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Tumor immune microenvironment lncRNAs

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Abstract

Long non-coding ribonucleic acids (RNAs) (lncRNAs) are key players in tumorigenesis and immune responses. The nature of their cell type-specific gene expression and other functional evidence support the idea that lncRNAs have distinct cellular functions in the tumor immune microenvironment (TIME). To date, the majority of lncRNA studies have heavily relied on bulk RNA-sequencing data in which various cell types contribute to an averaged signal, limiting the discovery of cell type-specific lncRNA functions. Single-cell RNA-sequencing (scRNA-seq) is a potential solution for tackling this limitation despite the lack of annotations for low abundance yet cell type-specific lncRNAs. Hence, updated annotations and further understanding of the cellular expression of lncRNAs will be necessary for characterizing cell type-specific functions of lncRNA genes in the TIME. In this review, we discuss lncRNAs that are specifically expressed in tumor and immune cells, summarize the regulatory functions of the lncRNAs at the cell type level and highlight how a scRNA-seq approach can help to study the cell type-specific functions of TIME lncRNAs.

Keywords: long non-coding RNA, immune cells, tumor immune microenvironment, bulk RNA-sequencing, single-cell RNA-sequencing, cell type-specific expression

INTRODUCTION

Long non-coding ribonucleic acid (RNA) (lncRNA) genes are independent transcription units that are transcribed into non-coding RNAs of ≥200 nucleotides in length. Thanks to high-throughput sequencing in diverse mammalian tissues and cells, the census of lncRNA genes has expanded a great deal in recent years [1–3]. In the human genome, >20,000 lncRNA genes have been annotated, mostly from cell lines and tissues, a count that is comparable to that of protein-coding genes (PCGs) [4, 5]. Despite the lack of lncRNA coding potential, the biogenesis of lncRNAs and mRNAs is similar. A majority of lncRNAs are transcribed by RNA polymerase II and matured by 5' capping, 3' cleavage and polyadenylation and splicing [6].

lncRNAs display a unique feature in their expression. Unlike messenger RNAs (mRNAs), very few lncRNAs are ubiquitously expressed across tissues; instead, most are specifically expressed in certain conditions and tissues, implying functional relevance [7–11]. In general, instead of serving as coding templates, the lncRNAs, together with their protein binding partners, are themselves functional. These RNAs participate in the control of chromatin states, transcription, RNA stability, RNA

processing, protein synthesis and RNA/protein modifications and can function as competitive endogenous RNAs (ceRNAs) and protein scaffolds [12–14]. Rarely, some lncRNAs also include small open reading frames that encode short peptides, which have functions distinct from intrinsic function of the lncRNAs [15]. The lncRNAs with coding and non-coding functions are referred to as bifunctional RNAs [16] or as coding and non-coding RNAs [17, 18]. Such versatile functions imply pivotal roles in critical, pathological cellular processes, including tumorigenesis [19, 20].

lncRNAs are often dysregulated during tumorigenesis, which can be either causal or consequent outcomes of tumor development [21–23]. In general, lncRNAs with oncogenic roles tend to be upregulated in tumors compared to paired normal samples, and the inactivation of these lncRNAs often reduces tumorigenesis or increases apoptosis [24]. On the other hand, lncRNAs with tumor-suppressive roles tend to be downregulated in tumors and the depletion of these lncRNAs often increases tumorigenesis [24, 25]. Previous studies showed that activation of the lncRNA gene *EPIC1* enhances tumorigenesis via control of MYC targets, suggesting an

oncogenic role [26], whereas inactivation of the lncRNA gene growth arrest-specific 5 (*GAS5*) promotes cell proliferation and tumor formation in cancers, indicating its tumor-suppressive role [27, 28]. Moreover, lncRNAs are also involved in tumor progression and metastasis and are strongly associated with prognosis [29]. For instance, lung cancer associated transcript 1 (*LUCAT1*) is significantly upregulated in lung and esophageal cancers and is known to be involved in tumor progression, and patients with a high level of *LUCAT1* have a poor prognosis [30, 31].

Tumor masses are composed of various cell types that range from normal to malignant cells as well as from resident to infiltrating immune and stromal cells. The cellular phenotypes and behaviors exhibited by malignant cells, such as proliferation, invasion, the epithelial-mesenchymal transition (EMT), angiogenesis and drug resistance, are known to be affected by nearby immune cells and by the interactions between the various cell types, collectively known as the tumor immune microenvironment (TIME) [32–34]. It is well known that cell type-specific gene expression helps to confer cellular functions. However, despite the high cellular complexity of the TIME, lncRNA studies in tumors have mostly been done with bulk tumor samples displaying convoluted transcriptomic signals from different cell types. Not all lncRNAs specific to bulk tumors are expressed in malignant cells, and lncRNAs expressed in non-malignant cells, including immune and stromal cells, could play oncogenic or tumor-suppressive roles [35, 36]. Hence, it is important to examine lncRNA functions in cells in which these RNAs are specifically expressed at the single-cell level.

In this review, we first summarize information about functional lncRNAs involved in cancer development and progression as well as those expressed in immune cells. We then provide an overview of current knowledge about the *bona fide* expression of cancer- and immune-related lncRNAs at the cellular level as well as possible cellular functions of lncRNAs in the TIME. Our discussion about the promises and challenges of single-cell analyses for studying lncRNAs offer a glimpse of the future potential of single-cell technology for examining the cellular function of TIME lncRNAs.

MAIN
Functional lncRNAs in cancers
Studies of high-throughput RNA-sequencing (RNA-seq) data and characterization of diverse RNAs have provided accumulating evidence for the functional relevance of lncRNAs in cancers. Recently, the Pan-Cancer Analysis of Whole Transcriptome (PCAWT) study provided excellent resources for the identification of many lncRNAs that are dysregulated in bulk tumors [36–40]. The cancer-related lncRNAs display aberrant expression in cancers, which is sometimes indicative of oncogenic or tumor-suppressive functions. These lncRNAs often regulate the initiation, progression and/or metastasis of tumors by modulating cancer-signaling pathways at the epigenetic, transcriptional, post-transcriptional, translational or post-translational levels. Metastasis-associated lung adenocarcinoma transcript1 (*MALAT1*) is a conserved lncRNA in mammals, which is highly abundant in many cancers, including lung cancer [41]. Transforming growth factor beta (TGF-β)-induced upregulation of *MALAT1* was found to enhance cancer metastasis, an effect mediated by an interaction with suz12 at the transcriptional level which alters downstream events [42]. Conversely, *MALAT1* silencing reduces cell proliferation and invasion and increased apoptosis by reducing *MALAT1*-EZH2-mediated target silencing at the epigenetic level, indicating the oncogenic, cancer-progressing roles of *MALAT1* [43]. In contrast, nuclear factor-κB (NF-κB) interacting lncRNA (*NKILA*) plays a tumor-suppressive role by regulating a protein modification. *NKILA*, which is upregulated by NF-κB, prevents overactivation of the NF-κB pathway by inhibiting IκB phosphorylation in inflammation-stimulated epithelial cells, whereas downregulation of *NKILA* is associated with increased metastasis and poor prognosis [44]. Likewise, lncRNAs often act as cancer drivers or as controllers of cancer progression.

The oncogenic or tumor-suppressive functions of lncRNAs have been elucidated through diverse techniques, such as population-based, *in vitro*, *in vivo* and *in silico* approaches, either alone or in combination (Figure 1). Abnormal expression of lncRNA in cancer samples is regarded as the first line of evidence for lncRNA involvement in the disease. lncRNA candidates with such analytic evidence obtained via bioinformatics (*in silico*) are then prioritized by their clinical relevance and/or genetic associations in large cancer cohorts, including The Cancer Genome Atlas (TCGA) and PCAWT. The clinical relevance is normally determined using the diagnostic and prognostic values of lncRNA expression levels in tumor samples. The lncRNAs can be further prioritized by expression-based guilt-by-association and RNA–RNA/protein interactions (Figure 1**A**). For the guilt-by-association approach, lncRNAs with expression levels that are highly correlated with that of PCGs are inferred to have a similar function, allowing one to predict lncRNA functions *in silico* (Figure 1**A**). lncRNAs often directly interact with other RNA molecules, such as mRNAs originating from the sense strand or microRNAs (miRNAs), controlling the stability of sense mRNAs [45–48] or miRNA functions [49–55]. lncRNAs with abundant miRNA binding sites appear to function as ceRNAs that 'sponge up' miRNAs. To infer such roles, lncRNA abundance is first correlated with that of other genes and their miRNAs after which target sites are sought for those miRNAs *in silico*. Otherwise, researchers can explore pre-built ceRNA networks to facilitate the discovery of candidate regulatory axes (starBase [56]).

The prioritized candidates are subsequently validated by perturbing their gene expression with RNA
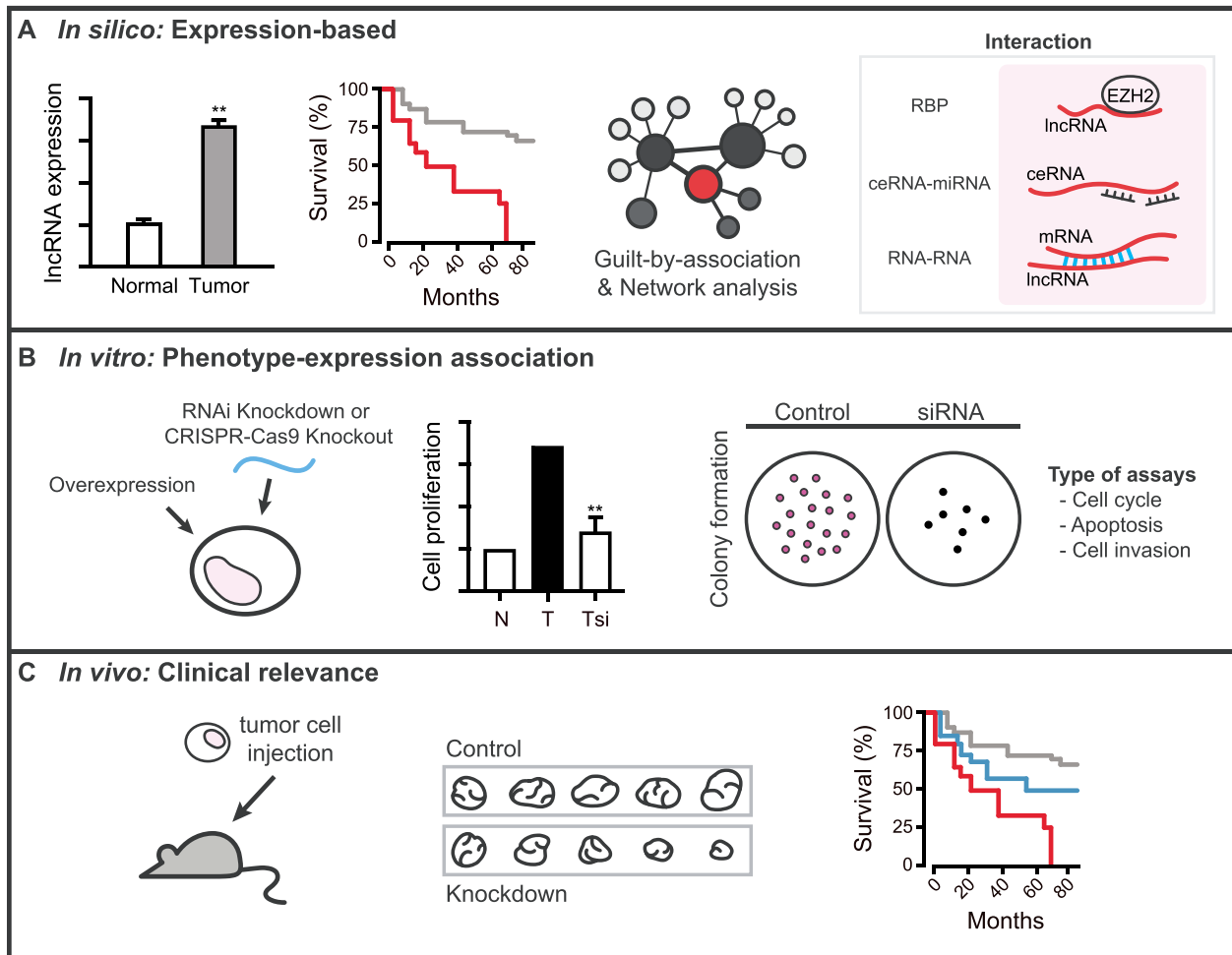
Figure 1. General approaches for functional studies of cancer-related lncRNAs. Three main approaches for functional studies of cancer-related lncRNAs. (**A**) *In silico* approaches. *In silico* functional studies are mainly based on analyses of the expression of lncRNAs, associated RNA-binding proteins (RBPs) and miRNAs. (i) Expression differences in normal versus tumor cell lines or in non-tumor versus tumor tissues are statistically examined. (ii) Clinical associations between lncRNAs and disease severity are statistically examined by correlating overall survival or disease (or relapse)-free survival rates in two groups separated by the lncRNA expression level. (iii) The guilt-by-association approach is used to infer the functions of lncRNAs from those of PCGs with a similar expression pattern. (iv) Systemic use of the guilt-by-association method can be done together with pathway analysis to identify functional modules associated with lncRNAs and similarly expressed PCGs. (v) Searches of databases of RBPs and miRNAs that associate with the lncRNAs and RNA–RNA interactions can also provide functional evidence. (**B**) *In vitro* approaches. Overexpression and knockdown (or knockout) of lncRNAs are techniques that are often used for functional studies of lncRNAs in normal and cancer cell lines. RNAi and the CRISPR/Cas9 system are often used to downregulate or delete lncRNA genes. Following the perturbation of lncRNA expression, cell-based functional assays are carried out to examine cell proliferation, invasion, migration, wound healing, colony formation, cell-cycle arrest and apoptosis. (**C**) *In vitro* results are often confirmed at the *in vivo* level using a xenograft model followed by RNAi or antisense oligonucleotide treatment.

