OXFORD

*Briefings in Bioinformatics*, 2022, **23**, 1–25
https://doi.org/10.1093/bib/bbab504
**Review**

# 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 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

**Eun-Gyeong Park** is a master candidate at the Department of Life Science at Hanyang University and is studying TIME lncRNAs.
**Sung-Jin Pyo** is a master candidate at the Department of Life Science at Hanyang University and is working with lncRNA annotations in immune cells.
**Youxi Cui** is a master candidate at the Department of Life Science at Hanyang University and is working with lncRNA annotations in immune cells.
**Sang-Ho Yoon** is a PhD candidate at the Department of Life Science at Hanyang University and is studying TIME lncRNAs.
**Jin-Wu Nam** is a full professor at Hanyang University. He received a PhD in bioinformatics from Seoul National University and studied computational biology at the Whitehead Institute for Biomedical Research.

**Received:** August 20, 2021. **Revised:** October 15, 2021. **Accepted:** November 2, 2021

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-$\beta$)-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-$\kappa$B (NF-$\kappa$B) interacting lncRNA (*NKILA*) plays a tumor-suppressive role by regulating a protein modification. *NKILA*, which is upregulated by NF-$\kappa$B, prevents overactivation of the NF-$\kappa$B pathway by inhibiting I$\kappa$B 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

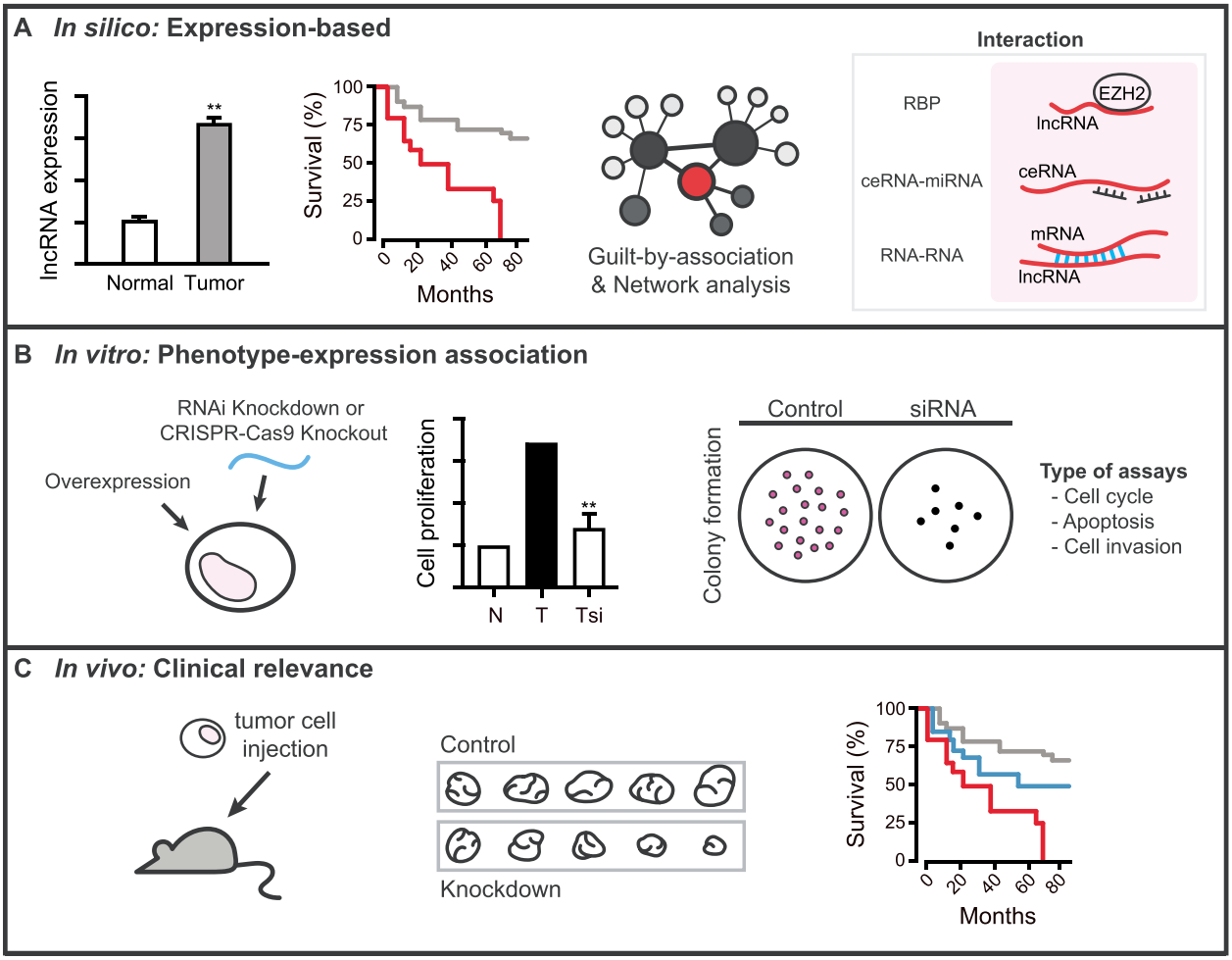


**Figure 1.** General approaches for functional studies of cancer-related lncRNAs. Three main approaches for functional studies of cancer-related lncRNAs. (**A**) *In silico* approaches. *In silico* functional studies are mainly based on analyses of the expression of lncRNAs, associated RNA-binding proteins (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-$\kappa$B 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].

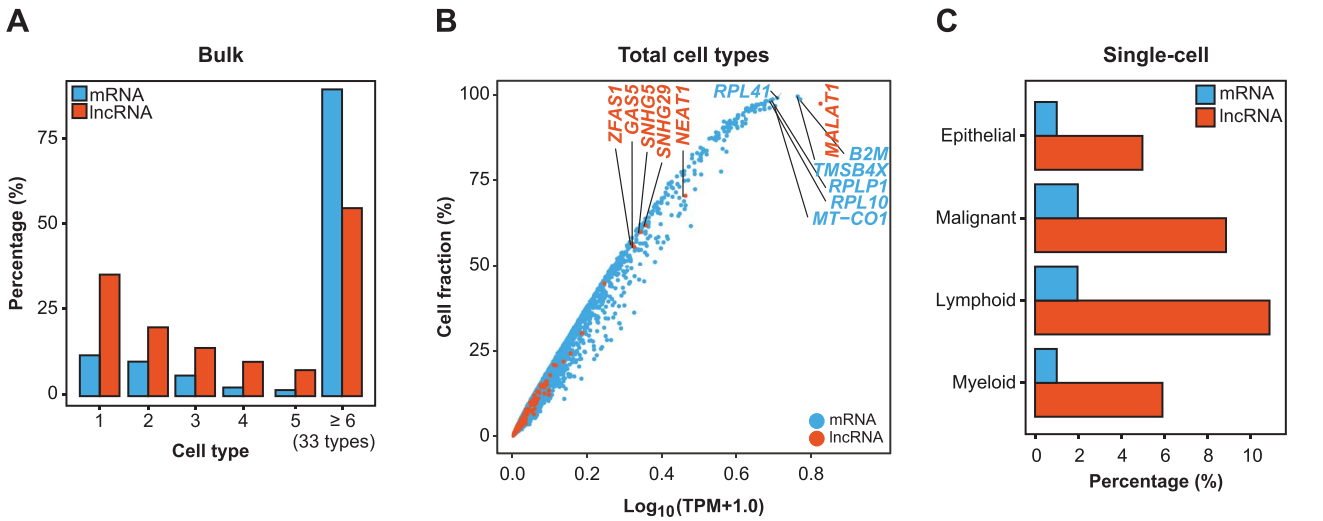


**Figure 2.** Cell type-specific expression of lncRNAs. (**A**) The percentages (Y-axis) of mRNAs (blue) and lncRNAs (red) expressed in certain cell types (X-axis; ≥1 TPM). Expression analyses of mRNAs and lncRNAs were done with bulk RNA-seq datasets from 33 human cell types. (**B**) Scatter plot of 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-$\beta$-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-$\kappa$B-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 I$\kappa$B$\alpha$ degradation, which directs the translocation of NF-$\kappa$B to the nucleus to

