomes, high levels of lnc-CAF were detected. By using immunofluorescence labeling, the researchers observed that exosomes could be absorbed by NFs and up-regulate the expression of lnc-CAF in NFs. This effect was also observed in CAFs, indicating that tumor cells could secrete exosomal lnc-CAF into the stroma and induce lnc-CAF expression in stromal fibroblasts. These indicate that there is a lnc-CAF-mediated positive feedback loop between NFs/CAFs and tumor cells.[83] Similar feedforward loop was observed in multiple cancers. A CAF-specific lncRNA, LINC01614, participating in mediating enhancement of

glutamine uptake in LUAD cells via exosomes. And reciprocally, tumor-derived proinflammatory cytokines upregulate LINC01614 in CAFs, constituting a feedforward loop between CAFs and cancer cells.[84]

Exosomes seems to be an extensive activation in CAFs (Figure 3). Compared with tumor tissues, lncRNA CCAL is highly expressed in CAFs. After the co-cultivation of CAFs and tumor cells, the drug resistance of tumor cells was enhanced. The researchers used GW4869, an exosome generation inhibitor, to block the production of CAFs exosomes. Then, they found that cell viability was decreased and cell apoptosis was induced. The level of CCAL in the exosomes and tumor cells, and intracellular CCAL levels were significantly increased upon incubation with exosomes from control CAFs but not with CCAL-knockdown CAFs. These findings revealed that functional CCAL could be transferred from CAFs to CRC cells via exosomes.[83] Similar results were reported in other cancers, especially in cancer cell's drug resistance. For example, lncRNA H19, WEE2-AS1 and FAL1 in colorectal cancer,[85–87] DNM3OS in esophageal cancer,[88] and MEG3 in small cell lung cancer.[89]

It can be seen from the above experiments that lncRNAs can maintain the stromal phenotype of CAFs, and participate in the formation of the feedback loop between fibroblasts and tumor cells in the tumor microenvironment. In addition, cytokines secretion of CAFs regulated by lncRNAs was also a pivotal cross-talk between CAFs and cancer cells.[90] Through a network-based "guilt-by-association" approach and GO annotations, other lncRNAs related to CAFs can be screened out. However, the specific mechanism of these lncRNAs still needs further experimental proof.[91] In addition, due to immunosuppressive effect of CAFs, it may be an interesting topic about how T cell and other immune cells involves in CAFs' regulation by lncRNAs.

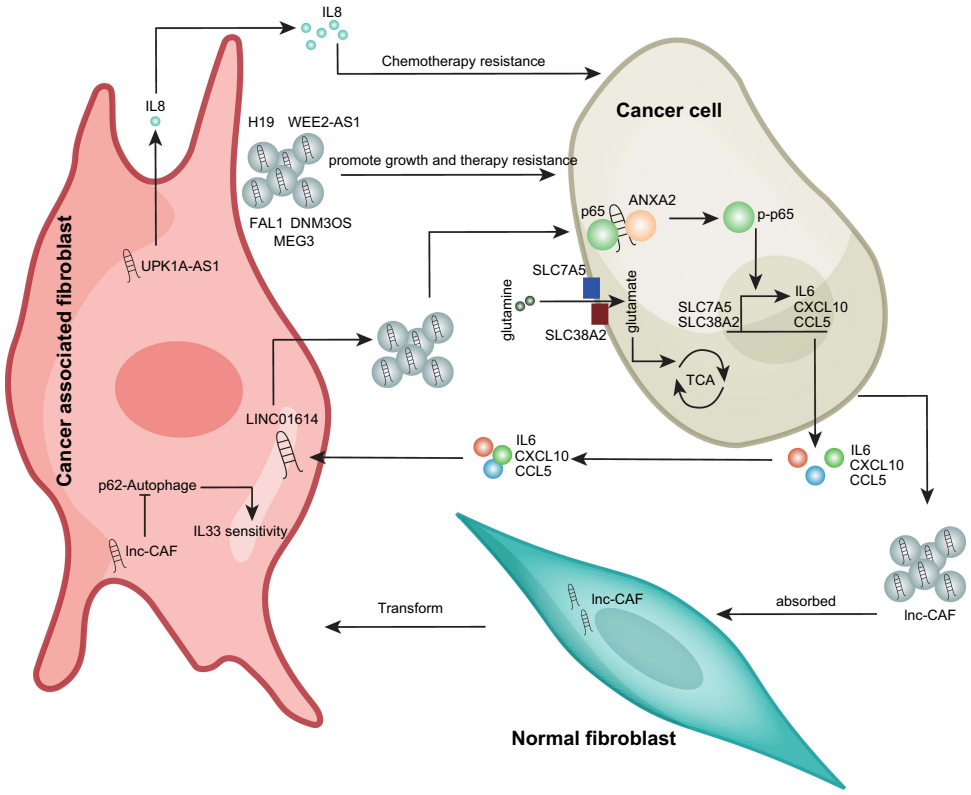

Figure 3 LncRNAs participate in pro-cancer effect of cancer associated fibroblasts (CAFs). LncRNAs can be altered in CAFs by cancer -derived exosomes and thus promote transformation of normal fibroblasts to CAFs. Moreover, CAFs could promote cancer cell's growth and therapy resistance via exosomes containing lncRNAs and cytokines regulated by lncRNAs.