interference (RNAi)- or CRISPR-based inactivation and by their overexpression in cancer cell lines (Figure 1**B**, *in vitro*) or in mouse xenograft models (Figure 1**C**, *in vivo*). Many oncogenic, cancer-progressing and tumor-suppressing lncRNAs have been identified through the above procedure or by a similar approach. Highly Expressed lncRna in ESophageal squamous cell carcinoma (*HERES*) is a representative example of a novel cancer-promoting lncRNA identified through this procedure [57].

Documented cancer-controlling lncRNAs are summarized below based on function: those with oncogenic and cancer-progressing (cell proliferation, invasion and metastasis) functions are shown in Table 1 and those with tumor-suppressing functions are shown in Table 2.

Oncogenic and cancer-progressing lncRNAs

Oncogenic (tumorigenic) lncRNAs are generally expressed at higher levels in tumors versus paired normal samples and function as cancer drivers that activate the cell cycle, promote proliferation and/or exert anti-apoptosis effects (Table 1). The functional verification of oncogenic lncRNAs has been carried out via a series of cell-based assays examining cell cycle arrest, proliferation and anti-apoptotic activity, following the perturbation (knockout, knockdown or overexpression) of lncRNAs. In contrast, cancer-progressing lncRNAs have been verified as controllers of the EMT, cell migration and cell invasion, which are often more expressed in cancer patients with poor prognosis than in others (Table 1). Although the cellular processes of tumorigenesis are different from those of cancer progression (EMT, cell migration and

Table 1. lncRNAs with oncogenic and cancer-promoting functions

Cancer	lncRNA	Expression in cancer	Function	Functional validation	Reference
BLCA	H19[a]	Up	Tumor progression (migration and invasion)	OE/siRNA KD in cancer cell lines and mouse model	[59]
	LNMAT1	Up	Tumor progression (migration and invasion)	OE/shRNA KD in cancer cell line and mouse model	[133]
	UCA1	Up	Tumorigenesis (proliferation)	OE in cancer cell line	[134, 135]
BRCA	EPIC1	Up	Tumorigenesis (cell cycle)	OE/KD in cancer cell line and mouse model	[26]
	H19[a]	Up	Tumorigenesis (cell cycle and proliferation)	OE in cancer cell line and mouse model	[60]
	HISLA	Up	Tumorigenesis (anti-apoptosis)	siRNA, shRNA KD in cancer cell line	[136]
	HOTAIR[a]	Up	Tumorigenesis (proliferation), tumor progression (migration and invasion)	OE/siRNA KD in cancer cell line	[137]
	NEAT1[a]	Up	Tumorigenesis (cell cycle, proliferation and anti-apoptosis)	shRNA KD in cancer cell line and mouse model	[102]
	SRA	Bimorphic	Tumor progression (invasion)	–	[138]
CESC	SRA	Up	Tumorigenesis (proliferation), tumor progression (invasion and migration)	KD in cancer cell line	[139]
CRC	CASC15	Up	Tumorigenesis (proliferation), tumor progression (migration and invasion)	OE/shRNA KD in cancer cell line and mouse model	[140]
	CCAT1	Up	Tumorigenesis (cell cycle and cell proliferation), tumor progression (invasion)	OE/shRNA KD in cancer cell line	[141, 142]
	CCAT2	Up	Tumorigenesis (proliferation), tumor progression (migration and invasion)	OE/siRNA KD in cancer cell line and mouse model	[143]
	PACER[a]	Up	Tumorigenesis (proliferation), tumor progression (invasion and migration)	siRNA KD in cancer cell line and mouse model	[62]
	PURPL	Up	Tumorigenesis (proliferation)	lncRNA KO in cancer cell line	[144]
	PVT1	Up	Tumorigenesis (proliferation)	siRNA KD in cancer cell line and mouse model	[69]
	RAMS11	Up	Tumorigenesis (proliferation), tumor progression (invasion and migration)	OE/KO in cancer cell line and KO in mouse model	[145]
ESCC	HERES	Up	Tumorigenesis (cell cycle, proliferation and anti-apoptosis), tumor progression (migration and invasion)	OE/siRNA KD in cancer cell line and mouse model	[57]
	LUCAT1[a]	Up	Tumorigenesis (proliferation and anti-apoptosis), tumor progression (migration and invasion)	OE/siRNA KD in cancer cell line	[31]
GBC	CCAT1	Up	Tumorigenesis (proliferation), tumor progression (migration)	OE/siRNA KD in cancer cell line and KD in mouse model	[146]
	PVT1	Up	Tumorigenesis (proliferation) tumor progression (invasion and migration)	siRNA KD in cancer cell line and shRNA KD/OE in mouse model	[147]
GC	CASC15	Up	Tumorigenesis (proliferation), tumor progression (migration)	OE/siRNA KD in cancer cell line and mouse model	[148]
	FENDRR	Down	Tumorigenesis	–	[61]
	H19[a]	Up	Tumorigenesis (proliferation and anti-apoptosis)	siRNA KD in cancer cell line	[149]
	HIF1A-AS2	Up	Tumorigenesis (proliferation), tumor progression (invasion)	OE/siRNA KD in cancer cell line and mouse model	[150]
	HOTAIR[a]	Up	Tumorigenesis (cell cycle, proliferation and anti-apoptosis), tumor progression (migration and invasion)	OE/siRNA KD in cancer cell line and mouse model	[151]
	PCGEM1	Up	Tumor progression (invasion and migration)	OE/siRNA KD in cancer cell line	[152]
HCC	AC096579.7	Down	Tumor progression	siRNA KD in cancer cell line	[61]
	ANRIL	Up	Tumorigenesis (cell proliferation and anti-apoptosis), tumor progression (migration and invasion)	siRNA KD in cancer cell line and shRNA KD in mouse model	[153]
	BCTRN1	Up	Tumorigenesis	–	[61]
	CASC15	Bimorphic	Tumor progression	–	[61]
	CCAT1	Up	Tumorigenesis	–	[61]
	CRNDE	Up	Tumorigenesis (cell cycle, proliferation and anti-apoptosis)	–	[61]
	H19[a]	Up	Tumor progression	–	[61]
	HAND2-AS1	Down	Tumorigenesis, tumor progression (migration)	–	[61]
	HIF1A-AS2	Bimorphic	Tumor progression, tumor progression (migration)	–	[61]
	HOTTIP	Up	Tumorigenesis (anti-apoptosis), tumor progression (invasion and migration)	siRNA KD in cancer cell line	[154]
	HULC	Up	Tumorigenesis (proliferation)	siRNA KD in cancer cell line	[155]
	LINC01018	Down	Tumor progression	siRNA KD in cancer cell line	[61]
	LINC00662	Up	Tumorigenesis (proliferation), tumor progression (migration and invasion)	OE/siRNA KD in cancer cell line and mouse model	[156]
	NEST	Down	Tumor progression	–	[61]
	PVT1	Up	Tumorigenesis (cell cycle and proliferation)	–	[61]
	RP11-166D19.1	Bimorphic	Tumorigenesis, tumor progression (migration)	siRNA KD in cancer cell line	[61]
	RP1-153P14.5	Down	Tumorigenesis, tumor progression (migration)	siRNA KD in cancer cell line	[61]
	RP11-731F5.2	Down	Tumor progression	siRNA KD in cancer cell line	[61]
	SNHG6	Up	Tumorigenesis	–	[61]
	TERC	Up	Tumorigenesis	–	[61]
	TEX41	Up	Tumor progression	–	[61]

(Continued)

Table 1. Continued

Cancer	lncRNA	Expression in cancer	Function	Functional validation	Reference
HCC	TUC338	Up	Tumorigenesis (proliferation), tumor progression (invasion)	siRNA KD in cancer cell line and mouse model	[157, 158]
	WDFY3-AS2	Down	Tumorigenesis, tumor progression (migration)	siRNA KD in cancer cell line	[61]
	XLOC_014515	Up	Tumor progression	siRNA KD in cancer cell line	[61]
	XLOC_015969	Up	Tumorigenesis, tumor progression (migration)	siRNA KD in cancer cell line	[61]
	XLOC_030220	Up	Tumor progression	–	[61]
	XLOC_050370	Down	Tumorigenesis	–	[61]
	XLOC_055355	Down	Tumorigenesis, tumor progression (migration)	siRNA KD in cancer cell line	[61]
	XLOC_056573	Up	Tumorigenesis	–	[61]
	XLOC_066981	Down	Tumorigenesis	–	[61]
	ZFAS1	Up	Tumorigenesis	–	[61]
MEL	SPRY4-IT1	Up	Tumorigenesis (proliferation and anti-apoptosis), tumor progression (invasion and migration)	OE/siRNA KD in cancer cell line	[159]
LC	MALAT1[a]	Up	Tumorigenesis (proliferation), tumor progression (migration and invasion)	OE/shRNA KD in cancer cell line and mouse model	[41, 160]
	NNT-AS1	Up	Tumorigenesis (proliferation), tumor progression (migration and invasion)	siRNA KD in cancer cell line	[161]
	UCA1	Up	Tumorigenesis (proliferation)	OE/KD in cancer cell line	[162]
OSCC	OIP5-AS1	Up	Tumorigenesis (cancer stemness and dedifferentiation)	OE in cancer cell line and mouse model	[163]
	HOTAIR[a]	Up	Tumor progression (invasion and migration)	siRNA KD in cancer cell line	[164]
OVC	FAL1	Up	Tumorigenesis (proliferation)	OE/siRNA, shRNA KD in cancer cell line and mouse model	[165]
	HOTAIR[a]	Up	Tumorigenesis (cell cycle, proliferation, anti-apoptosis)	OE/KD in cancer cell line and KD in mouse model	[166]
PAAD	NORAD	Up	Tumor progression (invasion and migration)	OE/shRNA KD in cancer cell line and KD mouse model	[167]
Pan	DANCR	Up	Tumorigenesis (proliferation), tumor progression (migration and invasion)	KD in cancer cell line	[168]
	HOXA-AS2	Up	Tumorigenesis (proliferation and anti-apoptosis), tumor progression (invasion and migration)	OE/siRNA KD in cancer cell line	[91]
	lincRNA-p21	Up	Tumorigenesis (anti-apoptosis)	siRNA KD in cancer cell line	[169]
	LUCAT1[a]	Up	Tumorigenesis (cell cycle, proliferation and anti-apoptosis), tumor progression (migration and invasion)	OE/KD in cancer cell line and mouse model	[170]
	PANDA	Up	Tumorigenesis (cell cycle, proliferation and anti-apoptosis)	siRNA KD in cancer cell line	[171]
	PVT1	Up	Tumorigenesis (cell cycle and proliferation), tumor progression (invasion and migration)	OE/siRNA KD in cancer cell line and mouse model	[70]
	SNHG1	Up	Tumorigenesis (proliferation and anti-apoptosis), tumor progression (migration and invasion)	OE/KD in cancer cell line and mouse model	[172]
	TRINGS	Up	Tumorigenesis (anti-necrosis)	OE/shRNA KD in cancer cell line	[173]
	TRMP	Up	Tumorigenesis (cell cycle and proliferation)	KD in cancer cell line and mouse model	[174]
	TUG1	Up	Tumorigenesis (proliferation)	siRNA KD in cancer cell line	[39]
	WT1-AS	Up	Tumorigenesis (proliferation)	siRNA KD in cancer cell line	[39]
PRAD	PCAT-1	Up	Tumorigenesis (proliferation)	OE/siRNA KD in cancer cell line	[175]
	PCGEM1	Up	Tumorigenesis (proliferation)	OE in cancer cell line	[176]
	SCHLAP1	Up	Tumor progression (invasion)	OE/siRNA KD in cancer cell line	[177, 178]
PRAD, Leukemia	ANRIL/p15AS	Up	Tumorigenesis	Gene silencing in mouse	[179–181]
PTC	MIAT	Up	Tumorigenesis (cell cycle and proliferation), tumor progression (invasion)	OE/siRNA KD in cancer cell line	[182]