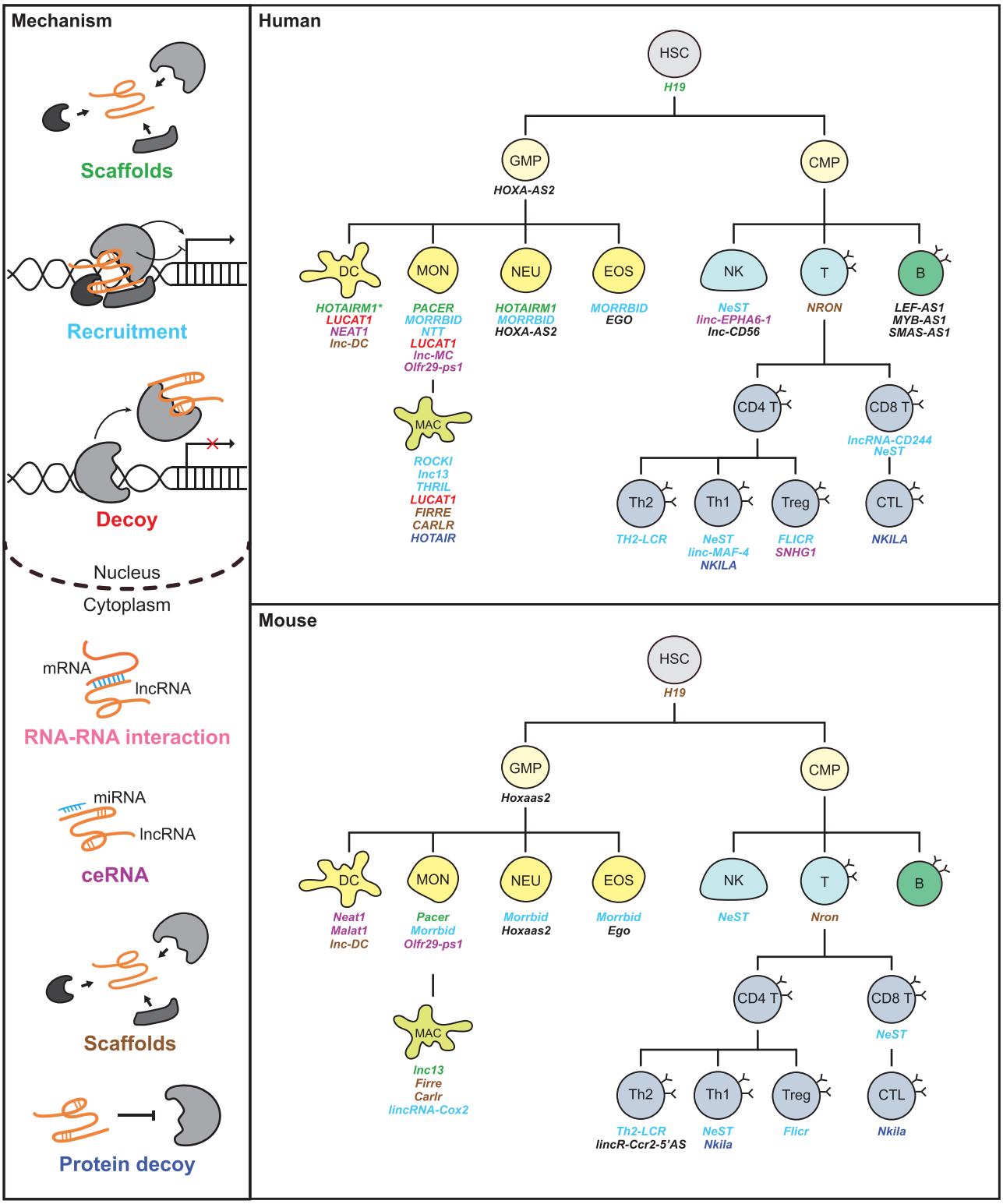


**Figure 3.** Functions of immune-related lncRNAs. Human and murine lncRNAs that have functional roles in HSCs, progenitor cells and immune cells are shown (lncRNAs are listed under each cell type) as are those that function during immune cell differentiation (lncRNAs are indicated on lines). The functional 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 IFN$\gamma$ 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 IFN$\gamma$ expression | [198–200] |
| *NKILA*[a] | Human, mouse | Cytotoxic T/Th1 cell | RT-qPCR | Induces hyperactivated immune cell death by the NF-$\kappa$B 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-$\kappa$B-mediated inflammatory pathway | [96] |
| *NTT* | Human | Monocyte | RT-qPCR | Regulates inflammation and monocyte differentiation | [211] |
| *THRIL* | Human | Macrophage | Microarray | Activates TNF-$\alpha$ 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-$\kappa$B 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-$\kappa$B signaling pathway is active in human macrophages [100]. Downregulation of the lncRNA was shown to impair activation of the NF-$\kappa$B 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-$\alpha$ (TNF-α) and interleukin-1$\beta$ (IL-1β), via NF-$\kappa$B signaling in inflammation-stimulated breast epithelial cells and plays an anti-tumor function by inhibiting NF-$\kappa$B activation (Figure 5**A**) [44]. The repression of *NKILA* by miR-103/107 targeting induces NF-$\kappa$B signaling, increasing cell invasiveness in breast cancer cell lines. Later work revealed that the lncRNA is also an NF-$\kappa$B-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-$\kappa$B 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

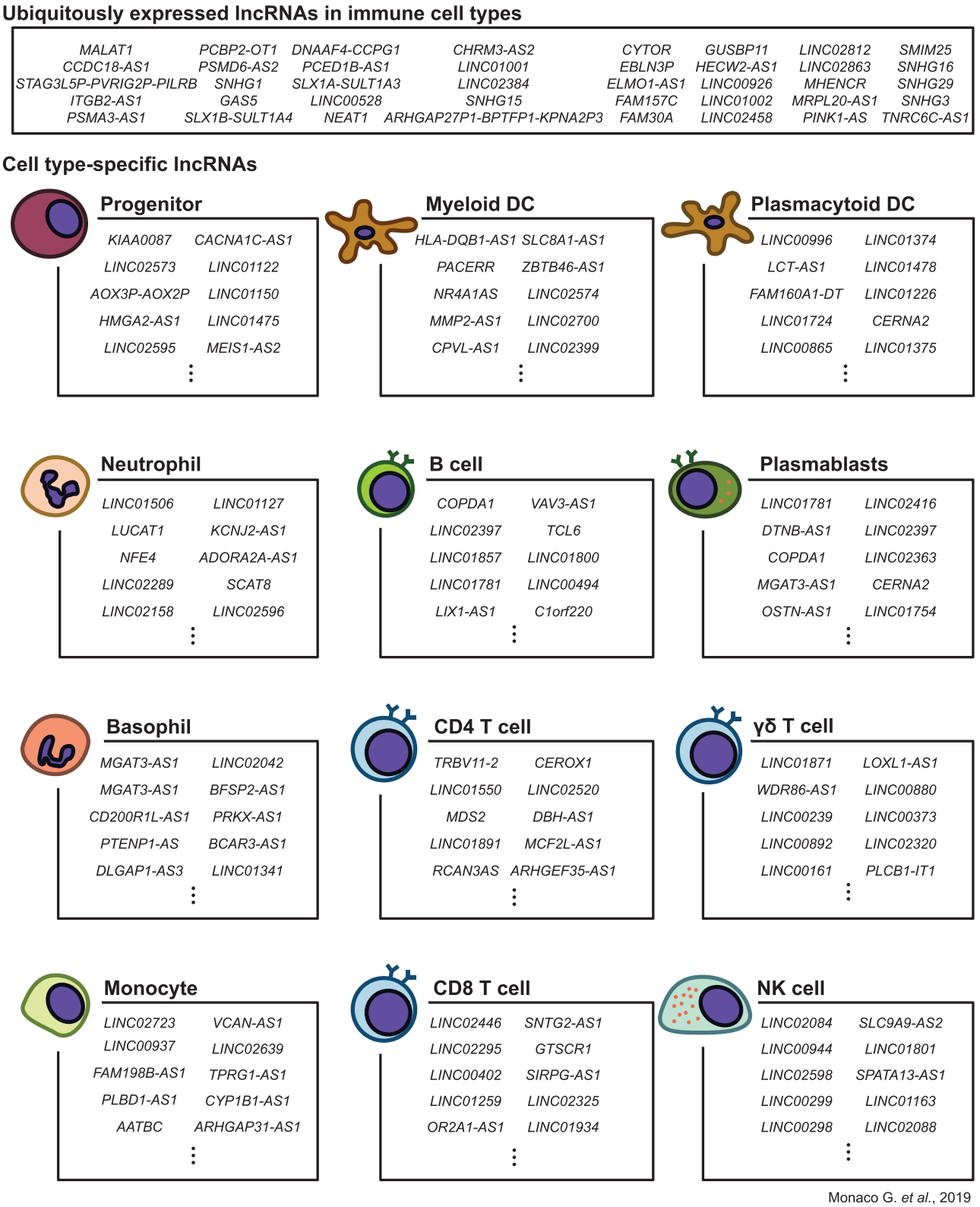


**Figure 4.** Ubiquitously expressed lncRNAs and the top 10 most abundant cell type-specific lncRNAs in immune cell types. lncRNAs that are expressed in >50% of all cell types (ubiquitously expressed lncRNAs, top) and the top 10 most abundant cell type-specific lncRNAs in progenitor cells, myeloid DCs, 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].

