Tumor immune microenvironment lncRNAs

Eun-Gyeong Park†, Sung-Jin Pyo†, Youxi Cui†, Sang-Ho Yoon† and Jin-Wu Nam†

Corresponding author: Jin-Wu Nam, Department of Life Science, College of Nature Sciences, Hanyang University, Seoul 04763, Republic of Korea.
Tel: +82-2-2220-2428, Fax: +82-2-2298-0319, E-mail: jwnam@hanyang.ac.kr
†These authors contributed equally to this work.

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 IncRNA genes has expanded a great deal in recent years [1–3]. In the human genome, >20,000 IncRNA 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 IncRNA 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 (GASS5) 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 κB 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 1A). 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 1A). 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
interference (RNAi)- or CRISPR-based inactivation and by their overexpression in cancer cell lines (Figure 1B, in vitro) or in mouse xenograft models (Figure 1C, in vivo). Many oncogenic, cancer-progressing and tumor-suppressing lncRNAs have been identified through the above procedure or by a similar approach. Highly Expressed IncRNA in ESoophageal squamous cell carcinoma (HERES) is a representative example of a novel cancer-promoting IncRNA 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. IncRNAs with oncogenic and cancer-promoting functions

| Cancer   | IncRNA    | Expression in cancer | Function                                                                 | Functional validation                                      | Reference  |
|----------|-----------|----------------------|--------------------------------------------------------------------------|-----------------------------------------------------------|------------|
| BLCA     | H19       | Up                   | Tumor progression (migration and invasion)                                | OE/shRNA KD in cancer cell lines and mouse model          | [59]       |
|          | TNMAT1    | Up                   | Tumor progression (migration and invasion)                                | OE/shRNA KD in cancer cell line and mouse model          | [133]      |
|          | UCA1      | Up                   | Tumor progression (proliferation)                                         | OE in cancer cell line                                   | [134, 135]|
| BRCA     | EPIC1     | Up                   | Tumor progression (cell cycle)                                            | OE/KD in cancer cell line and mouse model                | [26]       |
|          | H19       | Up                   | Tumor progression (cell cycle and proliferation)                         | OE in cancer cell line and mouse model                   | [60]       |
|          | HSILA     | Up                   | Tumor progression (anti-apoptosis)                                        | siRNA, shRNA KD in cancer cell line                     | [136]      |
|          | HOTAIR     | Up                   | Tumor progression (proliferation), tumor progression (migration and invasion) | OE/shRNA KD in cancer cell line                          | [137]      |
|          | NEAT1     | Up                   | Tumor progression (cell cycle, proliferation and anti-apoptosis)         | shRNA KD in cancer cell line and mouse model             | [102]      |
| CESC     | SRA       | Bimorphic            | Tumor progression (invasion)                                             | –                                                         | [138]      |
|          | SRA       | Up                   | Tumor progression (proliferation), tumor progression (invasion and migration) | KD in cancer cell line                                   | [139]      |
| CRC      | CASC15    | Up                   | Tumor progression (proliferation), tumor progression (migration and invasion) | OE/shRNA KD in cancer cell line and mouse model          | [140]      |
|          | CCA1      | Up                   | Tumor progression (cell cycle and cell proliferation), tumor progression (migration and invasion) | OE/shRNA KD in cancer cell line                          | [141, 142]|
|          | CCAT2     | Up                   | Tumor progression (proliferation), tumor progression (migration and invasion) | OE/shRNA KD in cancer cell line and mouse model          | [143]      |
|          | PACER     | Up                   | Tumor progression (proliferation), tumor progression (invasion and migration) | siRNA KD in cancer cell line and mouse model             | [62]       |
|          | PURPL     | Up                   | Tumor progression (proliferation)                                         | IncRNA KD in cancer cell line                           | [144]      |
|          | PVT1      | Up                   | Tumor progression (proliferation)                                         | siRNA KD in cancer cell line and mouse model             | [69]       |
|          | RAMS11    | Up                   | Tumor progression (proliferation), tumor progression (invasion and migration) | OE/KO in cancer cell line and KO in mouse model          | [145]      |
| ESCC     | HERES     | Up                   | Tumor progression (cell cycle, proliferation and anti-apoptosis), tumor progression (migration and invasion) | OE/shRNA KD in cancer cell line                           | [57]       |
|          | LUCA1     | Up                   | Tumor progression (proliferation and anti-apoptosis), tumor progression (migration and invasion) | OE/shRNA KD in cancer cell line                          | [31]       |