Note. OE, overexpression; KD, knockdown; KO, knockout; siRNA, small interference RNA; shRNA, short hairpin RNA; BLCA, bladder urothelial carcinoma; BRCA, breast cancer; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CRC, colorectal cancer; GBC, gallbladder cancer; GBM, glioblastoma; GC, gastric cancer; HCC, hepatocellular carcinoma; MEL, melanoma; LC, lung cancer; OSCC, oral squamous cell carcinoma; OVC, ovarian cancer; PAAD, pancreatic adenocarcinoma; Pan, pan-cancer; PRAD, prostate adenocarcinoma; PTC, papillary thyroid cancer. [a]lncRNAs that were found to be both cancer-related and immune-specific.

cell invasion), the oncogenic functions of lncRNAs have mostly been verified in cancer cell lines rather than in normal or precancerous cells. Due to this fact, most oncogenic lncRNAs have also been reported to be cancer-progressing genes that control the EMT, migration and invasion. In fact, *NEAT1*, *HERES*, *H19*, *MALAT1*, *LUCAT1*,

plasmacytoma variant translocation 1 (*PVT1*), colon cancer-associated transcript 1 (*CCAT1*), p50-associated COX2-extragenic RNA (*PACER*) and HOX transcript antisense RNA (*HOTAIR*) control both tumorigenesis and cancer progression. To date, ~100 lncRNAs have been identified as key factors that regulate both cancer

Table 2. lncRNAs with tumor-suppressive functions

Cancer	lncRNA	Expression in cancer	Functional validation	Reference
APL	NEAT1[a]	Down	siRNA KD in cancer cell line	[103]
Blood cancer	XIST	Absent	KO in mouse model	[183]
BRCA	GAS5	Down	OE in cancer cell line	[72]
	LINC01184	Down	siRNA KD in cancer cell line	[39]
	NKILA[a]	Down	shRNA KD in cancer cell line	[44]
CRC	GAS5	Down	OE in cancer cell line	[184]
	LINC01133	Down	OE/sh RNA, siRNA KD in cancer cell line and KD in mouse model	[185]
	loc285194	Down	siRNA KD in cancer cell line and mouse model	[186]
	PTENP1	Down	siRNA KD in cancer cell line	[187]
GC	AA174084	Down	–	[188]
	GAS5	Down	siRNA KD in cancer cell line	[27]
	MEG3	Down	siRNA KD in cancer cell line	[75]
	PTCSC3	Down	OE/siRNA KD in cancer cell line	[189]
HCC	GAS5	Down	–	[190]
	MEG3	Down	OE in cancer cell line	[76]
	NRON[a]	Down	OE in cancer cell line and mouse model	[105]
NB	NBAT-1	Down	siRNA KD in cancer cell line	[191]
Pan	DINO	Down	OE/sh RNA, siRNA KD in cancer cell line and KO in mouse model	[192]
	LINC-PINT	Down	Antisense oligo KD in cancer cell line and OE in mouse model	[193]
	OIP5-AS1	Down	siRNA KD in cancer cell line	[39]
PTC	PTCSC3	Down	OE in cancer cell line	[194]

Note. APL, acute promyelocytic leukemia; NB, neuroblastoma. [a]lncRNAs that were found to be both cancer-related and immune-specific

development and progression in multiple cancer types, and the majority of these lncRNAs have been validated *in vitro* and *in vivo* (Table 1; Box 1). These oncogenic and cancer-progressing lncRNAs may become not only promising diagnostic and/or prognostic biomarkers but also potential therapeutic targets for cancer therapy.

Box 1. Functional studies of well-characterized oncogenic, cancer-progressing lncRNAs

- *HERES*, first detected in esophageal squamous cell carcinoma (ESCC), is an oncogene, upregulated in tumor tissue compared to normal or non-tumor tissue, and is a tumor promoter, exhibiting higher expression in ESCC patients with poor prognosis [57]. *HERES* controls both canonical and non-canonical Wnt signaling pathways at the epigenetic level via a *HERES*-EZH2 axis. These functions were validated via a series of *in vitro* cellular assays that examined wound-healing, invasion and colony formation after *HERES* expression was reduced by RNAi in ESCC cell lines as well as by *ex vivo* xenograft experiments.

- *H19* is an imprinted oncogene that shows increased expression induced by the p53/HIF1-alpha pathway following hypoxia stress [58]. This oncogenic lncRNA, interacting with EZH2, also enhances cancer metastasis by promoting cancer cell migration via epigenetic inhibition of E-cadherin expression in bladder cancer cell lines [59]. High *H19* expression contributes to adverse outcomes in breast [60] and liver cancers [61].

- *PACER* is another lncRNA that regulates both tumorigenesis and tumor progression by promoting PGE2 production through an interaction with p50, a subunit of the NF-κB transcription factor, in colorectal cancer. The increased PGE2 abundance leads to cancer proliferation, metastasis and invasion in colorectal cancer cell lines [62].

- *LUCAT1*, also known as the smoke- and cancer-associated lncRNA-1, was first identified as an lncRNA upregulated in lung cancer. Cell-based assays performed after RNAi treatment revealed that this lncRNA plays protumorigenic and cancer-progressing roles in ESCC, lung cancer and papillary thyroid cancer cell lines [30, 31, 63].

- *NEAT1* is overexpressed in a variety of cancer types, including lung, colorectal, prostate and breast cancers [64, 65], and promotes tumor cell growth and metastasis by modulating the expression of *E2F3* [66]. *NEAT1*, known to be transcriptionally regulated by the HIF transcription factor, enhances cell proliferation and has an anti-apoptosis effect in cancer cells [66–68]. Cancer patients with high *NEAT1* expression were found to show adverse clinical outcomes [68]. The cancer-progressing function of *NEAT1* was validated in experiments involving a mouse xenograft model that examined tumor volumes and survival rates [67].

- *PVT1* displays expression levels that are highly correlated with that of the MYC protein level; increased *PVT* expression was required for a high MYC protein level in 8q24-amplified human cancer cells [69]. This lncRNA regulates both tumorigenesis and cancer progression in various cancers, controlling cell growth, proliferation and apoptosis via an interaction with MYC. When *PVT1* was depleted in colon cancer cell lines, the viability of the cancer cells decreased, the abundance of apoptotic cells increased [70] and tumorigenesis was suppressed [69].
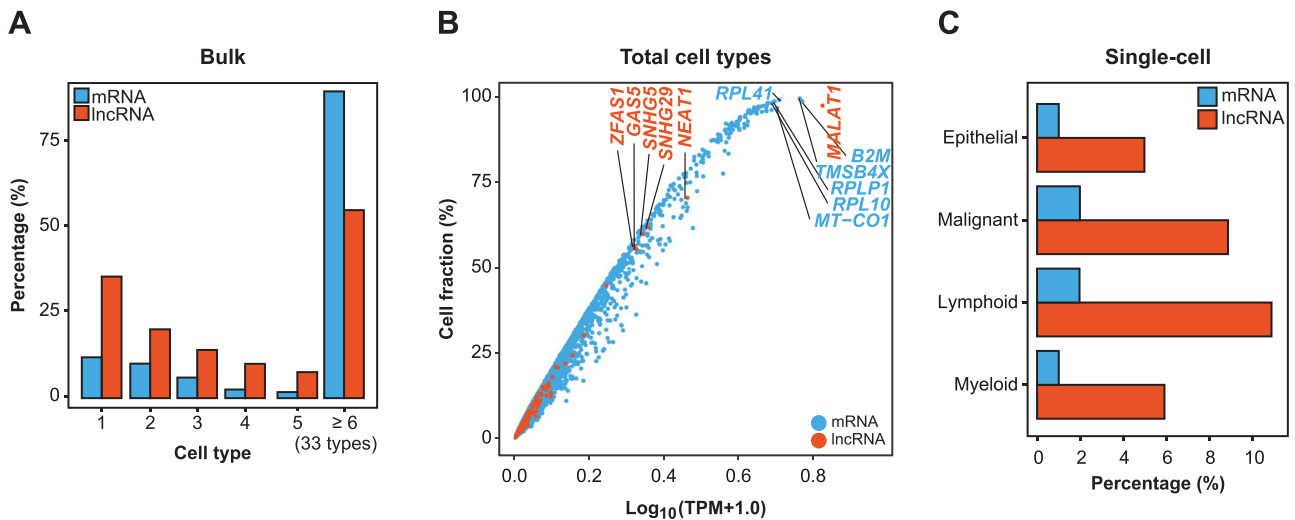
Figure 2. Cell type-specific expression of lncRNAs. (**A**) The percentages (Y-axis) of mRNAs (blue) and lncRNAs (red) expressed in certain cell types (X-axis; ≥1 TPM). Expression analyses of mRNAs and lncRNAs were done with bulk RNA-seq datasets from 33 human cell types. (**B**) Scatter plot of the fractions (Y-axis) of cells in which the indicated genes are expressed and the log-transformed expression value (TPM + 1.0; X-axis) of the respective gene. (**C**) The percentages (X-axis) of mRNAs and lncRNAs specifically expressed in each group of cells (≥1 TPM). (**B**, **C**) Public scRNA-seq data from lung cancers were reanalyzed [79].

- *MALAT1* is a highly conserved lncRNA, also known as nuclear-enriched abundant transcript 2 (*NEAT2*), which is abundant in many cancer types. TGF-β-induced upregulation of *MALAT1* enhances cancer metastasis, an effect mediated via an interaction with suz12 at the transcriptional level [42]. The knockdown of *MALAT1*, however, reduces cell proliferation and invasion but increases apoptosis by derepressing *MALAT1*-EZH2-mediated targets at the epigenetic level [43]. *MALAT1* also functions as a ceRNA that quenches tumor-suppressing miRNAs, relieving miRNA targeting [71].