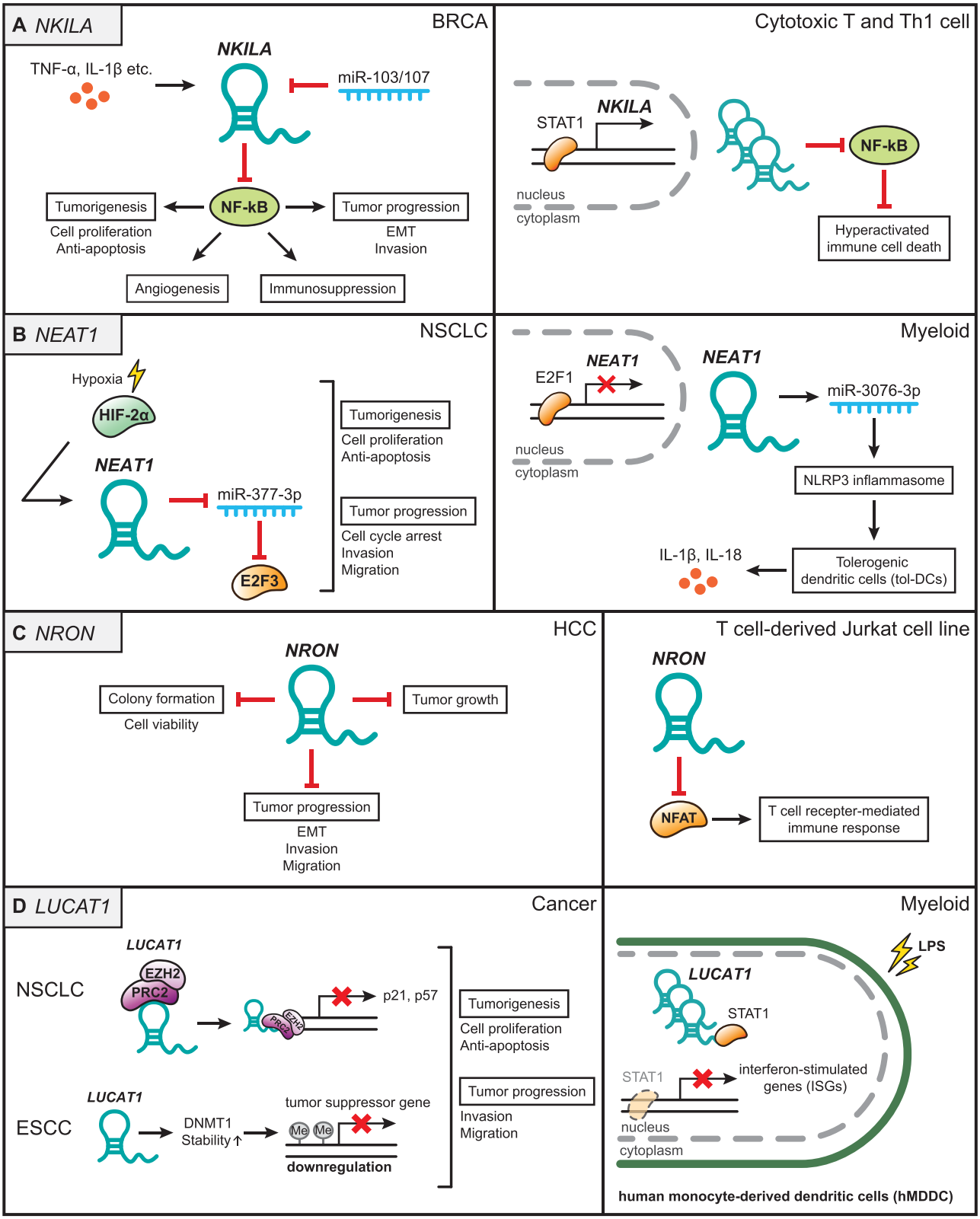


**Figure 5.** Multifaceted functions of lncRNAs in tumor and immune cells. (**A**) Two distinct functions of *NKILA* in tumor cells and T cells. In tumor cells, *NKILA* is upregulated by several inflammatory mediators (TNF-α and IL-1β) that inhibit the activation of NF-κB, which controls tumorigenesis 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 IFN$\gamma$ 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-$\alpha$ 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

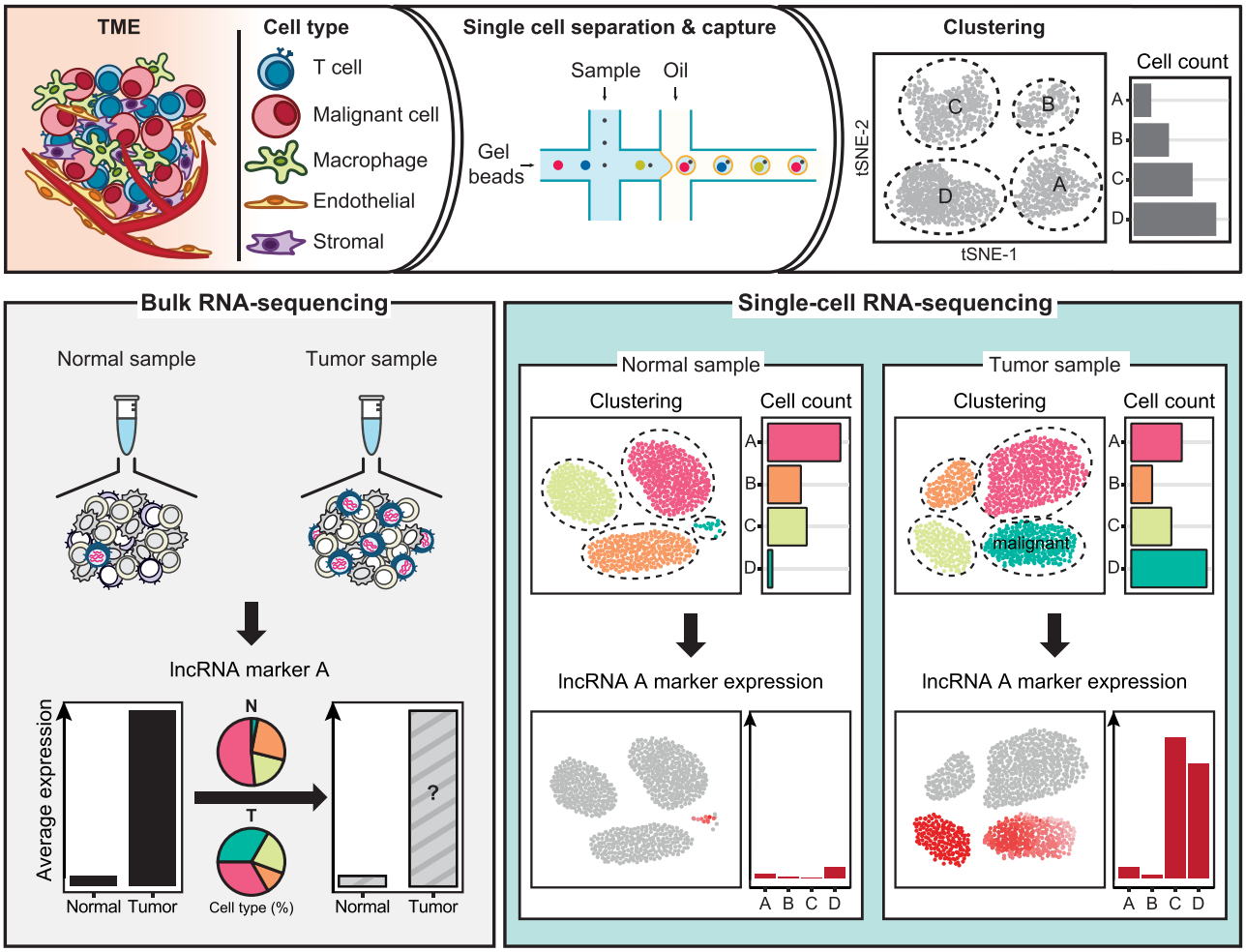


**Figure 6.** Detection of lncRNA markers via scRNA-seq versus bulk RNA-seq. The general procedure for scRNA-seq is summarized in the top panel. In the bottom panels, marker analyses at the bulk and single-cell levels are compared. Bulk RNA-seq mainly captures lncRNA markers that are differentially expressed 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

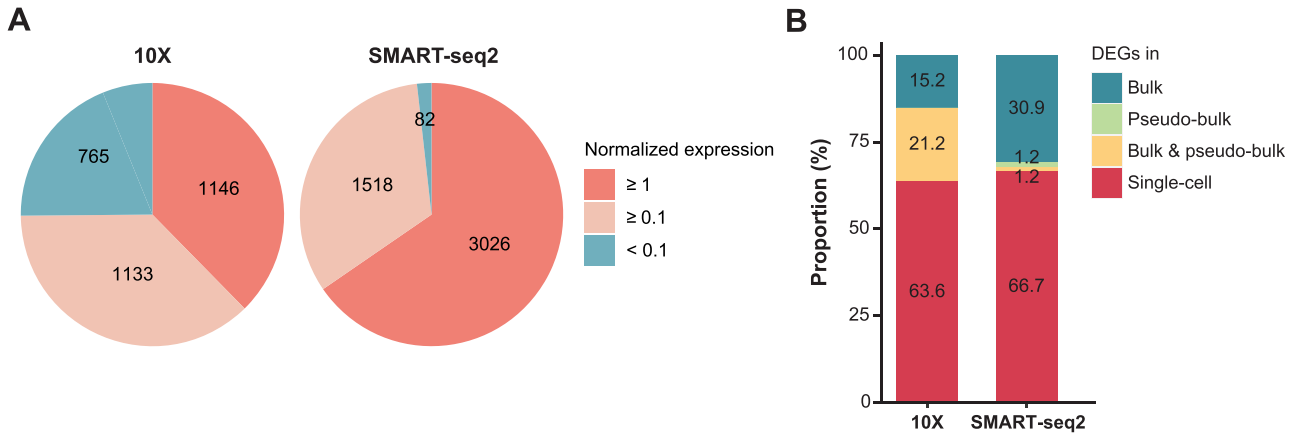


**Figure 7.** Comparison of expressed lncRNAs and DEGs in scRNA-seq datasets versus bulk RNA-seq datasets. (**A**) TPM distribution for genes represented in single-cell RNA-seq datasets that were detected at ≥1 TPM in bulk RNA-seq data from TCGA (lung adenocarcinoma and squamous cell carcinoma for 10X 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 7**B**). 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.

## Acknowledgements

We thank all members of the BIG lab and Basic Research Laboratory team for helpful discussion and comments.

## Funding

This work was supported by the Basic Research Program of the National Research Foundation of Korea (NRF) and funded by the Korean government (MSIT) (2021R1A2C3005835 and 2020R1A4A1018398).