| GBC      | CCAT1     | Up                   | Tumor progression (proliferation), tumor progression (migration)          | OE/shRNA KD in cancer cell line and mouse model          | [146]      |
|          | PVT1      | Up                   | Tumor progression (proliferation), tumor progression (migration)          | siRNA KD in cancer cell line and shRNA KD/OE in mouse model | [147]      |
| GC       | CASC15    | Up                   | Tumor progression (proliferation), tumor progression (migration)          | OE/shRNA KD in cancer cell line and mouse model          | [148]      |
|          | FENDRR    | Down                 | Tumor progression                                                           | –                                                         | [61]       |
|          | H19       | Up                   | Tumor progression (proliferation and anti-apoptosis)                       | siRNA KD in cancer cell line                             | [149]      |
|          | HIF1A-AS2 | Up                   | Tumor progression (proliferation), tumor progression (migration and invasion) | OE/shRNA KD in cancer cell line and mouse model          | [150]      |
|          | HOTAIR     | Up                   | Tumor progression (cell cycle, proliferation and anti-apoptosis), tumor progression (migration and invasion) | OE/shRNA KD in cancer cell line and mouse model          | [151]      |
|          | PCGEM1    | Up                   | Tumor progression (invasion and migration)                                 | OE/shRNA KD in cancer cell line                          | [152]      |
| HCC      | AC096579.7 | Down             | Tumor progression                                                           | siRNA KD in cancer cell line                             | [61]       |
|          | ANRIL     | Up                   | Tumor progression (cell cycle and proliferation), tumor progression (migration and invasion) | OE/shRNA KD in cancer cell line and mouse model          | [153]      |
|          | BCTRNI    | Up                   | Tumor progression                                                           | –                                                         | [61]       |
|          | CASC15    | Bimorphic            | Tumor progression                                                           | –                                                         | [61]       |
|          | CCAT1     | Up                   | Tumor progression                                                           | –                                                         | [61]       |
|          | CKNDE     | Up                   | Tumor progression (cell cycle, proliferation and anti-apoptosis)           | –                                                         | [61]       |
|          | H19       | Up                   | Tumor progression                                                           | –                                                         | [61]       |
|          | HAND2-AS1 | Down                 | Tumor progression, tumor progression (migration)                           | –                                                         | [61]       |
|          | HIF1A-AS2 | Up                   | Tumor progression, tumor progression (migration)                           | –                                                         | [61]       |
|          | HOTTIP    | Bimorphic            | Tumor progression (anti-apoptosis), tumor progression (invasion and migration) | siRNA KD in cancer cell line                             | [154]      |
|          | HULC      | Up                   | Tumor progression (proliferation)                                          | siRNA KD in cancer cell line                             | [155]      |
|          | LINC01018 | Down                 | Tumor progression (proliferation), tumor progression (migration and invasion) | OE/shRNA KD in cancer cell line and mouse model          | [156]      |
|          | LINC00662 | Down                 | Tumor progression (proliferation), tumor progression (migration and invasion) | OE/shRNA KD in cancer cell line and mouse model          | [156]      |
|          | NEST      | Down                 | Tumor progression                                                           | –                                                         | [61]       |
|          | PVT1      | Up                   | Tumor progression (cell cycle and proliferation)                           | –                                                         | [61]       |
|          | RP11-166D19.1 | Bimorphic             | Tumor progression (cell cycle and proliferation)                           | –                                                         | [61]       |
|          | RP1-153P14.5 | Down               | Tumor progression (migration and invasion)                                 | –                                                         | [61]       |
|          | RP1-173P5.2 | Down               | Tumor progression (invasion and migration)                                 | –                                                         | [61]       |
|          | SNHG6     | Up                   | Tumor progression                                                           | –                                                         | [61]       |
|          | TERC      | Up                   | Tumor progression                                                           | –                                                         | [61]       |
|          | TEX41     | Up                   | Tumor progression                                                           | –                                                         | [61]       |
Table 1. Continued