Tumor-suppressing lncRNAs

To date, a handful of lncRNAs have been identified as tumor suppressors. These lncRNAs are generally downregulated in tumor samples compared to paired normal samples. They usually control the cell cycle and/or apoptosis, and reducing their abundance in cells often causes clonal expansion, increased cell proliferation and tumor growth. Patients with high expression of tumor-suppressing lncRNAs often display better clinical outcomes than those with lower expression. The functions of the tumor-suppressing lncRNAs have mostly been verified in cancer cell lines following perturbation of lncRNA expression. The documented tumor-suppressing lncRNAs are *GAS5* [72], maternally expressed gene 3 (*MEG3*) [73] and *NKILA* [44] (Table 2). *GAS5*, a well-characterized tumor-suppressing lncRNA, is downregulated in multiple cancer types, including breast, colorectal, gastric and liver cancers (Table 2). *GAS5* was earlier reported as a host gene that encodes 10 small nucleolar RNAs in its introns; its noncoding isoforms induce an anti-tumor effect, inhibiting tumor proliferation and metastasis

or promoting apoptosis [72, 74]. *MEG3* is another well-known tumor-suppressing lncRNA that is downregulated in liver and gastric cancers (Table 2). Depletion of *MEG3* enhances angiogenesis and promotes cell proliferation in cancer cell lines [75, 76]. *NKILA* is a tumor suppressor that was first reported in breast cancer. This lncRNA inhibits NF-κB-mediated metastasis and its low expression is correlated with adverse outcomes in breast cancer [44]. In a few cases, lncRNAs can also be translated into stable small peptides (micropeptides). For example, *HOXB-AS3* encodes a 53-amino acid HOXB-AS3 peptide which is well conserved in primates [77]. The HOXB-AS3 peptide then suppresses glucose metabolism reprogramming by inhibiting splicing of the pyruvate kinase M gene. *LINC00908* is a unique tumor-suppressing lncRNA which encodes a small regulatory peptide of STAT3 (ASRPS) [78]. ASRPS downregulates the phosphorylation of STAT3 through direct binding and consequently reduces the expression of vascular endothelial growth factor in triple-negative breast cancer.

Cell type-specific expression of lncRNAs in the TIME

Many lncRNAs display a strong cell type-specific expression pattern (Figure 2**A**). Expression profiling of mRNAs and lncRNAs across 33 different human cell types showed that the fraction of lncRNAs that exhibits a cell type-specific expression pattern is greater than that of mRNAs. However, expression-based studies performed using bulk tumor samples are limited in their ability to unveil cell type-specific lncRNA functions due to the lack of information about expression in specific cell types (Figure 1). To date, cancer-related functions of lncRNAs have been examined in cancer cell lines even in cases in which the lncRNAs are more highly expressed in other cell types, such as immune and stromal cells. A

reanalysis of public single-cell RNA-sequencing (scRNA-seq) data from lung cancers [79, 80] showed that the majority of cancer-related lncRNAs were present in <25% of the cells in the TIME, indicating cell type-specific expression in minor cell types or the consequence of the dropout effect for low abundant lncRNAs (Figure 2**B**). A greater fraction of mRNAs displayed ubiquitous expression, whereas only a few lncRNAs, such as *MALAT1*, *NEAT1*, *SNHG29*, *SNHG5*, *GAS5* and *ZFAS1*, were present in more than half of the cells (Figure 2**B**). Similar trends in lncRNA expression patterns were also observed in recent studies: lncRNAs showed lower expression levels, and were expressed in a lower proportion of cells, compared to PCGs in cancerous [81] and other tissues [82, 83]. At the single-cell level, 9% of the expressed lncRNAs were specifically present in malignant cells, 11% were present in lymphoid-lineage cells, 6% were present in myeloid cells and 5% were present in epithelial cells, which are much higher proportions than observed for mRNAs (Figure 2**C**).

On the other hand, the cell type-specific expression of lncRNAs raises another issue in annotating lncRNAs that are specifically expressed in rare cell types. lncRNAs specific to minor cell types, such as regulatory T cells (Tregs) and dendritic cells (DCs) in the TIME, appear to be absent in the current lncRNA annotations, which have mostly been constructed from bulk tissues or cancer cell lines [3]. Because rare cell types can be involved in tumor progression or anti-tumor activities through their interactions with tumor cells in the TIME, lncRNAs specifically expressed in those cell types should be considered as well. If present, Treg- and CD8+ T-specific lncRNAs might well be involved in oncogenic or tumor-suppressive functions, but many of them unfortunately remain undocumented. Hence, it is important to determine which lncRNAs are specific to rare immune cell types to understand their cellular functions in the TIME.

Immune-specific lncRNAs
lncRNAs are specifically expressed in a variety of immune cell types, ranging from hematopoietic stem cells (HSCs) to innate and adaptive immune cells in humans and mice (Table 3). Of these, several lncRNAs, including *lnc-DC*, *lnc13* and HOXA cluster antisense RNA 2 (*HOXA-AS2*), appear to be expressed in matched human and mouse immune cell types, suggesting a conserved role in these cell types. Immune-specific lncRNAs affect hematopoietic differentiation via diverse modes of action, which include functioning as miRNA/protein decoys and playing roles in protein scaffolding, protein trafficking and protein recruitment in the nucleus and cytoplasm (Figure 3). In particular, a majority of immune-specific lncRNAs appear to recruit protein complexes to specific genomic loci to regulate target gene expression at the epigenetic and transcriptional levels, thereby modulating immune cell activity and differentiation in the nucleus. For instance, *H19*, *ROCKI*, *lnc13* and *HOXA-AS2* play protein-recruiting functions or control

chromatin accessibility to regulate their target genes in immune cells (Figure 3).

- *H19*, a *trans*-regulator of imprinted genes, is highly expressed in both human and mouse HSCs and plays a conserved functional role that maintains HSC quiescence [84]. This lncRNA is known to scaffold S-adenosylhomocysteine hydrolase, which blocks the hydrolysis of S-adenosylhomocysteine, an inhibitor of adenosylmethionine-dependent DNA methyltransferases in the nucleus [85]. Hence, *H19* appeared to induce the demethylation of several primary hematopoietic transcription factors, including Runx1 and Spi1 [86].
- *ROCKI* bound to APEX1 has been shown to recruit the histone deacetylase HDAC1 to the *MARCKS* promoter in macrophages; HDAC1 then removed the H3K27ac modification from the target promoter [87]. Its function is known to be related to the phagocytosis activity of macrophages [88].
- *lnc13* was reported to be an inflammation-dependent lncRNA, and it has a celiac disease-related function in human and mouse macrophages. Reduced abundance of the lncRNA, observed in biopsy samples from celiac patients, leads to the derepression of inflammation-related genes, which are normally repressed by binding of *lnc13* to hnRNPD and Hdac1 at the gene loci [89].
- *HOXA-AS2* is encoded by a gene located between the *HOXA3* and four genes and is expressed in promyelocytic leukemia cells and human peripheral blood neutrophils. This lncRNA was reported to act as an apoptotic repressor in all *trans* retinoic acid-treated promyelocytic leukemia cells [90]. Overexpression of *HOXA-AS2* is involved in processes related to cancer progression, such as cell proliferation, metastasis and invasion [91].
- *lincRNA-Cox2* expression is induced by the Toll-like receptor-mediated inflammatory response. This lncRNA controls the expression of many immune-related genes by interacting with repressors and heterochromatin remodelers [92, 93].

On the other hand, cytoplasmic immune-specific lncRNAs activate or suppress a target at the RNA or protein level. For instance, *lnc-DC*, *lnc-MC*, *FIRRE* and cardiac and apoptosis-related lncRNA (*CARLR*) regulate immune cell activation and differentiation by controlling protein localization, modification or sponging miRNAs (Figure 3). Interestingly, *MALAT1*, *NEAT1* and *HOTAIR*, known to be nuclear-localized lncRNAs, are also reported to have functional roles in the cytoplasm. Although *NEAT1* and *MALAT1* are known to induce paraspeckle assembly in the nucleus, they have also been reported to function as ceRNAs in the cytoplasm of DCs: as a miR-155 sponge in the case of *MALAT1* [94] and as a miR-3076-3p sponge in the case of *NEAT1* [95]. Additionally, cytoplasmic *HOTAIR* facilitates IκBα degradation, which directs the translocation of NF-κB to the nucleus to
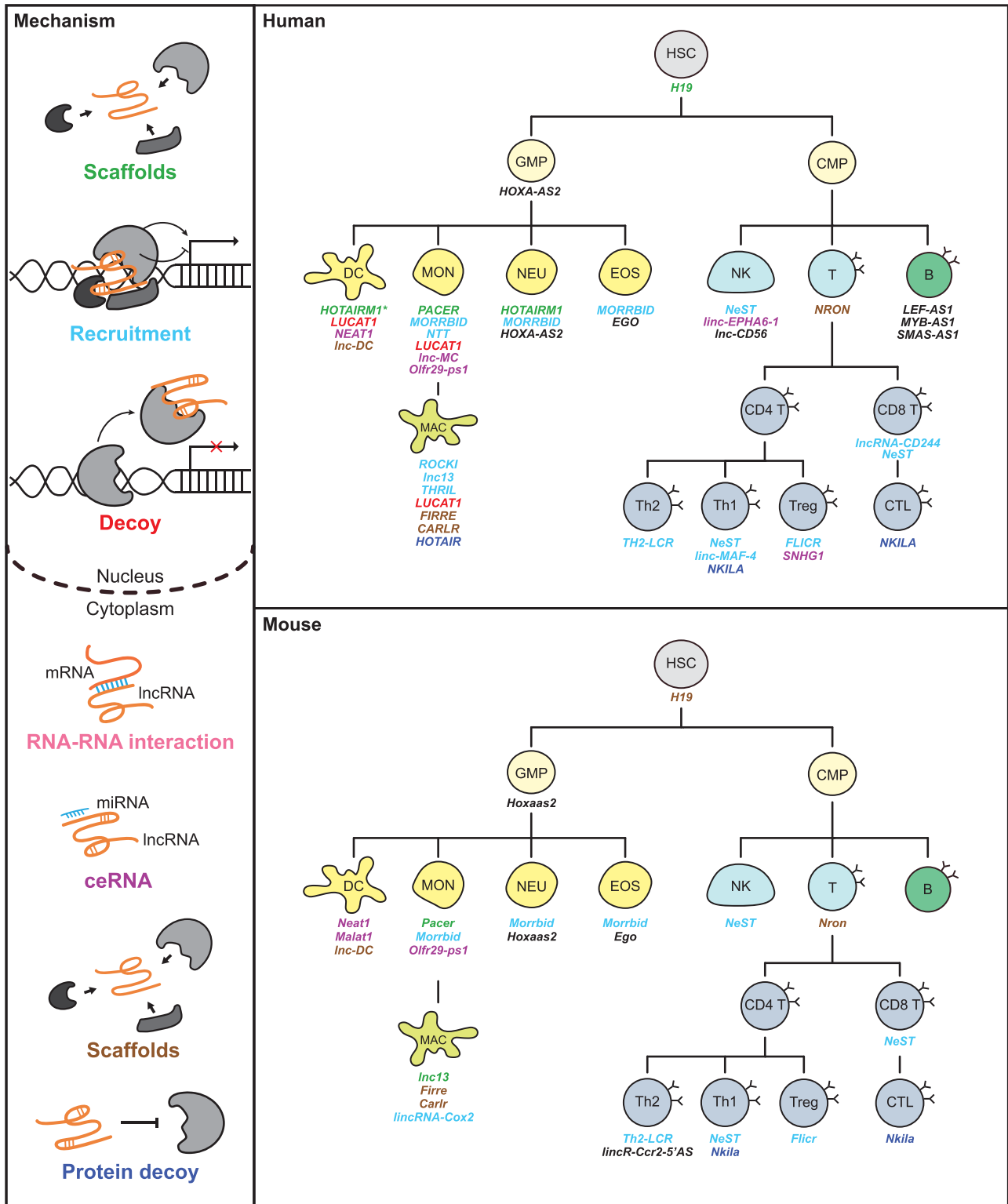
Figure 3. Functions of immune-related lncRNAs. Human and murine lncRNAs that have functional roles in HSCs, progenitor cells and immune cells are shown (lncRNAs are listed under each cell type) as are those that function during immune cell differentiation (lncRNAs are indicated on lines). The functional mechanisms of the lncRNAs are indicated by the color of the lncRNA name; the key on the left shows which color is assigned to each function, which is separated by localization in the nucleus versus cytoplasm. A black color indicates that the mechanism in immune cells is unclear (i.e. *EGO*, *HOXA-AS2*, *LEF-AS1*, *MYB-AS1*, *SMAS-AS1*, *lnc-CD56* and *lincR-Ccr2-5'AS*). GMP, granulocyte-monocyte progenitor; CMP, common myeloid progenitor; MON, monocyte; NEU, neutrophil; EOS, eosinophil; NK, natural killer cell; CTL, cytotoxic T cell; MAC, macrophage; *, also functions as a ceRNA.