## References

1. Xu J, Bai J, Zhang X, *et al.* A comprehensive overview of lncRNA annotation resources. *Brief Bioinform* 2017;**18**(2):236–49.
2. You B-H, Yoon S-H, Nam J-W. High-confidence coding and noncoding transcriptome maps. *Genome Res* 2017;**27**(6):1050–62.
3. Uszczynska-Ratajczak B, Lagarde J, Frankish A, *et al.* Towards a complete map of the human long non-coding RNA transcriptome. *Nat Rev Genet* 2018;**19**(9):535–48.
4. Iyer MK, Niknafs YS, Malik R, *et al.* The landscape of long noncoding RNAs in the human transcriptome. *Nat Genet* 2015;**47**(3):199–208.
5. Hon CC, Ramilowski JA, Harshbarger J, *et al.* An atlas of human long non-coding RNAs with accurate 5' ends. *Nature* 2017;**543**(7644):199–204.
6. Quinn JJ, Chang HY. Unique features of long non-coding RNA biogenesis and function. *Nat Rev Genet* 2016;**17**(1):47–62.
7. Ward M, McEwan C, Mills JD, *et al.* Conservation and tissue-specific transcription patterns of long noncoding RNAs. *J Hum Transcr* 2015;**1**(1):2–9.
8. Cabili MN, Trapnell C, Goff L, *et al.* Integrative annotation of human large intergenic noncoding RNAs reveals global properties and specific subclasses. *Genes Dev* 2011;**25**(18):1915–27.
9. Tsoi LC, Iyer MK, Stuart PE, *et al.* Analysis of long non-coding RNAs highlights tissue-specific expression patterns and epigenetic profiles in normal and psoriatic skin. *Genome Biol* 2015;**16**(1):24.
10. le Béguec C, Wucher V, Lagoutte L, *et al.* Characterisation and functional predictions of canine long non-coding RNAs. *Sci Rep* 2018;**8**(1):13444.
11. Jiang C, Li Y, Zhao Z, *et al.* Identifying and functionally characterizing tissue-specific and ubiquitously expressed human lncRNAs. *Oncotarget* 2016;**7**(6):7120–33.
12. Yao RW, Wang Y, Chen LL. Cellular functions of long noncoding RNAs. *Nat Cell Biol* 2019;**21**(5):542–51.
13. Statello L, Guo CJ, Chen LL, *et al.* Gene regulation by long non-coding RNAs and its biological functions. *Nat Rev Mol Cell Biol* 2021;**22**(2):96–118.
14. Kopp F, Mendell JT. Functional classification and experimental dissection of Long noncoding RNAs. *Cell* 2018;**172**(3):393–407.
15. Choi SW, Kim HW, Nam JW. The small peptide world in long noncoding RNAs. *Brief Bioinform* 2019;**20**(5):1853–64.
16. Nam JW, Choi SW, You BH. Incredible RNA: dual functions of coding and noncoding. *Mol Cells* 2016;**39**(5):367–74.
17. Kumari P, Sampath K. cncRNAs: Bi-functional RNAs with protein coding and non-coding functions. *Semin Cell Dev Biol* 2015;**47-48**:40–51.
18. Huang Y, Wang J, Zhao Y, *et al.* cncRNAdb: a manually curated resource of experimentally supported RNAs with both protein-coding and noncoding function. *Nucleic Acids Res* 2021;**49**(D1):D65–70.
19. Huarte M. The emerging role of lncRNAs in cancer. *Nat Med* 2015;**21**(11):1253–61.
20. Chen YG, Satpathy AT, Chang HY. Gene regulation in the immune system by long noncoding RNAs. *Nat Immunol* 2017;**18**(9):962–72.
21. Schmitt AM, Chang HY. Long noncoding RNAs in cancer pathways. *Cancer Cell* 2016;**29**(4):452–63.
22. Du Z, Fei T, Verhaak RGW, *et al.* Integrative genomic analyses reveal clinically relevant long noncoding RNAs in human cancer. *Nat Struct Mol Biol* 2013;**20**(7):908–13.
23. Prensner JR, Chinnaiyan AM. The emergence of lncRNAs in cancer biology. *Cancer Discov* 2011;**1**(5):391–407.
24. Zhu S, Li W, Liu J, *et al.* Genome-scale deletion screening of human long non-coding RNAs using a paired-guide RNA CRISPR-Cas9 library. *Nat Biotechnol* 2016;**34**(12):1279–86.
25. Goodall GJ, Wickramasinghe VO. RNA in cancer. *Nat Rev Cancer* 2021;**21**(1):22–36.
26. Wang Z, Yang B, Zhang M, *et al. lncRNA* epigenetic landscape analysis identifies EPIC1 as an oncogenic lncRNA that interacts with MYC and promotes cell-cycle progression in cancer. *Cancer Cell* 2018;**33**(4):706–20.e9.
27. Sun M, Jin FY, Xia R, *et al.* Decreased expression of long noncoding RNA GAS5 indicates a poor prognosis and promotes cell proliferation in gastric cancer. *BMC Cancer* 2014;**14**:319.

28. Chang L, Li C, Lan T, *et al.* Decreased expression of long noncoding RNA GAS5 indicates a poor prognosis and promotes cell proliferation and invasion in hepatocellular carcinoma by regulating vimentin. *Mol Med Rep* 2016;**13**(2):1541–50.
29. Yang Z, Li X, Yang Y, *et al.* Long noncoding RNAs in the progression, metastasis, and prognosis of osteosarcoma. *Cell Death Dis* 2016;**7**(9):e2389.
30. Sun Y, Jin SD, Zhu Q, *et al.* Long non-coding RNA LUCAT1 is associated with poor prognosis in human non-small lung cancer and regulates cell proliferation via epigenetically repressing p21 and p57 expression. *Oncotarget* 2017;**8**(17):28297–311.
31. Yoon JH, You BH, Park CH, *et al.* The long noncoding RNA LUCAT1 promotes tumorigenesis by controlling ubiquitination and stability of DNA methyltransferase 1 in esophageal squamous cell carcinoma. *Cancer Lett* 2018;**417**:47–57.
32. Taube JM, Galon J, Sholl LM, *et al.* Implications of the tumor immune microenvironment for staging and therapeutics. *Mod Pathol* 2018;**31**(2):214–34.
33. Binnewies M, Roberts EW, Kersten K, *et al.* Understanding the tumor immune microenvironment (TIME) for effective therapy. *Nat Med* 2018;**24**(5):541–50.
34. Galli F, Aguilera JV, Palermo B, *et al.* Relevance of immune cell and tumor microenvironment imaging in the new era of immunotherapy. *J Exp Clin Cancer Res* 2020;**39**(1):89.
35. Shen Y, Peng X, Shen C. Identification and validation of immune-related lncRNA prognostic signature for breast cancer. *Genomics* 2020;**112**(3):2640–6.
36. Li Y, Jiang T, Zhou W, *et al.* Pan-cancer characterization of immune-related lncRNAs identifies potential oncogenic biomarkers. *Nat Commun* 2020;**11**(1):1000.
37. Ali MM, Akhade VS, Kosalai ST, *et al.* PAN-cancer analysis of S-phase enriched lncRNAs identifies oncogenic drivers and biomarkers. *Nat Commun* 2018;**9**(1):883.
38. Cabanski CR, White NM, Dang HX, *et al.* Pan-cancer transcriptome analysis reveals long noncoding RNAs with conserved function. *RNA Biol* 2015;**12**(6):628–42.
39. Chiu HS, Somvanshi S, Patel E, *et al.* Pan-cancer analysis of lncRNA regulation supports their targeting of cancer genes in each tumor context. *Cell Rep* 2018;**23**(1):297–312.e12.
40. Carlevaro-Fita J, Lanzós A, Feuerbach L, *et al.* Cancer LncRNA census reveals evidence for deep functional conservation of long noncoding RNAs in tumorigenesis. *Commun Biol* 2020;**3**(1):56.
41. Ji P, Diederichs S, Wang W, *et al.* MALAT-1, a novel noncoding RNA, and thymosin beta4 predict metastasis and survival in early-stage non-small cell lung cancer. *Oncogene* 2003;**22**(39):8031–41.
42. Fan Y, Shen B, Tan M, *et al.* TGF-$\beta$–induced upregulation of malat1 promotes bladder cancer metastasis by associating with suz12. *Clin Cancer Res* 2014;**20**(6):1531–41.
43. Hirata H, Hinoda Y, Shahryari V, *et al.* Long noncoding RNA MALAT1 promotes aggressive renal cell carcinoma through Ezh2 and interacts with miR-205. *Cancer Res* 2015;**75**(7):1322–31.
44. Liu B, Sun L, Liu Q, *et al.* A cytoplasmic NF-$\kappa$B interacting long noncoding RNA blocks I$\kappa$B phosphorylation and suppresses breast cancer metastasis. *Cancer Cell* 2015;**27**(3):370–81.
45. Sebastian-delaCruz M, Gonzalez-Moro I, Olazagoitia-Garmendia A, *et al.* The role of lncRNAs in gene expression regulation through mRNA stabilization. *Noncoding RNA* 2021;**7**(1):3.
46. Jadaliha M, Gholamalamdari O, Tang W, *et al.* A natural antisense lncRNA controls breast cancer progression by promoting tumor suppressor gene mRNA stability. *PLoS Genet* 2018;**14**(11):e1007802.
47. Pan K, Xie Y. LncRNA FOXC2-AS1 enhances FOXC2 mRNA stability to promote colorectal cancer progression via activation of Ca(2+)-FAK signal pathway. *Cell Death Dis* 2020;**11**(6):434.
48. Wang A, Bao Y, Wu Z, *et al.* Long noncoding RNA EGFR-AS1 promotes cell growth and metastasis via affecting HuR mediated mRNA stability of EGFR in renal cancer. *Cell Death Dis* 2019;**10**(3):154.
49. Chen X, Xu J, Zeng F, *et al.* Inferring cell subtypes and LncRNA function by a cell-specific CeRNA network in breast cancer. *Front Oncol* 2021;**11**:656675.
50. Li J, Han T, Wang X, *et al.* Identification of novel survival-related lncRNA-miRNA-mRNA competing endogenous RNA network associated with immune infiltration in colorectal cancer. *Am J Transl Res* 2021;**13**(6):5815–34.
51. Sun CC, Zhu W, Li SJ, *et al.* Correction to: FOXC1-mediated LINC00301 facilitates tumor progression and triggers an immune-suppressing microenvironment in non-small cell lung cancer by regulating the HIF1$\alpha$ pathway. *Genome Med* 2021;**13**(1):25.
52. Ni C, Fang QQ, Chen WZ, *et al.* Breast cancer-derived exosomes transmit lncRNA SNHG16 to induce CD73+$\gamma\delta$1 Treg cells. *Signal Transduct Target Ther* 2020;**5**(1):41.
53. Zhang K, Zhang L, Mi Y, *et al.* A ceRNA network and a potential regulatory axis in gastric cancer with different degrees of immune cell infiltration. *Cancer Sci* 2020;**111**(11):4041–50.
54. Zhao Y, Yu Z, Ma R, *et al.* lncRNA-Xist/miR-101-3p/KLF6/C/EBP$\alpha$ axis promotes TAM polarization to regulate cancer cell proliferation and migration. *Mol Ther Nucleic Acids* 2021;**23**:536–51.
55. Wang Y, Yang L, Chen T, *et al.* A novel lncRNA MCM3AP-AS1 promotes the growth of hepatocellular carcinoma by targeting miR-194-5p/FOXA1 axis. *Mol Cancer* 2019;**18**(1):28.
56. Li JH, Liu S, Zhou H, *et al.* starBase v2.0: decoding miRNA-ceRNA, miRNA-ncRNA and protein-RNA interaction networks from large-scale CLIP-Seq data. *Nucleic Acids Res* 2014;**42**(D1):D92–7.
57. You BH, Yoon JH, Kang H, *et al.* HERES, a lncRNA that regulates canonical and noncanonical Wnt signaling pathways via interaction with EZH2. *Proc Natl Acad Sci U S A* 2019;**116**(49):24620–9.
58. Matouk IJ, Mezan S, Mizrahi A, *et al.* The oncofetal H19 RNA connection: hypoxia, p53 and cancer. *Biochim Biophys Acta* 2010;**1803**(4):443–51.
59. Luo M, Li Z, Wang W, *et al.* Long non-coding RNA H19 increases bladder cancer metastasis by associating with EZH2 and inhibiting E-cadherin expression. *Cancer Lett* 2013;**333**(2):213–21.
60. Lottin S, Adriaenssens E, Dupressoir T, *et al.* Overexpression of an ectopic H19 gene enhances the tumorigenic properties of breast cancer cells. *Carcinogenesis* 2002;**23**(11):1885–95.
61. Yang Y, Chen L, Gu J, *et al.* Recurrently deregulated lncRNAs in hepatocellular carcinoma. *Nat Commun* 2017;**8**(1):14421.
62. Sun P, Quan JC, Wang S, *et al.* lncRNA-PACER upregulates COX-2 and PGE2 through the NF-$\kappa$B pathway to promote the proliferation and invasion of colorectal-cancer cells. *Gastroenterology Rep* 2020;**9**(3):257–68.
63. Luzón-Toro B, Fernández RM, Martos-Martínez JM, *et al.* LncRNA LUCAT1 as a novel prognostic biomarker for patients with papillary thyroid cancer. *Sci Rep* 2019;**9**(1):14374.
64. Yu X, Li Z, Zheng H, *et al.* NEAT1: a novel cancer-related long non-coding RNA. *Cell Prolif* 2017;**50**(2):e12329.
65. Li S, Li J, Chen C, *et al.* Pan-cancer analysis of long non-coding RNA NEAT1 in various cancers. *Genes Dis* 2018;**5**(1):27–35.