| Cancer   | IncRNA       | Expression in cancer | Function                                      | Functional validation                                      | Reference |
|----------|--------------|----------------------|-----------------------------------------------|-----------------------------------------------------------|-----------|
| HCC      | TUC338       | Up                   | Tumorigenesis (proliferation, tumor progression) | 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_00220 | Up           | Tumor progression    | –                                             |                                                           | [61]      |
| XLOC_00370 | Down         | Tumorigenesis        | –                                             |                                                           | [61]      |
| XLOC_055355 | Down        | Tumorigenesis, tumor progression (migration) | siRNA KD in cancer cell line                  |                                                           | [61]      |
| XLOC_056573 | Up           | 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<sup>a</sup> | Up                 | Tumorigenesis (proliferation), tumor progression (migration and invasion) | OE/shRNA KD in cancer cell line and mouse model            | [41, 160]|
| NNT-AS1   | Up           | Tumorigenesis, tumor progression (migration and invasion) | siRNA KD in cancer cell line                  |                                                           | [165]     |
| OCA1      | Up           | Tumorigenesis (proliferation) | siRNA KD in cancer cell line                  |                                                           | [165]     |
| OSCC      | OIP5-AS1     | Up                   | Tumorigenesis (cancer cell cycle and proliferation) | OE/KD in cancer cell line                                  | [166]     |
|          |              |                      | Tumorigenesis (cancer cell cycle and proliferation) | OE/KD in cancer cell line and mouse model                  | [166]     |
| OVC       | HOTAIR<sup>a</sup> | Up                 | Tumor progression (invasion and migration)    | siRNA KD in cancer cell line                               | [164]     |
|          | FAI1         | Up                   | Tumorigenesis (proliferation)                 | OE/siRNA, shRNA KD in cancer cell line and mouse model     | [165]     |
|          | HOTAIR<sup>a</sup> | Up                 | Tumor progression (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 mouse model            | [167]     |
| Pan       | DANCN        | 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<sup>a</sup> | 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-apoptosis)                | siRNA KD in cancer cell line                               | [173]     |
|          | TRMP         | Up                   | Tumorigenesis (cell cycle and proliferation)  | siRNA KD in cancer cell line                               | [174]     |
|          | TUG1         | Up                   | Tumorigenesis (proliferation)                 | siRNA KD in cancer cell line                               | [69]      |
|          | WT1-AS       | Up                   | Tumorigenesis (proliferation)                 | siRNA KD in cancer cell line                               | [89]      |
| PRAD      | PCAT-1       | Up                   | Tumorigenesis (proliferation)                 | OE/shRNA KD in cancer cell line                            | [175]     |
|          | PCEGEM1      | Up                   | Tumorigenesis (proliferation)                 | OE in cancer cell line                                     | [176]     |
|          | SCHLAP1      | Up                   | Tumor progression (invasion)                  | OE/shRNA KD in cancer cell line                            | [177, 178]|
| PRAD,     | ANRIL/p15AS  | Up                   | Tumorigenesis                                 | Gene silencing in mouse                                    | [179-181]|
| Leukemia  |              |                      |                                               |                                                           |           |
| PTC       | MIAT         | Up                   | Tumorigenesis (cell cycle and proliferation), tumor progression (invasion) | OE/shRNA KD in cancer cell line                            | [182]     |