Table 3. Immune lncRNAs expressed in human and mouse

lncRNA	Species	Cell type	Expression validation	Function	Reference
Stem cell					
H19[a]	Mouse	HSC	RT-qPCR	Regulates self-renewal of long-term HSCs	[86]
Lymphoid cells					
NRON[a]	Human, mouse	T cell	RT-qPCR	Regulates activated T cells	[104]
linc-MAF-4	Human	Th1 cell	RNA-seq	Regulates the expression of MAF and promotes Th1 differentiation	[195, 196]
lncRNA-CD244	Human	CD8+ T cell	Microarray	Inhibits the expression of IFNγ and TNF in CD8+ T cells	[197]
NeST (TMEVPG1)	Human, mouse	Th1 cell/ CD8+ T cell/NK cell	RT-qPCR	Binds to WDR5 in *cis* or *trans* to promote IFNγ expression	[198–200]
NKILA[a]	Human, mouse	Cytotoxic T/Th1 cell	RT-qPCR	Induces hyperactivated immune cell death by the NF-κB pathway	[101]
TH2-LCR	Human, mouse	Th2 cell	RT-qPCR	Co-expresses with IL-4, IL-5 and IL-13 genes regulating Th2 cytokines	[201, 202]
lincR-Ccr2-5-'AS	Mouse	Th2 cell	RNA-seq	Regulates Th cell development along with GATA3	[203]
lnc-CD56	Human	NK cell	RT-qPCR	Positively regulates CD56 gene	[204]
FLICR	Human, mouse	Tregs	RNA-seq RT-qPCR	Decreases the expression of Foxp3 in Tregs	[205]
LEF-AS1	Human	B cell	RNA-seq	Expressed in pre-B1 and pre-B2 cells	[206]
MYB-AS1	Human	B cell	RNA-seq	Expressed in pre-B1 and pre-B2 cells	[206]
SMAD1-AS1	Human	B cell	RNA-seq	Expressed in pre-B1 and pre-B2 cells	[206]
Myeloid cells					
LUCAT1[a]	Human	Myeloid cell	RNA-seq RT-qPCR	Interacts with STAT1 to inhibit ISGs transcription	[106]
NEAT1[a]	Human, mouse	DC	RT-qPCR	Induces tolerogenic phenotype in DCs	[95]
lnc-DC	Human, mouse	DC	RNA-seq RT-qPCR	Promotes the nuclear translocation and function of STAT3	[97]
MALAT1[a] (NEAT2)	Mouse	DC	Microarray RT-qPCR	Induces LPS-stimulated DCs to switch to tolerogenic DCs	[94]
HOXA-AS2	Human, mouse	Progranulocyte/neutrophil	RNA-seq RT-qPCR	Suppresses apoptosis of granulocytes	[90]
MORRBID	Human, mouse	Neutrophil/eosinophil/-monocyte	RNA-seq	Regulates granulocyte differentiation	[207]
HOTAIRM1	Human	Monocyte/DC/neutrophil	RT-qPCR	Promotes monocyte and DC differentiation	[208, 209]
lnc-MC	Human	Monocyte/-macrophage	RT-qPCR	Promotes monocyte/macrophage differentiation	[98]
PACER[a]	Human, mouse	Monocyte	RT-qPCR	Activates monocyte by inflammatory	[210]
HOTAIR[a]	Human	Macrophage (AML-stimulated)	RT-qPCR	Promotes the NF-κB-mediated inflammatory pathway	[96]
NTT	Human	Monocyte	RT-qPCR	Regulates inflammation and monocyte differentiation	[211]
THRIL	Human	Macrophage	Microarray	Activates TNF-α transcription in macrophages	[212]
ROCKI	Human	Macrophage	RNA-seq RT-qPCR	TLR stimulation in macrophages induces ROCKI expression	[87]
CARLR	Human, mouse	Macrophage	RT-qPCR	Regulates interaction between macrophages and intestinal cells	[100]
EGO	Human, mouse	Mature eosinophil	Microarray RT-qPCR	Regulates eosinophil development	[213]
lnc13	Human, mouse	Macrophage	RT-qPCR	Binds to hnRNPD to suppress transcription of immune response genes	[89]
FIRRE	Human, mouse	Macrophage	RT-qPCR	Regulates the stability of inflammatory mRNAs by interacting with hnRNPU	[99]

Note. AML, acute myeloid leukemia. [a]lncRNAs that were found to be both cancer-related and immune-specific.

activate *HOTAIR*, *iNOS* and *IL6* gene transcription in macrophages [96].

- *lnc-DC* is an lncRNA, identified in both human and mouse DCs, and is involved in the differentiation of human monocytes and mouse bone marrow cells to DCs. For this function, *lnc-DC* directly binds to STAT3

in the cytoplasm, maintaining STAT3 phosphorylation by preventing an interaction with the tyrosine phosphatase SHP1 [97].

- *lnc-MC* is highly expressed during monocyte/ macrophage differentiation and functions as a miRNA decoy in the cytoplasm. Gain- and

loss-of-function studies showed that *lnc-MC* promotes monocyte/macrophage differentiation of THP-1 cells and HSCs by sequestering miR-199a-5p, which represses *ACVR1B* [98].

- *FIRRE*, an lncRNA that is conserved between human and mouse, is also induced by NF-κB in macrophages. This lncRNA interacts with hnRNPU to regulate the stability of some inflammatory genes with AU-rich elements [99].
- *CARLR* is expressed in diverse human and mouse tissues, and its expression is increased when the NF-κB signaling pathway is active in human macrophages [100]. Downregulation of the lncRNA was shown to impair activation of the NF-κB signaling pathway, which affected inflammatory signals between macrophages and intestinal cells. This phenomenon could play a causal role in human celiac disease.

Collectively, various studies have shown that a considerable number of immune-specific lncRNAs are involved in cellular differentiation, activation and inflammation-based signaling in both lymphoid and myeloid lineages. Despite the tremendous efforts that have been made to functionally characterize immune-specific lncRNAs, only a few of them have been examined to determine whether they are involved in tumor progression or suppression in the TIME. Moreover, many more lncRNAs expressed in immune cells remain functionally uncharacterized in their respective cell types (Figure 4). Studying such uncharacterized lncRNAs will expand the reservoir of lncRNA candidates, which may exhibit tumor-regulating functions in the TIME.

Multifaceted functions of TIME lncRNAs

Some cancer-promoting or -suppressing lncRNAs could play their roles not only in malignant cells but also in tumor-specific immune cells. Such multicellular functions of lncRNAs could be unexpectedly prevalent in the TIME through cell–cell interactions. *NKILA* is upregulated by the inflammatory cytokines tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), via NF-κB signaling in inflammation-stimulated breast epithelial cells and plays an anti-tumor function by inhibiting NF-κB activation (Figure 5**A**) [44]. The repression of *NKILA* by miR-103/107 targeting induces NF-κB signaling, increasing cell invasiveness in breast cancer cell lines. Later work revealed that the lncRNA is also an NF-κB-interacting RNA, upregulated in cytotoxic T cells [101]. *NKILA* overexpression in cytotoxic T and Th1 cells appears to control the immune escape of cancer cells by inducing the apoptosis of stimulated T cells via inhibition of NF-κB activity.

The multifaceted functions of *NKILA* in the TIME suggest the possibility of unknown cell type-specific functions of other TIME lncRNAs. In fact, *NEAT1*, *H19*, *NRON*, *LUCAT1* and *HOTAIR*, which play oncogenic or tumor-suppressive roles in cancer cells, have also been shown to play functional roles in diverse types of immune cells (Table 3). *NEAT1* is upregulated in various cancers and

is known to play oncogenic roles [64–68, 102]. It also plays a tumor-suppressive role, preventing impairment of myeloid cell differentiation [103] (Figure 5**B**). *NRON* was first characterized as a repressor of the nuclear factor of activated T cells (*NFAT*) in the T cell-derived Jurkat cell line [104] and was later revealed to be a tumor-suppressing lncRNA that limits liver tumor growth and metastasis [105] (Figure 5**C**). Furthermore, *NRON* overexpression was shown to attenuate the level of EMT markers. The oncogenic lncRNA *LUCAT1* was also reported to negatively regulate interferon responses in myeloid cells [106] (Figure 5**D**). The immunological functions of cancer-promoting and -suppressing lncRNAs suggest that the lncRNAs could participate in regulating the cross talk between tumor and immune cells during cancer development and progression.
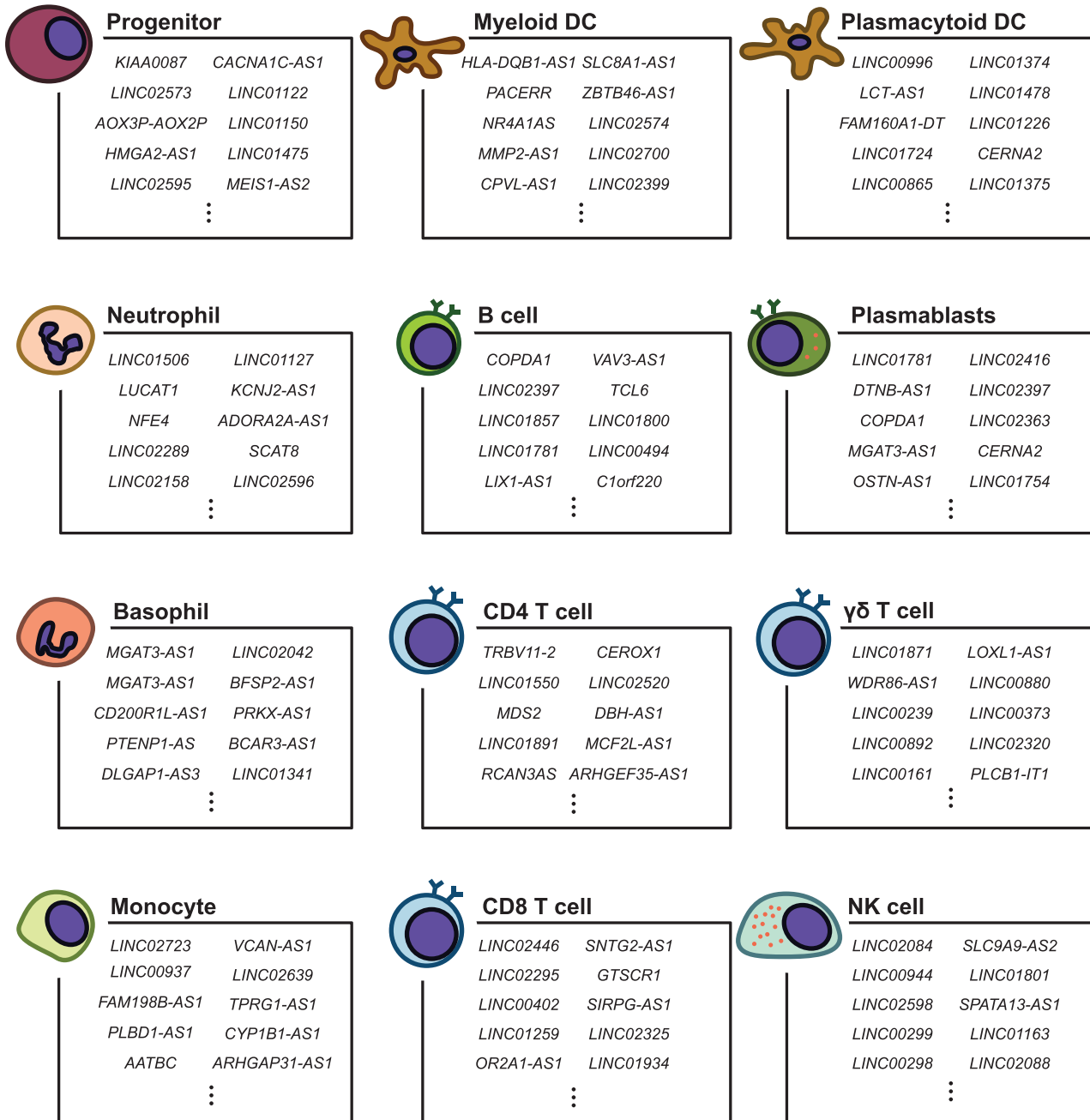
lncRNAs in cancer immunity