66. Sun C, Li S, Zhang F, *et al.* Long non-coding RNA NEAT1 promotes non-small cell lung cancer progression through regulation of miR-377-3p-E2F3 pathway. *Oncotarget* 2016;**7**(32):51784–814.
67. Chakravarty D, Sboner A, Nair SS, *et al.* The oestrogen receptor alpha-regulated lncRNA NEAT1 is a critical modulator of prostate cancer. *Nat Commun* 2014;**5**(1):5383.
68. Choudhry H, Albukhari A, Morotti M, *et al.* Tumor hypoxia induces nuclear paraspeckle formation through HIF-2α dependent transcriptional activation of NEAT1 leading to cancer cell survival. *Oncogene* 2015;**34**(34):4482–90.
69. Tseng YY, Moriarity BS, Gong W, *et al.* PVT1 dependence in cancer with MYC copy-number increase. *Nature* 2014;**512**(7512):82–6.
70. Derderian C, Orunmuyi AT, Olapade-Olaopa EO, *et al.* PVT1 signaling is a mediator of cancer progression. *Front Oncol* 2019;**9**:502.
71. Sun Y, Ma L. New insights into long non-coding RNA MALAT1 in cancer and metastasis. *Cancers (Basel)* 2019;**11**(2):216.
72. Mourtada-Maarabouni M, Pickard MR, Hedge VL, *et al.* GAS5, a non-protein-coding RNA, controls apoptosis and is downregulated in breast cancer. *Oncogene* 2009;**28**(2):195–208.
73. Zhou Y, Zhong Y, Wang Y, *et al.* Activation of p53 by MEG3 noncoding RNA. *J Biol Chem* 2007;**282**(34):24731–42.
74. Yang X, Xie Z, Lei X, *et al.* Long non-coding RNA GAS5 in human cancer (review). *Oncol Lett* 2020;**20**(3):2587–94.
75. Sun M, Xia R, Jin F, *et al.* Downregulated long noncoding RNA MEG3 is associated with poor prognosis and promotes cell proliferation in gastric cancer. *Tumour Biol* 2014;**35**(2):1065–73.
76. Zhuo H, Tang J, Lin Z, *et al.* The aberrant expression of MEG3 regulated by UHRF1 predicts the prognosis of hepatocellular carcinoma. *Mol Carcinog* 2016;**55**(2):209–19.
77. Huang JZ, Chen M, Chen D, *et al.* A peptide encoded by a putative lncRNA HOXB-AS3 suppresses colon cancer growth. *Mol Cell* 2017;**68**(1):171–184.e6.
78. Wang Y, Wu S, Zhu X, *et al.* LncRNA-encoded polypeptide ASRPS inhibits triple-negative breast cancer angiogenesis. *J Exp Med* 2020;**217**(3).
79. Lambrechts D, Wauters E, Boeckx B, *et al.* Phenotype molding of stromal cells in the lung tumor microenvironment. *Nat Med* 2018;**24**(8):1277–89.
80. Maynard A, McCoach CE, Rotow JK, *et al.* Therapy-induced evolution of human lung cancer revealed by single-cell RNA sequencing. *Cell* 2020;**182**(5):1232–51.e22.
81. Li X, Meng X, Wei C, *et al.* Dissecting LncRNA roles in renal cell carcinoma metastasis and characterizing genomic heterogeneity by single-cell RNA-seq. *Mol Cancer Res* 2018;**16**(12):1879–88.
82. Bocchi VD, Conforti P, Vezzoli E, *et al.* The coding and long noncoding single-cell atlas of the developing human fetal striatum. *Science* 2021;**372**(6542):eabf5759.
83. Liu SJ, Nowakowski TJ, Pollen AA, *et al.* Single-cell analysis of long non-coding RNAs in the developing human neocortex. *Genome Biol* 2016;**17**(1):67.
84. Venkatraman A, He XC, Thorvaldsen JL, *et al.* Maternal imprinting at the H19-Igf2 locus maintains adult haematopoietic stem cell quiescence. *Nature* 2013;**500**(7462):345–9.
85. Zhou J, Yang L, Zhong T, *et al.* H19 lncRNA alters DNA methylation genome wide by regulating S-adenosylhomocysteine hydrolase. *Nat Commun* 2015;**6**(1):10221.
86. Zhou J, Xu J, Zhang L, *et al.* Combined single-cell profiling of lncRNAs and functional screening reveals that H19 is pivotal for embryonic hematopoietic stem cell development. *Cell Stem Cell* 2019;**24**(2):285–98.e5.
87. Zhang Q, Chao TC, Patil VS, *et al.* The long noncoding RNA ROCKI regulates inflammatory gene expression. *EMBO J* 2019;**38**(8):e100041.
88. Carballo E, Pitterle DM, Stumpo DJ, *et al.* Phagocytic and macropinocytic activity in MARCKS-deficient macrophages and fibroblasts. *Am J Physiol* 1999;**277**(1):C163–73.
89. Castellanos-Rubio A, Fernandez-Jimenez N, Kratchmarov R, *et al.* A long noncoding RNA associated with susceptibility to celiac disease. *Science* 2016;**352**(6281):91–5.
90. Zhao H, Zhang X, Frazão JB, *et al.* HOX antisense lincRNA HOXA-AS2 is an apoptosis repressor in all trans retinoic acid treated NB4 promyelocytic leukemia cells. *J Cell Biochem* 2013;**114**(10):2375–83.
91. Wang J, Su Z, Lu S, *et al.* LncRNA HOXA-AS2 and its molecular mechanisms in human cancer. *Clin Chim Acta* 2018;**485**:229–33.
92. Carpenter S, Aiello D, Atianand MK, *et al.* A long noncoding RNA mediates both activation and repression of immune response genes. *Science* 2013;**341**(6147):789–92.
93. Hu G, Gong AY, Wang Y, *et al.* LincRNA-Cox2 promotes late inflammatory gene transcription in macrophages through modulating SWI/SNF-mediated chromatin remodeling. *J Immunol* 2016;**196**(6):2799–808.
94. Wu J, Zhang H, Zheng Y, *et al.* The long noncoding RNA MALAT1 induces tolerogenic dendritic cells and regulatory T cells via miR155/dendritic cell-specific intercellular adhesion molecule-3 grabbing nonintegrin/IL10 axis. *Front Immunol* 2018;**9**:1847.
95. Zhang M, Zheng Y, Sun Y, *et al.* Knockdown of NEAT1 induces tolerogenic phenotype in dendritic cells by inhibiting activation of NLRP3 inflammasome. *Theranostics* 2019;**9**(12):3425–42.
96. Obaid M, Udden SMN, Deb P, *et al.* LncRNA HOTAIR regulates lipopolysaccharide-induced cytokine expression and inflammatory response in macrophages. *Sci Rep* 2018;**8**(1):15670.
97. Wang P, Xue Y, Han Y, *et al.* The STAT3-binding long noncoding RNA lnc-DC controls human dendritic cell differentiation. *Science* 2014;**344**(6181):310–3.
98. Chen MT, Lin HS, Shen C, *et al.* PU.1-regulated Long noncoding RNA lnc-MC controls human monocyte/macrophage differentiation through interaction with microRNA 199a-5p. *Mol Cell Biol* 2015;**35**(18):3212–24.
99. Lu Y, Liu X, Xie M, *et al.* The NF-κB–responsive long noncoding RNA FIRRE regulates posttranscriptional regulation of inflammatory gene expression through interacting with hnRNPU. *J Immunol* 2017;**199**(10):3571–82.
100. Castellanos-Rubio A, Kratchmarov R, Sebastian M, *et al.* Cytoplasmic form of Carlr lncRNA facilitates inflammatory gene expression upon NF-κB activation. *J Immunol* 2017;**199**(2):581–8.
101. Huang D, Chen J, Yang L, *et al.* NKILA lncRNA promotes tumor immune evasion by sensitizing T cells to activation-induced cell death. *Nat Immunol* 2018;**19**(10):1112–25.
102. Shin VY, Chen J, Cheuk IWY, *et al.* Long non-coding RNA NEAT1 confers oncogenic role in triple-negative breast cancer through modulating chemoresistance and cancer stemness. *Cell Death Dis* 2019;**10**(4):270.
103. Zeng C, Xu Y, Xu L, *et al.* Inhibition of long non-coding RNA NEAT1 impairs myeloid differentiation in acute promyelocytic leukemia cells. *BMC Cancer* 2014;**14**(1):693.
104. Willingham AT, Orth AP, Batalov S, *et al.* A strategy for probing the function of noncoding RNAs finds a repressor of NFAT. *Science* 2005;**309**(5740):1570–3.
105. Yao Z, Xiong Z, Li R, *et al.* Long non-coding RNA NRON is downregulated in HCC and suppresses tumour cell proliferation and metastasis. *Biomed Pharmacother* 2018;**104**:102–9.