Note. OE, overexpression; KD, knockdown; KD, 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; 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. *IncRNAs 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 IncRNAs have been identified as key factors that regulate both cancer
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].
Tumor immune microenvironment lncRNAs

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 NKLIA [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 2A). 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 IncRNAs 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 IncRNAs (Figure 2B). A greater fraction of mRNAs displayed ubiquitous expression, whereas only a few IncRNAs, such as MALAT1, NEAT1, SNHG29, SNHG5, GASS and ZFAS1, were present in more than half of the cells (Figure 2B). Similar trends in IncRNA expression patterns were also observed in recent studies: IncRNAs 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 IncRNAs 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 2C).

On the other hand, the cell type-specific expression of IncRNAs raises another issue in annotating IncRNAs that are specifically expressed in rare cell types. IncRNAs 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 IncRNA 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, IncRNAs specifically expressed in those cell types should be considered as well. If present, Treg- and CD8+ T-specific IncRNAs might well be involved in oncogenic or tumor-suppressive functions, but many of them unfortunately remain undocumented. Hence, it is important to determine which IncRNAs are specific to rare immune cell types to understand their cellular functions in the TIME.

Immune-specific IncRNAs
IncRNAs 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 IncRNAs, 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 IncRNAs affect hematopoietic differentiation via diverse modes of action, which include functioning as mRNA/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 IncRNAs 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 IncRNA 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 IncRNA, and it has a celiac disease-related function in human and mouse macrophages. Reduced abundance of the IncRNA, 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 IncRNA 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].
- lncRNA-Cox2 expression is induced by the Toll-like receptor-mediated inflammatory response. This IncRNA controls the expression of many immune-related genes by interacting with repressors and heterochromatin remodelers [92, 93].

On the other hand, cytoplasmic immune-specific IncRNAs activate or suppress a target at the RNA or protein level. For instance, lnc-DC, lnc-MC, FIRE and cardiac and apoptosis-related IncRNA (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 IncRNAs, 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. EG0, HOXA-AS2, LEF-AS1, MYB-AS1, SMAS-AS1, Inc-CD56 and Inc-R-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 IncRNAs expressed in human and mouse

| IncRNA   | Species     | Cell type                  | Expression validation | Function                                                                 | Reference |
|----------|-------------|----------------------------|-----------------------|--------------------------------------------------------------------------|-----------|
| **Stem cell** |             |                            |                       |                                                                           |           |
| H19α     | Mouse       | HSC                        | RT-qPCR               | Regulates self-renewal of long-term HSCs                                  | [86]      |
| **Lymphoid cells** |         |                             |                       |                                                                           |           |
| NRONβ    | 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]|
| IncRNA-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]|
| NKL1a    | Human, mouse| Cytotoxic T/Th1 cell       | RT-qPCR               | Induces hyperactivated immune cell death by the NFκB 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]     |
| linc-CD56 | Human       | NK cell                    | RT-qPCR               | Positively regulates CD56 gene                                            | [204]     |
| FLICR    | Human, mouse| Treg                       | RNA-seq               | 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** |       |                            |                       |                                                                           |           |
| LUCAT1a  | Human       | Myeloid cell               | RNA-seq               | Interacts with STAT1 to inhibit ISGs transcription                       | [106]     |
| NEAT1β   | Human, mouse| DC                         | RT-qPCR               | Induces tolerogenic phenotype in DCs                                      | [95]      |
| linc-DC  | Human, mouse| DC                         | RT-qPCR               | Promotes the nuclear translocation and function of STAT3                | [97]      |
| MALAT1a  | Mouse       | DC                         | Microarray            | Induces LPS-stimulated DCs to switch to tolerogenic DCs                  | [94]      |
| HOXA-AS2 | Human, mouse| Progranulocyte/neutrophil  | RNA-seq               | Suppresses apoptosis of granulocytes                                      | [90]      |
| MORR8ID  | 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]|
| linc-MC  | Human       | Monocyte/macrophage        | RT-qPCR               | Promotes monocyte/macrophage differentiation                             | [98]      |
| PACERα   | Human, mouse| Monocyte                   | RT-qPCR               | Activates monocyte by inflammatory pathway                               | [210]     |
| HOTAIRα  | Human       | Macrophage (AML-stimulated)| RT-qPCR               | Promotes the NFκB-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               | 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            | Regulates eosinophil development                                         | [213]     |
| linc13   | 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. *IncRNAs that were found to be both cancer-related and immune-specific.