Cancer immunotherapy primarily targets immune checkpoint molecules, such as PD-1 or PD-L1, to relieve the suppression of conventional cytotoxic CD8$^+$ T cells so that they recover antitumor activity [107, 108]. Several immune checkpoint inhibitors have already been approved by the US Food and Drug Administration; however, only a small number of patients have benefited from them [109–111]. A number of factors in the TIME, including the expression of immune checkpoint molecules, the number of tumor-infiltrating lymphocytes (TILs) and the presence of neoantigens, may be able to predict patient responses and discriminate immunotherapy responders from nonresponders with limited sensitivity. Meanwhile, there is growing evidence that lncRNAs regulate crucial mechanisms of cancer immunity which range from antigen presentation to T cell exhaustion [112]. There are a handful of lncRNAs, summarized in Table 4, that are well characterized and can be used as diagnostic markers or even as therapeutic targets in TIME [113–115].

Along with individual lncRNAs, a collective lncRNA set can also predict the prognosis of cancer patients. For example, the lncRNA signature of tumor-infiltrating B lymphocytes (TILBlncSig) is a collection of eight lncRNAs specifically expressed in B cells [116]. Expression of the individual lncRNAs can be used to predict different outcomes of bladder cancer patients (good prognosis, *TNRC6C-AS1*, *WASIR2*, *GUSBP11*, *OGFRP1* or *AC090515.2* expression; poor prognosis, *PART1*, *MAFG-DT* or *LINC01184* expression); however, the combination of these lncRNAs weighted by coefficients of the multivariate Cox regression model confidently dichotomized bladder cancer patients with different prognoses in multiple independent datasets. TILBlncSig is also correlated with the infiltration of NK, immature dendritic and mast cells along with activated B cells and the expression of the immune checkpoint molecules, PD-1 and PD-L1. Furthermore, individuals with low PD-1 or PD-L1 expression levels in the TILBlncSig high-risk group showed worse outcomes than individuals with any

Ubiquitously expressed lncRNAs in immune cell types

MALAT1	PCBP2-OT1	DNAAF4-CCPG1	CHRM3-AS2	CYTOR	GUSBP11	LINC02812	SMIM25
CCDC18-AS1	PSMD6-AS2	PCED1B-AS1	LINC01001	EBLN3P	HECW2-AS1	LINC02863	SNHG16
STAG3L5P-PVRIG2P-PILRB	SNHG1	SLX1A-SULT1A3	LINC02384	ELMO1-AS1	LINC00926	MHENCR	SNHG29
ITGB2-AS1	GAS5	LINC00528	SNHG15	FAM157C	LINC01002	MRPL20-AS1	SNHG3
PSMA3-AS1	SLX1B-SULT1A4	NEAT1	ARHGAP27P1-BPTFP1-KPNA2P3	FAM30A	LINC02458	PINK1-AS	TNRC6C-AS1

Cell type-specific lncRNAs

Progenitor
KIAA0087	CACNA1C-AS1
LINC02573	LINC01122
AOX3P-AOX2P	LINC01150
HMGA2-AS1	LINC01475
LINC02595	MEIS1-AS2

Myeloid DC
HLA-DQB1-AS1	SLC8A1-AS1
PACERR	ZBTB46-AS1
NR4A1AS	LINC02574
MMP2-AS1	LINC02700
CPVL-AS1	LINC02399

Plasmacytoid DC
LINC00996	LINC01374
LCT-AS1	LINC01478
FAM160A1-DT	LINC01226
LINC01724	CERNA2
LINC00865	LINC01375

Neutrophil
LINC01506	LINC01127
LUCAT1	KCNJ2-AS1
NFE4	ADORA2A-AS1
LINC02289	SCAT8
LINC02158	LINC02596

B cell
COPDA1	VAV3-AS1
LINC02397	TCL6
LINC01857	LINC01800
LINC01781	LINC00494
LIX1-AS1	C1orf220

Plasmablasts
LINC01781	LINC02416
DTNB-AS1	LINC02397
COPDA1	LINC02363
MGAT3-AS1	CERNA2
OSTN-AS1	LINC01754

Basophil
MGAT3-AS1	LINC02042
MGAT3-AS1	BFSP2-AS1
CD200R1L-AS1	PRKX-AS1
PTENP1-AS	BCAR3-AS1
DLGAP1-AS3	LINC01341

CD4 T cell
TRBV11-2	CEROX1
LINC01550	LINC02520
MDS2	DBH-AS1
LINC01891	MCF2L-AS1
RCAN3AS	ARHGEF35-AS1

γδ T cell
LINC01871	LOXL1-AS1
WDR86-AS1	LINC00880
LINC00239	LINC00373
LINC00892	LINC02320
LINC00161	PLCB1-IT1

Monocyte
LINC02723	VCAN-AS1
LINC00937	LINC02639
FAM198B-AS1	TPRG1-AS1
PLBD1-AS1	CYP1B1-AS1
AATBC	ARHGAP31-AS1

CD8 T cell
LINC02446	SNTG2-AS1
LINC02295	GTSCR1
LINC00402	SIRPG-AS1
LINC01259	LINC02325
OR2A1-AS1	LINC01934

NK cell
LINC02084	SLC9A9-AS2
LINC00944	LINC01801
LINC02598	SPATA13-AS1
LINC00299	LINC01163
LINC00298	LINC02088

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Figure 4. Ubiquitously expressed lncRNAs and the top 10 most abundant cell type-specific lncRNAs in immune cell types. lncRNAs that are expressed in >50% of all cell types (ubiquitously expressed lncRNAs, top) and the top 10 most abundant cell type-specific lncRNAs in progenitor cells, myeloid DCs, plasmacytoid DCs, neutrophils, B cells, plasmablasts, basophils, CD4+ T cells, gamma-delta T cells, monocytes, CD8+ T cells and NK cells (bottom). Public RNA-seq datasets obtained from 29 immune cell types were reanalyzed for these classifications [132].
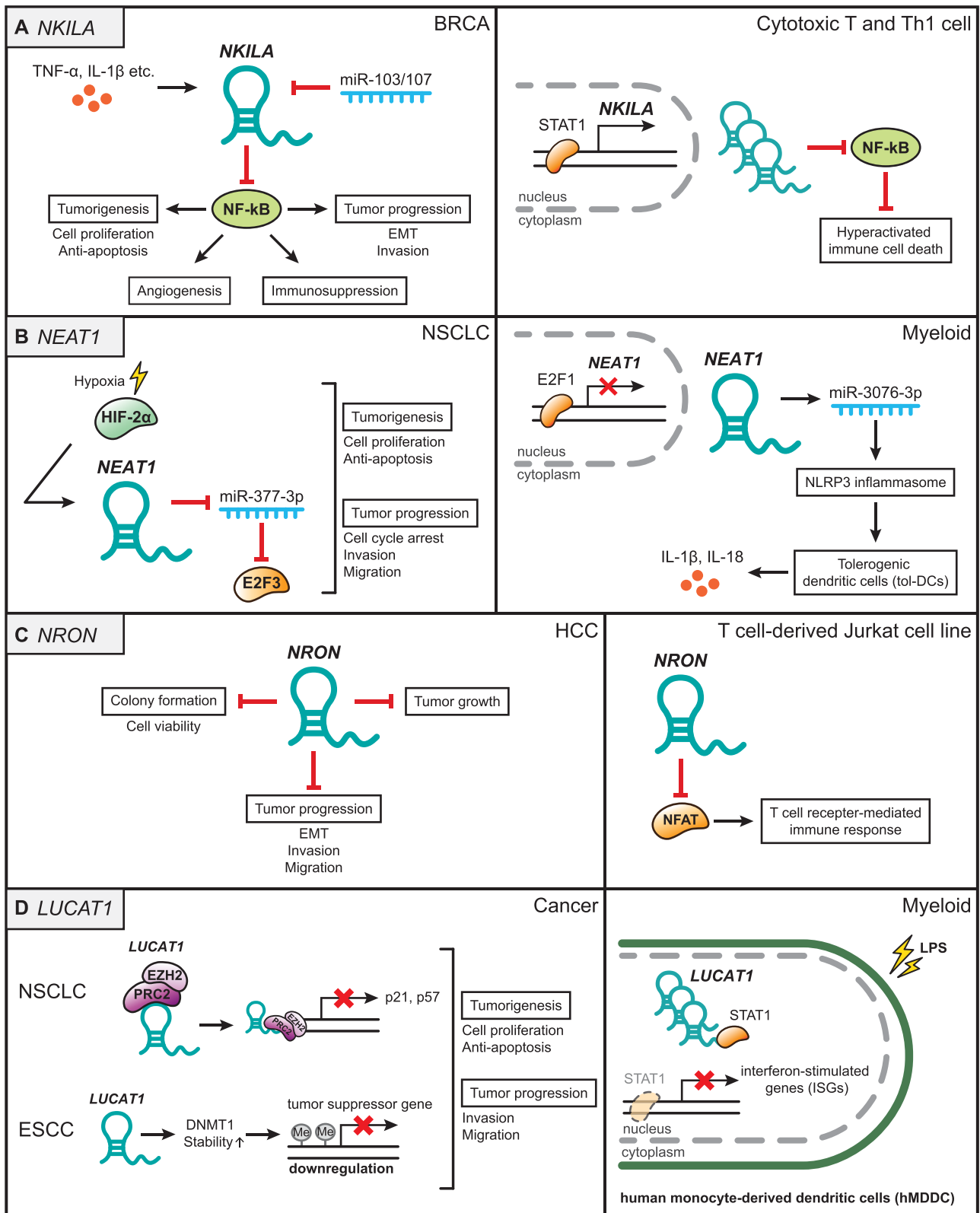
Figure 5. Multifaceted functions of lncRNAs in tumor and immune cells. (**A**) Two distinct functions of *NKILA* in tumor cells and T cells. In tumor cells, *NKILA* is upregulated by several inflammatory mediators (TNF-α and IL-1β) that inhibit the activation of NF-κB, which controls tumorigenesis and tumor progression. This regulation is blocked by miRNA targeting. In T cells, STAT1-mediated expression of *NKILA* inhibits NF-κB activity, thereby increasing immune cell death. Thus, the silencing of *NKILA* in tumor-reactive T cells enhances therapeutic effects in cancer by decreasing immune cell death. (**B**) Two distinct functions of *NEAT1* in tumor cells and DCs. (**C**) Two distinct functions of *NRON* in tumor cells and T cells. (**D**) Two distinct functions of *LUCAT1* in tumor cells and macrophages.