106. Agarwal S, Vierbuchen T, Ghosh S, *et al.* The long non-coding RNA LUCAT1 is a negative feedback regulator of interferon responses in humans. *Nat Commun* 2020;**11**(1):6348.
107. Patnaik A, Kang SP, Rasco D, *et al.* Phase I study of pembrolizumab (MK-3475; anti-PD-1 monoclonal antibody) in patients with advanced solid tumors. *Clin Cancer Res* 2015;**21**(19):4286–93.
108. Topalian SL, Hodi FS, Brahmer JR, *et al.* Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012;**366**(26):2443–54.
109. Wolchok JD, Chiarion-Sileni V, Gonzalez R, *et al.* Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med* 2017;**377**(14):1345–56.
110. Schachter J, Ribas A, Long GV, *et al.* Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). *Lancet* 2017;**390**(10105):1853–62.
111. Vokes EE, Ready N, Felip E, *et al.* Nivolumab versus docetaxel in previously treated advanced non-small-cell lung cancer (CheckMate 017 and CheckMate 057): 3-year update and outcomes in patients with liver metastases. *Ann Oncol* 2018;**29**(4):959–65.
112. Wu M, Fu P, Qu L, *et al.* Long noncoding RNAs, new critical regulators in cancer immunity. *Front Oncol* 2020;**10**:550987.
113. Denaro N, Merlano MC, Lo Nigro C. Long noncoding RNAs as regulators of cancer immunity. *Mol Oncol* 2019;**13**(1):61–73.
114. Zhou Y, Zhu Y, Xie Y, *et al.* The role of long non-coding RNAs in immunotherapy resistance. *Front Oncol* 2019;**9**:1292.
115. Pi YN, Qi WC, Xia BR, *et al.* Long non-coding RNAs in the tumor immune microenvironment: biological properties and therapeutic potential. *Front Immunol* 2021;**12**:697083.
116. Zhou M, Zhang Z, Bao S, *et al.* Computational recognition of lncRNA signature of tumor-infiltrating B lymphocytes with potential implications in prognosis and immunotherapy of bladder cancer. *Brief Bioinform* 2021;**22**(3).
117. Sun J, Zhang Z, Bao S, *et al.* Identification of tumor immune infiltration-associated lncRNAs for improving prognosis and immunotherapy response of patients with non-small cell lung cancer. *J Immunother Cancer* 2020;**8**(1):e000110.
118. Li G, Kryczek I, Nam J, *et al.* LIMIT is an immunogenic lncRNA in cancer immunity and immunotherapy. *Nat Cell Biol* 2021;**23**(5):526–37.
119. Ye Y, Xu Y, Lai Y, *et al.* Long non-coding RNA cox-2 prevents immune evasion and metastasis of hepatocellular carcinoma by altering M1/M2 macrophage polarization. *J Cell Biochem* 2018;**119**(3):2951–63.
120. Hwang B, Lee JH, Bang D. Single-cell RNA sequencing technologies and bioinformatics pipelines. *Exp Mol Med* 2018;**50**(8):1–14.
121. Kim DH, Marinov GK, Pepke S, *et al.* Single-cell transcriptome analysis reveals dynamic changes in lncRNA expression during reprogramming. *Cell Stem Cell* 2015;**16**(1):88–101.
122. Ren X, Kang B, Zhang Z. Understanding tumor ecosystems by single-cell sequencing: promises and limitations. *Genome Biol* 2018;**19**(1):211.
123. Ren X, Zhang L, Zhang Y, *et al.* Insights gained from single-cell analysis of immune cells in the tumor microenvironment. *Annu Rev Immunol* 2021;**39**(1):583–609.
124. Luo H, Bu D, Shao L, *et al.* Single-cell long non-coding RNA landscape of T cells in human cancer immunity. *Genomics, Proteomics & Bioinformatics* 2021.
125. Shaath H, Vishnubalaji R, Elango R, *et al.* Single-cell long noncoding RNA (lncRNA) transcriptome implicates MALAT1 in triple-negative breast cancer (TNBC) resistance to neoadjuvant chemotherapy. *Cell Death Dis* 2021;**7**(1):23.
126. Wang P, Guo Q, Hao Y, *et al.* LnCeCell: a comprehensive database of predicted lncRNA-associated ceRNA networks at single-cell resolution. *Nucleic Acids Res* 2021;**49**(D1):D125–33.
127. Gao Y, Shang S, Guo S, *et al.* Lnc2Cancer 3.0: an updated resource for experimentally supported lncRNA/circRNA cancer associations and web tools based on RNA-seq and scRNA-seq data. *Nucleic Acids Res* 2021;**49**(D1):D1251–8.
128. Macosko EZ, Basu A, Satija R, *et al.* Highly parallel genome-wide expression profiling of individual cells using nanoliter droplets. *Cell* 2015;**161**(5):1202–14.
129. Zheng GX, Terry JM, Belgrader P, *et al.* Massively parallel digital transcriptional profiling of single cells. *Nat Commun* 2017;**8**:14049.
130. Picelli S, Faridani OR, Björklund ÅK, *et al.* Full-length RNA-seq from single cells using Smart-seq2. *Nat Protoc* 2014;**9**(1):171–81.
131. Hagemann-Jensen M, Ziegenhain C, Chen P, *et al.* Single-cell RNA counting at allele and isoform resolution using Smart-seq3. *Nat Biotechnol* 2020;**38**(6):708–14.
132. Monaco G, Lee B, Xu W, *et al.* RNA-seq signatures normalized by mRNA abundance allow absolute deconvolution of human immune cell types. *Cell Rep* 2019;**26**(6):1627–40.e7.
133. Chen C, He W, Huang J, *et al.* LNMAT1 promotes lymphatic metastasis of bladder cancer via CCL2 dependent macrophage recruitment. *Nat Commun* 2018;**9**(1):3826.
134. Wang XS, Zhang Z, Wang HC, *et al.* Rapid identification of UCA1 as a very sensitive and specific unique marker for human bladder carcinoma. *Clin Cancer Res* 2006;**12**(16):4851–8.
135. Wang Y, Chen W, Yang C, *et al.* Long non-coding RNA UCA1a(CUDR) promotes proliferation and tumorigenesis of bladder cancer. *Int J Oncol* 2012;**41**(1):276–84.
136. Chen F, Chen J, Yang L, *et al.* Extracellular vesicle-packaged HIF-1$\alpha$-stabilizing lncRNA from tumour-associated macrophages regulates aerobic glycolysis of breast cancer cells. *Nat Cell Biol* 2019;**21**(4):498–510.
137. Gupta RA, Shah N, Wang KC, *et al.* Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. *Nature* 2010;**464**(7291):1071–6.
138. Leygue E, Dotzlaw H, Watson PH, *et al.* Expression of the steroid receptor RNA activator in human breast tumors. *Cancer Res* 1999;**59**(17):4190–3.
139. Eoh KJ, Paek J, Kim SW, *et al.* Long non-coding RNA, steroid receptor RNA activator (SRA), induces tumor proliferation and invasion through the NOTCH pathway in cervical cancer cell lines. *Oncol Rep* 2017;**38**(6):3481–8.
140. Jing N, Huang T, Guo H, *et al.* LncRNA CASC15 promotes colon cancer cell proliferation and metastasis by regulating the miR4310/LGR5/Wnt/betacatenin signaling pathway. *Mol Med Rep* 2018;**18**(2):2269–76.
141. He X, Tan X, Wang X, *et al.* C-Myc-activated long noncoding RNA CCAT1 promotes colon cancer cell proliferation and invasion. *Tumour Biol* 2014;**35**(12):12181–8.
142. McCleland ML, Mesh K, Lorenzana E, *et al.* CCAT1 is an enhancer-templated RNA that predicts BET sensitivity in colorectal cancer. *J Clin Invest* 2016;**126**(2):639–52.
143. Ling H, Spizzo R, Atlasi Y, *et al.* CCAT2, a novel noncoding RNA mapping to 8q24, underlies metastatic progression and chromosomal instability in colon cancer. *Genome Res* 2013;**23**(9):1446–61.
144. Li XL, Subramanian M, Jones MF, *et al.* Long noncoding RNA PURPL suppresses basal p53 levels and promotes tumorigenicity in colorectal cancer. *Cell Rep* 2017;**20**(10):2408–23.