Table 1 The lncRNAs and Their Respective Targets in Immune and Stromal Cells

Cell	LncRNAs	Targets	References
CD8+ T cells	Lnc-Tim3	Tim-3	[26]
	lncNDEPD	miR-3619-5p	[28]
	GM16343	IL-36β	[29]
	NEAT1	miR-155	[30]
CD4+ T cells	Linc-MAF-4	LSD1, EZH2	[19]
	SATB2-AS1	WDR5, GADD45A	[31]
	NKILA	NF-κB	[32]
	LincR-Ccr2-5'AS	GATA-3	[33]
Regulatory T (Treg) cells	linc-POU3F3	TGF-β	[34]
	lnc-EGFR	EGFR	[35]
	SNHG1	miR-448	[36]
Dendritic cells	Lnc-DC	the C-terminus of STAT3	[40]
	NEAT1	miR-3076-3p	[41]
	MALAT1	miR155	[42]
B cell	BCAR4	SNIP1	[48]
	PART1	TLR	[49]
Tumor-associated macrophage	Xist	miR-101-3p	[56]
	LncRNA-MM2P	STAT6	[57]
	RP11-389C8.2	STAT3	[58]
	CCAT1	miR-148a	[59]
	LINC01232	E2F2	[60]
	IRENA	NF-κB	[61]
	Cox-2	IL-12	[62]
	LIFR-AS1	miR-29a	[64]
	AFAP1-AS1	miR-26a	[65]
	CRNDE	SRSF6	[66]
Myeloid-derived suppressor cell	Lnc-CHOP	CHOP, C/EBPβ isoform	[69]
	RUNXOR	RUNX1	[70]
	Pvt1	C-myc	[71]
	MALAT1	MALAT1-siRNA	[72]
Natural killer cell	IFNG-AS1	IFN-γ	[18]
	NCAL1	Gab2 promoter	[80]
	GAS5	miR-544	[81]
Cancer-associated fibroblasts	lnc-CAF	IL-33	[83]
	LINC01614	ANXA2, p65	[84]

Conclusions and Future Directions

With the continuous progress of lncRNAs research, the role of lncRNAs in cancer progression has become more and more significant. Various studies have shown that lncRNAs are closely related to the tumor microenvironment in cellular immunosuppression and metabolic regulation, which affects tumor progression. LncRNAs can regulate the tumor microenvironment, affect the expression of immune checkpoint inhibitor genes, enhance cellular immunity, and ultimately affect tumor progression. By building the prognostic model, we have also observed that lncRNAs, as independent predictors, have great potential in predicting the outcome of immunotherapy.[92]

In this review, it can be summarized that lncRNAs in immune and stromal cells participated in cell differentiation, activation and cytokines secretion. The lncRNAs and their respective targets are summarized in Table 1. Overall, there has been a lot of studies about lncRNAs in T cell, macrophage and CAFs, while lacks evidences in other cells, such as B cell, DCs and NK cell. Current implication of lncRNAs was mainly based on bulk-seq data, in which cell locations of these lncRNAs were obscure. With development of sing cell RNA-seq, more dysregulated lncRNAs in immune and stromal cells may be identified.[93]

Mechanistically, we observed that many lncRNAs upregulate the expression of target genes by competitively binding to miRNAs to reduce miRNA repressive functions. These lncRNAs, miRNAs, and circular RNAs (circRNAs) all share the same miRNA response elements (MREs), which exposes a myriad of new targets for targeted cancer therapy, including immunotherapy.[94] However, the complexity of the ceRNA network determines that such targeted therapies are likely to trigger a butterfly effect, and whether this therapeutic concept can be applied to clinical treatment still needs to be explored in a long time. Current research on exosomal lncRNAs have focused on the secretion of exosomes by tumor cells to influence other immune cells in the TME. The exosomal lncRNA intercellular communications between immune and stromal cells in TME are still lacking. The cellchat role of lncRNAs between immune and stromal cells still needs further discussion.

Despite lncRNAs were involved in cancer growth and metastasis, related studies about how these lncRNAs affect therapies efficacy were still lacked, especially in immunotherapy. Notably, the feed-back loops between immune/stromal cell and cancer cell via lncRNAs were observed in macrophage and CAFs. Whether similar mechanisms were regulated in other immune and stromal cells, and whether these mechanisms were key elements in therapy resistance of cancer may be worthy further exploring.

Abbreviations

TME, tumor microenvironment; LncRNA, long noncoding RNA; HSCs, hematopoietic stem cells; DCs, dendritic cells; MDSC, myeloid-derived suppressor cell; CAFs, cancer-associated cells; Th1, T helper 1; Th2, T helper 2; Treg, Regulatory T; TIDC, tumor-infiltrating DC; cDCs, classic DCs; tDCs, tolerogenic dendritic cells; TAMs, Tumor-associated macrophages; M1, classically activated macrophage; M2, alternative activated macrophage; HISLA, HIF-1α-stabilizing long noncoding RNA; CHOP, C/EBP homologous protein; Arg1, arginase-1; NCAL1, NK cell activity-associated lncRNA 1; NFs, normal fibroblasts.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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