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

- **linc-DC** is an IncRNA, 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, linc-DC directly binds to STAT3 in the cytoplasm, maintaining STAT3 phosphorylation by preventing an interaction with the tyrosine phosphatase SHP1 [97].

- **linc-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 IncRNA that is conserved between human and mouse, is also induced by NF-κB in macrophages. This IncRNA interacts with hnRNP U 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 IncRNA 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 IncRNAs 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 IncRNAs, 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 IncRNAs expressed in immune cells remain functionally uncharacterized in their respective cell types (Figure 4). Studying such uncharacterized IncRNAs will expand the reservoir of IncRNA candidates, which may exhibit tumor-regulating functions in the TIME.

**Multifaceted functions of TIME IncRNAs**

Some cancer-promoting or -suppressing IncRNAs could play their roles not only in malignant cells but also in tumor-specific immune cells. Such multicellular functions of IncRNAs 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 5A) [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 IncRNA 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 IncRNAs. 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 5B). 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 IncRNA that limits liver tumor growth and metastasis [105] (Figure 5C). Furthermore, NRON overexpression was shown to attenuate the level of EMT markers. The oncogenic IncRNA LUCAT1 was also reported to negatively regulate interferon responses in myeloid cells [106] (Figure 5D). The immunological functions of cancer-promoting and -suppressing IncRNAs suggest that the IncRNAs could participate in regulating the cross talk between tumor and immune cells during cancer development and progression.

**IncRNAs 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 IncRNAs regulate crucial mechanisms of cancer immunity which range from antigen presentation to T cell exhaustion [112]. There are a handful of IncRNAs, 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 IncRNAs, a collective IncRNA set can also predict the prognosis of cancer patients. For example, the IncRNA signature of tumor-infiltrating B lymphocytes (TILBIncSig) is a collection of eight IncRNAs specifically expressed in B cells [116]. Expression of the individual IncRNAs can be used to predict different outcomes of bladder cancer patients (good prognosis, TNR6C6-AS1, WASIR2, GUSBP11, OGFRP1 or AC090515.2 expression; poor prognosis, PART1, MAFG-DT or LINCO1184 expression); however, the combination of these IncRNAs weighted by coefficients of the multivariate Cox regression model confidently dichotomized bladder cancer patients with different prognoses in multiple independent datasets. TILBIncSig 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 TILBIncSig high-risk group showed worse outcomes than individuals with any
Figure 4. Ubiquitously expressed IncRNAs and the top 10 most abundant cell type-specific IncRNAs in immune cell types. IncRNAs 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.
NK cell lncRNAs in cancer immunity