145. Silva-Fisher JM, Dang HX, White NM, *et al.* Long non-coding RNA RAMS11 promotes metastatic colorectal cancer progression. *Nat Commun* 2020;**11**(1):2156.
146. Ma MZ, Chu BF, Zhang Y, *et al.* Long non-coding RNA CCAT1 promotes gallbladder cancer development via negative modulation of miRNA-218-5p. *Cell Death Dis* 2015;**6**(1):e1583.
147. Chen J, Yu Y, Li H, *et al.* Long non-coding RNA PVT1 promotes tumor progression by regulating the miR-143/HK2 axis in gallbladder cancer. *Mol Cancer* 2019;**18**(1):33.
148. Wu Q, Xiang S, Ma J, *et al.* Long non-coding RNA CASC15 regulates gastric cancer cell proliferation, migration and epithelial mesenchymal transition by targeting CDKN1A and ZEB1. *Mol Oncol* 2018;**12**(6):799–813.
149. Zhou X, Yin C, Dang Y, *et al.* Identification of the long noncoding RNA H19 in plasma as a novel biomarker for diagnosis of gastric cancer. *Sci Rep* 2015;**5**(1):11516.
150. Chen WM, Huang MD, Kong R, *et al.* Antisense long noncoding RNA HIF1A-AS2 is upregulated in gastric cancer and associated with poor prognosis. *Dig Dis Sci* 2015;**60**(6):1655–62.
151. Liu XH, Sun M, Nie FQ, *et al.* Lnc RNA HOTAIR functions as a competing endogenous RNA to regulate HER2 expression by sponging miR-331-3p in gastric cancer. *Mol Cancer* 2014;**13**(1):92.
152. Zhang J, Jin HY, Wu Y, *et al.* Hypoxia-induced LncRNA PCGEM1 promotes invasion and metastasis of gastric cancer through regulating SNAI1. *Clin Transl Oncol* 2019;**21**(9):1142–51.
153. Huang MD, Chen WM, Qi FZ, *et al.* Long non-coding RNA ANRIL is upregulated in hepatocellular carcinoma and regulates cell apoptosis by epigenetic silencing of KLF2. *J Hematol Oncol* 2015;**8**(1):57.
154. Quagliata L, Matter MS, Piscuoglio S, *et al.* Long noncoding RNA HOTTIP/HOXA13 expression is associated with disease progression and predicts outcome in hepatocellular carcinoma patients. *Hepatology* 2014;**59**(3):911–23.
155. Panzitt K, Tschernatsch MMO, Guelly C, *et al.* Characterization of HULC, a novel gene with striking up-regulation in hepatocellular carcinoma, as noncoding RNA. *Gastroenterology* 2007;**132**(1):330–42.
156. Guo T, Gong C, Wu P, *et al.* LINC00662 promotes hepatocellular carcinoma progression via altering genomic methylation profiles. *Cell Death Differ* 2020;**27**(7):2191–205.
157. Braconi C, Valeri N, Kogure T, *et al.* Expression and functional role of a transcribed noncoding RNA with an ultraconserved element in hepatocellular carcinoma. *Proc Natl Acad Sci U S A* 2011;**108**(2):786–91.
158. Jin W, Chen L, Cai X, *et al.* Long non-coding RNA TUC338 is functionally involved in sorafenib-sensitized hepatocarcinoma cells by targeting RASAL1. *Oncol Rep* 2017;**37**(1):273–80.
159. Khaitan D, Dinger ME, Mazar J, *et al.* The melanoma-upregulated long noncoding RNA SPRY4-IT1 modulates apoptosis and invasion. *Cancer Res* 2011;**71**(11):3852–62.
160. Schmidt LH, Spieker T, Koschmieder S, *et al.* The long noncoding MALAT-1 RNA indicates a poor prognosis in non-small cell lung cancer and induces migration and tumor growth. *J Thorac Oncol* 2011;**6**(12):1984–92.
161. Shen Q, Jiang Y. LncRNA NNT-AS1 promotes the proliferation, and invasion of lung cancer cells via regulating miR-129-5p expression. *Biomed Pharmacother* 2018;**105**:176–81.
162. Nie W, Ge HJ, Yang XQ, *et al.* LncRNA-UCA1 exerts oncogenic functions in non-small cell lung cancer by targeting miR-193a-3p. *Cancer Lett* 2016;**371**(1):99–106.
163. Arunkumar G, Anand S, Raksha P, *et al.* LncRNA OIP5-AS1 is overexpressed in undifferentiated oral tumors and integrated analysis identifies as a downstream effector of stemness-associated transcription factors. *Sci Rep* 2018;**8**(1):7018.
164. Wu Y, Zhang L, Zhang L, *et al.* Long non-coding RNA HOTAIR promotes tumor cell invasion and metastasis by recruiting EZH2 and repressing E-cadherin in oral squamous cell carcinoma. *Int J Oncol* 2015;**46**(6):2586–94.
165. Hu X, Feng Y, Zhang D, *et al.* A functional genomic approach identifies FAL1 as an oncogenic long noncoding RNA that associates with BMI1 and represses p21 expression in cancer. *Cancer Cell* 2014;**26**(3):344–57.
166. Qiu JJ, Wang Y, Ding JX, *et al.* The long non-coding RNA HOTAIR promotes the proliferation of serous ovarian cancer cells through the regulation of cell cycle arrest and apoptosis. *Exp Cell Res* 2015;**333**(2):238–48.
167. Li H, Wang X, Wen C, *et al.* Long noncoding RNA NORAD, a novel competing endogenous RNA, enhances the hypoxia-induced epithelial-mesenchymal transition to promote metastasis in pancreatic cancer. *Mol Cancer* 2017;**16**(1):169.
168. Thin KZ, Liu X, Feng X, *et al.* LncRNA-DANCR: a valuable cancer related long non-coding RNA for human cancers. *Pathol Res Pract* 2018;**214**(6):801–5.
169. Huarte M, Guttman M, Feldser D, *et al.* A large intergenic noncoding RNA induced by p53 mediates global gene repression in the p53 response. *Cell* 2010;**142**(3):409–19.
170. Xing C, Sun SG, Yue ZQ, *et al.* Role of lncRNA LUCAT1 in cancer. *Biomed Pharmacother* 2021;**134**:111158.
171. Hung T, Wang Y, Lin MF, *et al.* Extensive and coordinated transcription of noncoding RNAs within cell-cycle promoters. *Nat Genet* 2011;**43**(7):621–9.
172. Thin KZ, Tu JC, Raveendran S. Long non-coding SNHG1 in cancer. *Clin Chim Acta* 2019;**494**:38–47.
173. Khan MR, Xiang S, Song Z, *et al.* The p53-inducible long noncoding RNA TRINGS protects cancer cells from necrosis under glucose starvation. *EMBO J* 2017;**36**(23):3483–500.
174. Yang Y, Wang C, Zhao K, *et al.* TRMP, a p53-inducible long noncoding RNA, regulates G1/S cell cycle progression by modulating IRES-dependent p27 translation. *Cell Death Dis* 2018;**9**(9):886.
175. Prensner JR, Iyer MK, Balbin OA, *et al.* Transcriptome sequencing across a prostate cancer cohort identifies PCAT-1, an unannotated lincRNA implicated in disease progression. *Nat Biotechnol* 2011;**29**(8):742–9.
176. Petrovics G, Zhang W, Makarem M, *et al.* Elevated expression of PCGEM1, a prostate-specific gene with cell growth-promoting function, is associated with high-risk prostate cancer patients. *Oncogene* 2004;**23**(2):605–11.
177. Prensner JR, Iyer MK, Sahu A, *et al.* The long noncoding RNA SChLAP1 promotes aggressive prostate cancer and antagonizes the SWI/SNF complex. *Nat Genet* 2013;**45**(11):1392–8.
178. Prensner JR, Zhao S, Erho N, *et al.* RNA biomarkers associated with metastatic progression in prostate cancer: a multi-institutional high-throughput analysis of SChLAP1. *Lancet Oncol* 2014;**15**(13):1469–80.
179. Kotake Y, Nakagawa T, Kitagawa K, *et al.* Long non-coding RNA ANRIL is required for the PRC2 recruitment to and silencing of p15(INK4B) tumor suppressor gene. *Oncogene* 2011;**30**(16):1956–62.
180. Pasmant E, Laurendeau I, Héron D, *et al.* Characterization of a germ-line deletion, including the entire INK4/ARF locus, in a melanoma-neural system tumor family: identification of ANRIL, an antisense noncoding RNA whose expression coclusters with ARF. *Cancer Res* 2007;**67**(8):3963–9.