Table 4. lncRNAs in cancer immunity

lncRNA	Cell/cancer type	Function	Reference
MORRBID	Myeloid cell	Promotes differentiation of granulocytes by recruiting PRC-2 to the Bcl2 promoter	[207]
THRIL	Monocyte	Activates TNF-α expression by recruiting the ribonucleoprotein complex hnRNPL	[212]
ANCR	Macrophage	Downregulates FOXO1 to repress M1 macrophage polarization	[214]
BCRT1	Macrophage	Binds with miR-1303 to inhibit repression of PTBP3 and promote M2 macrophage polarization	[215]
CASC2	Macrophage	Suppresses coagulation factor x and macrophage polarization to M2	[216]
CCAT1[a]	Macrophage	Downregulates miR-148a to inhibit M2 macrophage polarization	[217]
GNAS-AS1	Macrophage	Promotes M2 macrophage polarization by inhibiting miR-4319 or sponging up miR-433-3p	[218]
LIFR-AS1	Macrophage	Promotes osteosarcoma cell progression by sponging up miR-29a	[219]
LINC00662	Macrophage	Activates Wnt/β-catenin signaling in HCC and promotes M2 macrophage polarization	[220]
lincRNA-Cox2	Macrophage	Inhibits polarization of M2 macrophages; represses and activates a large number of immune-related genes	[92, 119]
lincRNA-p21	Macrophage	Promotes polarization of M2 macrophages	[221]
lnc13	Macrophage	Inhibits expression of inflammatory genes by binding to hnRNPD	[89]
lncRNA-MM2P	Macrophage	Promotes macrophage-mediated tumor growth and angiogenesis by polarization of M2 macrophages	[222]
MALAT1	Macrophage	Mediates secretion of FGF2 from TAMs to inhibit inflammatory cytokine release and promote proliferation, migration and invasion of thyroid cancer cells	[223]
NIFK-AS1N	Macrophage	Downregulates miR-146a and suppresses polarization of M2 macrophages	[224]
RP11-361F15.2	Macrophage	Downregulates miR-30c-5p and promotes polarization of M2 macrophages	[225]
RPPH1	Macrophage	Is transported from CRC cells via exosomes to TAMs and promotes polarization of M2 macrophages	[226]
SBF2-AS1	Macrophage	Acts as a ceRNA to repress miR-122-5p and upregulates XIAP expression via exosomes secreted by M2 macrophages	[227]
SNHG20	Macrophage	Activates STAT6 to induce M2 macrophage polarization	[228]
TUC339	Macrophage	Regulates M1/M2 macrophage polarization	[229]
XIST	Macrophage	Is regulated by TCF-4 and promotes polarization of M2 macrophages	[230]
HOTAIRM1	MDSC	Upregulates HOXA1 to suppress tumor progression and MDSC functions	[231]
lnc-C/EBPb	MDSC	Negatively controls immunosuppressive functions and differentiation of MDSCs	[232]
lnc-CHOP	MDSC	Promotes immunosuppressive functions of MDSCs	[233]
MALAT1	MDSC	Negatively regulates MDSCs	[234]
Olfr29-ps1	MDSC	Sponges up miR-214-3p to facilitate differentiation and development of MDSCs	[235]
Pvt1[a]	MDSC	Promotes immunosuppressive functions of granulocytic-MDSCs	[236]
RUNXOR	MDSC	Is associated with the development and immunosuppressive function of MDSCs	[237]
HOTAIRM1	DC	Competitively binds to miR-3960 to regulate DC differentiation	[208]
lnc-DC	DC	Promotes DC maturation and regulates TLR9/STAT3 signaling	[238]
lnc-Dpf3	DC	Suppresses DC migration by binding to HIF1a to inhibit its activity	[239]
NEAT1[a]	DC	Uses the NLRP3 inflammasome as a molecular decoy for miR-3076-3p and induces a tolerogenic phenotype in DCs	[95]
GAS5	NK cell	Negatively regulates miR-544 to enhance the cytotoxicity of NK cells	[240]
IFNG-AS1	NK cell	Augments IFNγ upon NK cell activation	[200]
linc-EPHA6-1	NK cell	A ceRNA for miR-4485-5p to induce expression of NKp46	[241]
lnc-CD56	NK cell	Positively regulates CD56 expression in NK cells	[204]
lnc-TIM3	T cell	Promotes T cell exhaustion by binding to Tim-3	[242]
lncRNA-CD244	T cell	Interacts with EZH2 and represses the *ifng* and *tnfa* loci by chromatin modification	[197]
NEAT1[a]	T cell	Increases T cell apoptosis by regulating miR-155/Tim-3	[243]
NeST	T cell	Binds to WDR5 in *cis* or *trans* to promote IFNγ expression	[198–200]
NRON[a]	T cell	Inhibits NFAT activity by preventing its accumulation in the nucleus and downregulates T cell activation	[104]
lincR-Ccr2-5'AS	Th2 cell	Regulates expression of genes involved in chemokine signaling pathways and migration of Th2 cells	[203]
TH2-LCR	Th2 cell	Regulates the expression of Th2 cytokines, IL-4, IL-5 and IL-13	[202]
Flatr	Tregs	Promotes the expression of Foxp3, the master transcription factor regulator of Tregs	[244]
Flicr	Tregs	Negatively regulates Foxp3 expression by modifying chromatin accessibility in the CNS3/AR5 region of *Foxp3*	[205]
lnc-EGFR	Tregs	Promotes Treg differentiation and HCC growth by stabilizing epidermal growth factor receptor	[245]
linc-POU3F3	Tregs	Promotes the distribution of Tregs in peripheral blood T cells and supports the proliferation of gastric cancer cells	[246]
SNHG1	Tregs	Sponges up miR-448 and upregulates IDO1 to support Treg differentiation	[247]
AC090515.2, GUSBP11, LINC01184, MAFG-DT, OGFRP1, PART1, TNRC6C-AS1, WASIR2	B cell (TILBlncSig)	A combination of eight lncRNAs expressed in B cells that can predict the outcome of bladder cancer	[116]

(Continued)

Table 4. Continued

lncRNA	Cell/cancer type	Function	Reference
HCG26, PSMB8-AS1, TNRC6C-AS1, CARD8-AS1, HCP5, LOC286437, LINC02256	TIL (TILSig)	A combination of seven immune-related lncRNAs that can predict the outcome of lung cancer	[117]
FENDRR	HCC	Sponges up miR-423-5p and upregulates GADD45B to inhibit Treg-mediated immune escape	[248]
LIMIT	MEL	Functions in antigen presentation by inducing the expression of MHC-I under IFNγ stimulation	[118]
lncMX1-215	HNSCC	Interacts with GCN5 H3K27 acetylase to inhibit the expression of PD-L1	[249]
linc-ROR	HCC	Induces resistance to chemotherapy in CD133+ tumor initiating cells	[250]
lnc-sox5	CRC	Upregulates the expression of IDO1 to modulate infiltration of CD3 + CD8+ T cells in CRC	[251]
linc-VLDLR	HCC	Is transported to neighboring cells in extracellular vesicles and Induces resistance to chemotherapy in the recipient cells	[252]
MALAT1[a]	DLBL	Increases the expression of PD-L1 by sponging up miR-195	[253]
RP11-323N12.5	GC	Contributes tumor growth and is transported by exosomes to T cells to enhance Treg differentiation by regulating the expression of YAP1	[254]
SNHG16	BC	Is transmitted by exosomes to $\gamma\delta$1 T cells and sponges up miR-16-5p to upregulate CD73 expression	[52]
SNHG20	ESCC	Promotes cancer cell growth and metastasis by modulating the ATM-JAK-PD-L1 pathway	[255]
UCA1	GC	Promotes PD-L1 expression by repressing miR-26a/b, miR-193a, and miR-214	[256]
BLACAT1	CRC	Epigenetically represses p15 expression by binding to PRC2	[257]

Note. MDSC, myeloid-derived suppressor cell; DLBL, diffuse large B-cell lymphoma. [a]lncRNAs that were found to be both cancer-related and immune-specific.

other combination of PD-1/PD-L1 expression levels and TILBlncSig, suggesting that TILBlncSig is an indicator of an immunosuppressive microenvironment. In a similar manner, a set of seven pan-immune lncRNAs specifically expressed by TILs (TILSig) was developed and validated in multiple lung cancer cohorts by the same research group [117].

Some lncRNAs specifically function in cancer cells by regulating antigen presentation or PD-L1 expression (Table 4). lncRNA inducing major histocompatibility complex-I (MHC-I) and immunogenicity of tumor (*LIMIT*), a conserved lncRNA in human and mouse, induces the expression of MHC-I in cancer cells, which is crucial for the antitumor immune response [118]. Transcription of *LIMIT* is activated by binding of the STAT1/IRF1 transcription factor to the promoter under interferon-γ (IFNγ) stimulation. *LIMIT* induces a cluster of guanylate-binding protein (GBP) genes in *cis*; GBPs in turn interact with the HSP90 chaperone to release heat shock factor-1 (HSF1) in the cytoplasm. The released HSF1 proteins trimerize and enter the nucleus to regulate several target genes, including MHC-I. Based on extensive experimental validation *in vivo* and *in vitro*, the authors suggested the *LIMIT*-GBP-HSF1 axis as a therapeutic target for immunotherapy, with the aim of regulating MHC-I expression. In contrast, *lincRNA-Cox2*, which is activated by inflammatory responses, is expressed in M1 and M2 macrophages in hepatocellular carcinoma (HCC) [119]. The expression of this lncRNA mediates the reduction of IL-12, iNOS and TNF-α in M1 macrophages, inactivating their tumor-suppressive function, while its expression in M2 macrophages promotes HCC cell proliferation.

Single-cell analysis of TIME lncRNAs

Advances in single-cell sequencing technology allowed us to profile transcriptomes at the single-cell level, providing a comprehensive, unbiased way to identify new cell type-specific markers and to identify novel regulators in a certain cell type (Figure 6) [120]. Likewise, the analysis of single-cell transcriptomes would also allow the detection of new lncRNA markers or their functions at the single-cell level [82, 83, 86, 121]. For example, Kim *et al.* [121] profiled single-cell data from diverse reprogramming stages in somatic cells and found several lncRNA sets showing dynamic changes in expression during reprogramming. Bocchi *et al.* [82] produced bulk sample and single-cell sequencing data from developing human striatum to discover novel lncRNA regulatory networks.