| IncRNA    | 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     | Macrophage      | Downregulates miR-146a 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]     |
| LINCO0662 | 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]     |
| HOTAIM1   | 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    | Macrophage      | Negatively regulates MDSCs                                                | [234]     |
| Ofp29-ps1 | MDSC            | Sponges up miR-214-3p to facilitate differentiation and development of MDSCs | [235]     |
| Putt1     | MDSC            | Promotes immunosuppressive functions of granulocytic-MDSCs                | [236]     |
| RUNXOR    | MDSC            | Is associated with the development and immunosuppressive function of MDSCs | [237]     |
| HOTAIM1   | DC              | Competitively binds to miR-3960 to regulate DC differentiation             | [208]     |
| lnc-DC    | DC              | Promotes DC maturation and regulates TLR9/STAT3 signaling                 | [238]     |
| lnc-Dp53  | DC              | Suppresses DC migration by binding to HIP1 to inhibit its activity        | [239]     |
| NEAT1     | 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]     |
| JING-AS1  | NK cell         | Promotes differentiation of granulocytes by recruiting PRC-2 to the Bcl2 promoter | [200]     |
| linc-EPHA6-1 | NK cell          | A ceRNA for miR-4485-5p to induce expression of NKP46                     | [241]     |
| linc-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 ifna loci by chromatin modification | [197]     |
| NEAT1     | 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 IFNy expression                  | [198-200] |
| NRON-4    | T cell          | Inhibits NFAT activity by preventing its accumulation in the nucleus and downregulates T cell activation | [104]     |
| lincr-Ccr2-S'AS | T 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 CNS5/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]     |
| ACO090515.2, GUSBP11, LINCO1184, MACG-DT, OGFPR1, PART1, TNRC6C-AS1, WASIR2 | B cell (TILBIncSig) | A combination of eight lncRNAs expressed in B cells that can predict the outcome of bladder cancer | [116]     |

(Continued)
other combination of PD-1/PD-L1 expression levels and TILBIncSig, suggesting that TILBIncSig 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-1 (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-1. 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, lncRNA-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.

### Table 4. Continued

| lncRNA               | Cell/cancer type | Function                                                                 | Reference |
|----------------------|------------------|--------------------------------------------------------------------------|-----------|
| HCG26, PSMB8-AS1,    | TIL (TILSig)     | A combination of seven immune-related lncRNAs that can predict the outcome of lung cancer | [117]     |
| TNRG6C-AS1, CARD8-AS1, HCP5, LOC286437, LINC02256 |                  |                                                                           |           |
| 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]     |
| IncMX1-215           | HNSCC            | Interacts with GCN5 H3K27 acetylase to inhibit the expression of PD-L1     | [249]     |
| Inc-sox5             | CRC              | Induces resistance to chemotherapy in CD133+ tumor initiating cells       | [250]     |
| Inc-VLDLR            | HCC              | Is transported to neighboring cells in extracellular vesicles and induces resistance to chemotherapy in the recipient cells | [252]     |
| MALAT1*              | 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 γδ 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. *lncRNAs that were found to be both cancer-related and immune-specific.

### 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 (∼0.1 transcripts per million (TPM)) in the 10X and SS2 platforms, respectively (Figure 7A). 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...
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.

Table 5. List of cancer scRNA-seq datasets

| Platform          | Cancer      | Database   | Samples | Library type | Reference |
|-------------------|-------------|------------|---------|--------------|-----------|
| 10X 3'-seq        | AML         | dbGaP      | 5       | 3'-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         | B-ALL      | 21      | 5'-seq       |           |
|                   | LC          | B-ALL      | 36      | 3'-seq       |           |
|                   | OVC         | B-ALL      | 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      | 52      | Full-length  | [270]      |
|                   | Oligodendrolioma | dbGaP    | 6       | Full-length  | [271]      |
|                   | BRCA        | SRA        | 6       | 3'-seq       | [272]      |
|                   | 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.

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.
CONCLUSION

IncRNAs play crucial roles in both cancer and immune systems through multiple regulatory mechanisms. Nevertheless, the expression and functional characterization of IncRNAs in the TIME have barely been investigated at the single-cell level, mainly due to the high level of cell type-specificity of IncRNAs and due to the lack of cell type-specific IncRNA annotations. Recent advances in single-cell technologies and related bioinformatic tools as well as efforts to improve the cell type-specific annotations of IncRNAs 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 IncRNAs 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 IncRNAs 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 IncRNAs at the cellular level as well as possible cellular functions of IncRNAs in the TIME.
- We discuss the promises and challenges of single-cell analyses for studying the cellular functions of TIME IncRNAs.

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