Recently, cross talk between tumor and nontumor cells has been intensively studied using single-cell analyses. However, most studies have focused on PCGs [122, 123]; only a few have profiled lncRNAs [81, 124–126]. For example, Li *et al.* [81] observed a specific role for lncRNAs in metastatic clear cell renal cell carcinoma (ccRCC) using single-cell sequencing data. The authors discovered that a total of 173 lncRNAs were related to ccRCC metastasis and named them as ccRCC metastasis-associated lncRNAs (CMALs). Based on a coexpression network between CMALs and PCGs, CMALs appeared to be contributing to cell adhesion, the immune response and cell proliferation, and 12 of them specifically regulated TNF and HIF1 signaling pathways to promote cancer metastasis. Although single-cell lncRNA studies at a global level
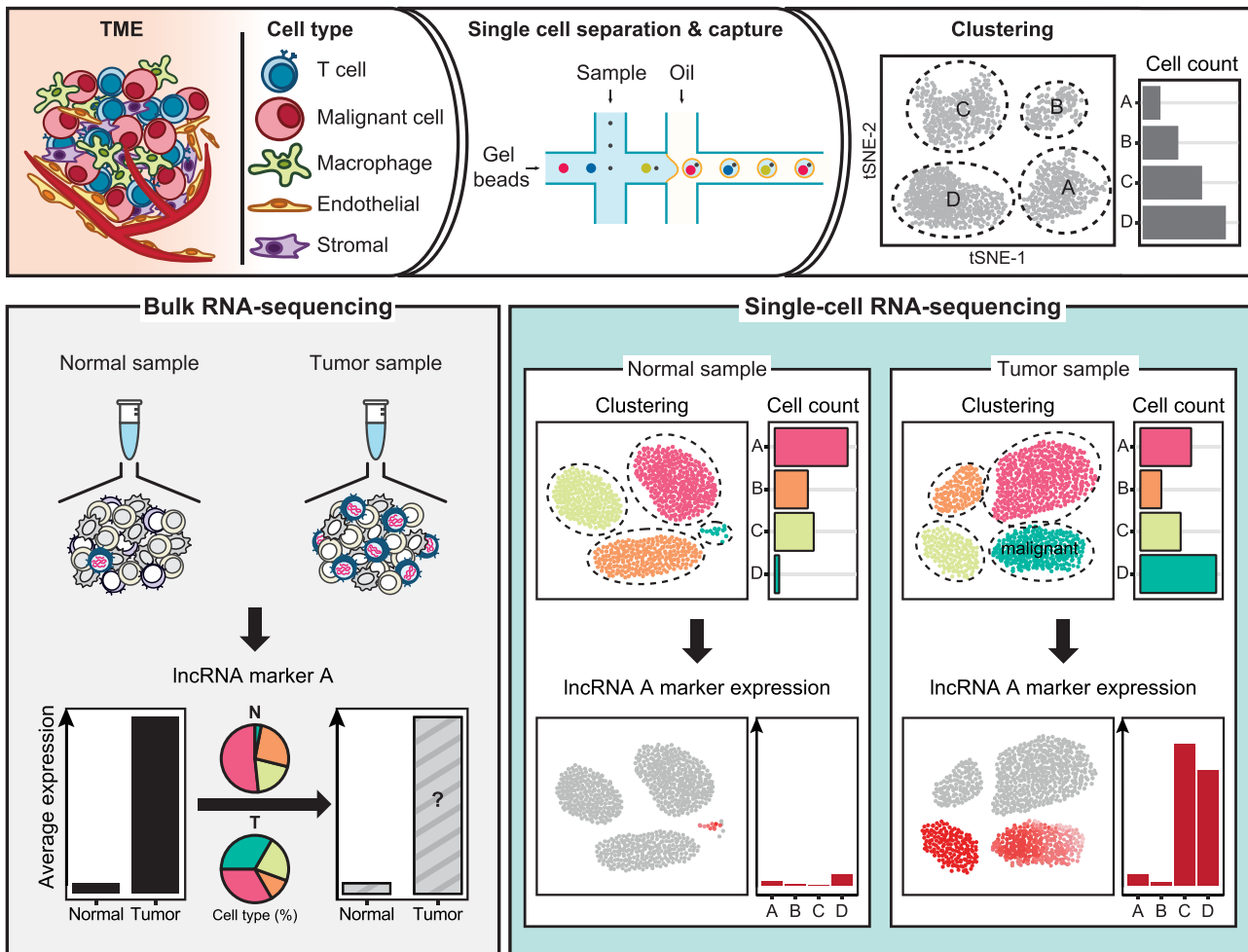
Figure 6. Detection of lncRNA markers via scRNA-seq versus bulk RNA-seq. The general procedure for scRNA-seq is summarized in the top panel. In the bottom panels, marker analyses at the bulk and single-cell levels are compared. Bulk RNA-seq mainly captures lncRNA markers that are differentially expressed in bulk tumor samples regardless of the cell type composition. scRNA-seq captures the lncRNA markers specific to certain cell types as well as markers specific to tumor-specific cell types.

are rare, databases such as Lnc2Cancer 3.0 [127] or LnCeCell [126] provide a comprehensive overview especially for cellular-specific lncRNA-associated ceRNA networks and RNA–RNA interactions. Reasons for such a limited number of single-cell studies of lncRNAs include incomplete annotations of cell type-specific lncRNAs and their relatively low expression in the TIME. Hence, a comprehensive map of TIME lncRNAs would be a great resource for the identification of functional lncRNAs in the TIME.

Single-cell platforms for lncRNA studies

Because the droplet-based approach (e.g. 10X or Drop-seq [128]) produces single-cell reads at the 3'-end of RNAs with poly-A tails (also known as 3'-end scRNA-seq) or at the 5'-end of RNAs (also known as 5'-end scRNA-seq), it is necessary to use high-confidence end positions of genes to properly quantify lncRNAs. Due to the low abundance of lncRNAs, some lncRNA sequences have only been partially assembled and a full-length sequence is not available in the current gene annotations. The plate-based approach (e.g. SMART-seq2) sequences full-length transcripts by cell. Because full-length

scRNA-seq generally captures information from many fewer cells compared to 3'-end scRNA-seq, the read coverages and the number of genes per cell are generally much higher than those of 3'-end scRNA-seq, suggesting that full-length scRNA-seq would provide a more sensitive means to identify cell type-specific lncRNAs in the TIME [124].

For this chapter, two representative single-cell platforms, 10X Chromium 3'-seq (10X) [129] and SMART-seq2 (SS2) [130] were compared over publicly available lung cancer scRNA-seq datasets [79, 80] with respect to their sensitivity for lncRNA detection. About 37.6% and ~65.4% of lncRNAs, represented in bulk RNA-seq data, were also detected at a similar level [≥1 transcripts per million (TPM)] in the 10X and SS2 platforms, respectively (Figure 7**A**). About 74.9% and ~98.2% were detectable (≥0.1 TPM) in the 10X and SS2 platforms, respectively. As expected, SS2 appeared to be more sensitive for the detection of lncRNAs, although the sensitivity depends on the sequencing depth.

Differentially expressed genes (DEGs) between tumor and nontumor samples at the single-cell level (single-cell DEGs) could differ from those at the bulk level
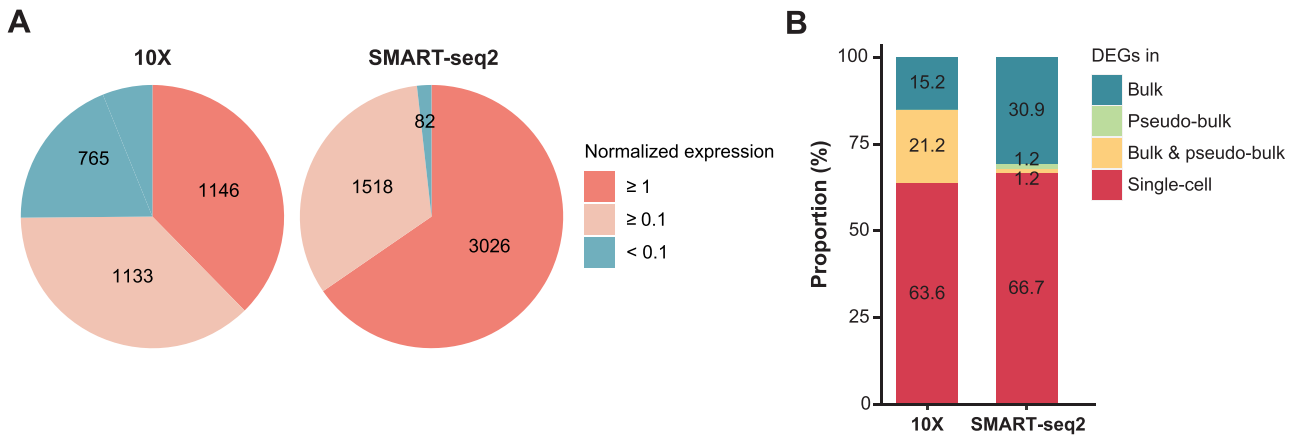
Figure 7. Comparison of expressed lncRNAs and DEGs in scRNA-seq datasets versus bulk RNA-seq datasets. (**A**) TPM distribution for genes represented in single-cell RNA-seq datasets that were detected at ≥1 TPM in bulk RNA-seq data from TCGA (lung adenocarcinoma and squamous cell carcinoma for 10X and lung adenocarcinoma for SS2) in each scRNA-seq platform. (**B**) The proportion of single-cell DEG lncRNAs between tumor and nontumor samples overlapped with those from bulk RNA-seq data or pseudo-bulk RNA-seq data. Single-cell DEGs were acquired by comparing gene expression between single-cells from tumor and nontumor samples for each cell type. Bulk and pseudo-bulk DEGs were acquired by comparing gene expression between bulk RNA-seq data from paired tumor and nontumor samples and between pseudo-bulk data transformed from scRNA-seq data from tumor and nontumor tissue, respectively.

Table 5. List of cancer scRNA-seq datasets

Platform	Cancer	Database	Samples	Library type	Reference
10X 3'-seq	AML	dbGaP	5	5'-seq	[258]
(v2 Chemistry)	GBM	SRA	11	3'-seq	[259]
	HCC	SRA	12	3'-seq	[260]
	LC	ERA	31	3'-seq	[79]
	CRC	EGA	33	3'-seq	[261]
		EBI	27	3'-seq	
	BRCA	EBI	36	5'-seq	[262]
	CRC		21	3'-seq	
	LC		36	3'-seq	
	OVC		10	3'-seq	
	HCC	dbGaP	19	3'-seq	[263]
	B-ALL	SRA	33	3'-seq	[264]
	Uveal melanoma	dbGaP	11	3'-seq	[265]
	LC	ERA	58	3'-seq	[266]
	EGC	SRA	13	3'-seq	[267]
SMART-seq2	HNSCC	Not available	18	Full-length	[268]
	LC	SRA	49	Full-length	[268]
	Melanoma	DUOS	19	Full-length	[269]
	Melanoma	DUOS/dbGaP	31	Full-length	[269]
	Melanoma	dbGAP	32	Full-length	[270]
	Oligodendroglioma	dbGaP	6	Full-length	[271]
	BRCA	SRA	6	Full-length	[271]
Drop-seq	OVC	SRA	6	3'-seq	[272]
C1	BRCA	SRA	33	Full-length	[273]
Seq-Well	AML	SRA	83	3'-seq	[274]

Note. B-ALL, acute B lymphoblastic leukemia; EGC, early gastric cancer; HNSCC, head and neck squamous cell carcinoma.

mostly because single-cell DEGs would be present at the cell type level. In fact, more than half of the cell type-specific tumor/nontumor markers (63.64% for 10X and 66.67% for SS2) were only found in the scRNA-seq data, indicating that scRNA-seq would be more specific to the detection of markers for major and minor cell types in the TIME (Figure 7B). Only 15.2% and 30.9% of single-cell DEGs were recapitulated by the bulk DEG analysis, suggesting that SS2 is more sensitive to the detection of DEGs as well. However, SS2 has a limitation in the accurate quantification of antisense transcripts

because SS2 produces reads without strand information (unstranded reads). The updated version of SS2, SMART-seq3, now provides strand information [131] and would quantify antisense transcripts more accurately. Therefore, the cell type-specific expression and function of many lncRNAs previously studied in bulk tumor samples can be validated using the variety of available scRNA-seq datasets (Table 5). This process could provide new insights about known and novel lncRNA functions and regulatory roles in specific cell types in the TIME.

CONCLUSION

lncRNAs play crucial roles in both cancer and immune systems through multiple regulatory mechanisms. Nevertheless, the expression and functional characterization of lncRNAs in the TIME have barely been investigated at the single-cell level, mainly due to the high level of cell type-specificity of lncRNAs and due to the lack of cell type-specific lncRNA annotations. Recent advances in single-cell technologies and related bioinformatic tools as well as efforts to improve the cell type-specific annotations of lncRNAs will help to overcome the current limitations of scRNA-seq analysis for this class of RNAs. This achievement will open a new chapter in which clinically relevant lncRNAs expressed in both malignant cells and infiltrated immune cells in the TIME will be revealed and gaps in previous studies will be bridged.

Key Points

- We summarize an information of functional lncRNAs involved in cancer development, progression and tumor suppression, which are studied in bulk tumors.
- This review overviews current knowledge about the *bona fide* expression of cancer- and immune-related lncRNAs at the cellular level as well as possible cellular functions of lncRNAs in the TIME.
- We discuss the promises and challenges of single-cell analyses for studying the cellular functions of TIME lncRNAs.

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