181. Yu W, Gius D, Onyango P, *et al.* Epigenetic silencing of tumour suppressor gene p15 by its antisense RNA. *Nature* 2008;**451**(7175):202–6.
182. Liu W, Wang Z, Wang C, *et al.* Long non-coding RNA MIAT promotes papillary thyroid cancer progression through upregulating LASP1. *Cancer Cell Int* 2019;**19**(1):194.
183. Yildirim E, Kirby JE, Brown DE, *et al.* Xist RNA is a potent suppressor of hematologic cancer in mice. *Cell* 2013;**152**(4):727–42.
184. Yin D, He X, Zhang E, *et al.* Long noncoding RNA GAS5 affects cell proliferation and predicts a poor prognosis in patients with colorectal cancer. *Med Oncol* 2014;**31**(11):253.
185. Kong J, Sun W, Li C, *et al.* Long non-coding RNA LINC01133 inhibits epithelial-mesenchymal transition and metastasis in colorectal cancer by interacting with SRSF6. *Cancer Lett* 2016;**380**(2):476–84.
186. Liu Q, Huang J, Zhou N, *et al.* LncRNA loc285194 is a p53-regulated tumor suppressor. *Nucleic Acids Res* 2013;**41**(9):4976–87.
187. Poliseno L, Salmena L, Zhang J, *et al.* A coding-independent function of gene and pseudogene mRNAs regulates tumour biology. *Nature* 2010;**465**(7301):1033–8.
188. Shao Y, Ye M, Jiang X, *et al.* Gastric juice long noncoding RNA used as a tumor marker for screening gastric cancer. *Cancer* 2014;**120**(21):3320–8.
189. Zhang G, Chi N, Lu Q, *et al.* LncRNA PTCSC3 is a biomarker for the treatment and prognosis of gastric cancer. *Cancer Biother Radiopharm* 2020;**35**(1):77–81.
190. Tu ZQ, Li RJ, Mei JZ, *et al.* Down-regulation of long non-coding RNA GAS5 is associated with the prognosis of hepatocellular carcinoma. *Int J Clin Exp Pathol* 2014;**7**(7):4303–9.
191. Pandey GK, Mitra S, Subhash S, *et al.* The risk-associated long noncoding RNA NBAT-1 controls neuroblastoma progression by regulating cell proliferation and neuronal differentiation. *Cancer Cell* 2014;**26**(5):722–37.
192. Schmitt AM, Garcia JT, Hung T, *et al.* An inducible long noncoding RNA amplifies DNA damage signaling. *Nat Genet* 2016;**48**(11):1370–6.
193. Marín-Béjar O, Mas AM, González J, *et al.* The human lncRNA LINC-PINT inhibits tumor cell invasion through a highly conserved sequence element. *Genome Biol* 2017;**18**(1):202.
194. Jendrzejewski J, He H, Radomska HS, *et al.* The polymorphism rs944289 predisposes to papillary thyroid carcinoma through a large intergenic noncoding RNA gene of tumor suppressor type. *Proc Natl Acad Sci U S A* 2012;**109**(22):8646–51.
195. Ranzani V, Rossetti G, Panzeri I, *et al.* The long intergenic noncoding RNA landscape of human lymphocytes highlights the regulation of T cell differentiation by linc-MAF-4. *Nat Immunol* 2015;**16**(3):318–25.
196. Zhang F, Liu G, Wei C, *et al.* Linc-MAF-4 regulates Th1/Th2 differentiation and is associated with the pathogenesis of multiple sclerosis by targeting MAF. *FASEB J* 2017;**31**(2):519–25.
197. Wang Y, Zhong H, Xie X, *et al.* Long noncoding RNA derived from CD244 signaling epigenetically controls CD8+ T-cell immune responses in tuberculosis infection. *Proc Natl Acad Sci U S A* 2015;**112**(29):E3883–92.
198. Collier SP, Collins PL, Williams CL, *et al.* Cutting edge: influence of Tmevpg1, a long intergenic noncoding RNA, on the expression of Ifng by Th1 cells. *J Immunol* 2012;**189**(5):2084–8.
199. Gomez JA, Wapinski OL, Yang YW, *et al.* The NeST Long ncRNA controls microbial susceptibility and epigenetic activation of the interferon-$\gamma$ locus. *Cell* 2013;**152**(4):743–54.
200. Stein N, Berhani O, Schmiedel D, *et al.* IFNG-AS1 enhances interferon gamma production in human natural killer cells. *iScience* 2019;**11**:466–73.
201. Koh BH, Hwang SS, Kim JY, *et al.* Th2 LCR is essential for regulation of Th2 cytokine genes and for pathogenesis of allergic asthma. *Proc Natl Acad Sci U S A* 2010;**107**(23):10614–9.
202. Spurlock CF, 3rd, Tossberg JT, Guo Y, *et al.* Expression and functions of long noncoding RNAs during human T helper cell differentiation. *Nat Commun* 2015;**6**(1):6932.
203. Hu G, Tang Q, Sharma S, *et al.* Expression and regulation of intergenic long noncoding RNAs during T cell development and differentiation. *Nat Immunol* 2013;**14**(11):1190–8.
204. Zhang R, Ni F, Fu B, *et al.* A long noncoding RNA positively regulates CD56 in human natural killer cells. *Oncotarget* 2016;**7**(45):72546–58.
205. Zemmour D, Pratama A, Loughhead SM, *et al.* Flicr, a long noncoding RNA, modulates Foxp3 expression and autoimmunity. *Proc Natl Acad Sci U S A* 2017;**114**(17):E3472–80.
206. Petri A, Dybkær K, Bøgsted M, *et al.* Long noncoding RNA expression during human B-cell development. *PLoS One* 2015;**10**(9):e0138236.
207. Kotzin JJ, Spencer SP, McCright SJ, *et al.* The long non-coding RNA Morrbid regulates Bim and short-lived myeloid cell lifespan. *Nature* 2016;**537**(7619):239–43.
208. Xin J, Li J, Feng Y, *et al.* Downregulation of long noncoding RNA HOTAIRM1 promotes monocyte/dendritic cell differentiation through competitively binding to endogenous miR-3960. *Onco Targets Ther* 2017;**10**:1307–15.
209. Zhang X, Lian Z, Padden C, *et al.* A myelopoiesis-associated regulatory intergenic noncoding RNA transcript within the human HOXA cluster. *Blood* 2009;**113**(11):2526–34.
210. Krawczyk M, Emerson BM. p50-associated COX-2 extragenic RNA (PACER) activates COX-2 gene expression by occluding repressive NF-$\kappa$B complexes. *Elife* 2014;**3**:e01776.
211. Yang CA, Li JP, Yen JC, *et al.* lncRNA NTT/PBOV1 axis promotes monocyte differentiation and is elevated in rheumatoid arthritis. *Int J Mol Sci* 2018;**19**(9):2806.
212. Li Z, Chao TC, Chang KY, *et al.* The long noncoding RNA THRIL regulates TNF expression through its interaction with hnRNPL. *Proc Natl Acad Sci U S A* 2014;**111**(3):1002–7.
213. Wagner LA, Christensen CJ, Dunn DM, *et al.* EGO, a novel, noncoding RNA gene, regulates eosinophil granule protein transcript expression. *Blood* 2007;**109**(12):5191–8.
214. Xie C, Guo Y, Lou S. LncRNA ANCR promotes invasion and migration of gastric cancer by regulating FoxO1 expression to inhibit macrophage M1 polarization. *Dig Dis Sci* 2020;**65**(10):2863–72.
215. Liang Y, Song X, Li Y, *et al.* LncRNA BCRT1 promotes breast cancer progression by targeting miR-1303/PTBP3 axis. *Mol Cancer* 2020;**19**(1):85.
216. Zhang Y, Feng J, Fu H, *et al.* Coagulation factor X regulated by CASC2c recruited macrophages and induced M2 polarization in glioblastoma multiforme. *Front Immunol* 2018;**9**:1557.
217. Liu J, Ding D, Jiang Z, *et al.* Long non-coding RNA CCAT1/miR-148a/PKC$\zeta$ prevents cell migration of prostate cancer by altering macrophage polarization. *Prostate* 2019;**79**(1):105–12.
218. Li Z, Feng C, Guo J, *et al.* GNAS-AS1/miR-4319/NECAB3 axis promotes migration and invasion of non-small cell lung cancer cells by altering macrophage polarization. *Funct Integr Genomics* 2020;**20**(1):17–28.
219. Zhang H, Yu Y, Wang J, *et al.* Macrophages-derived exosomal lncRNA LIFR-AS1 promotes osteosarcoma cell progression via miR-29a/NFIA axis. *Cancer Cell Int* 2021;**21**(1):192.

220. Tian X, Wu Y, Yang Y, *et al.* Long noncoding RNA LINC00662 promotes M2 macrophage polarization and hepatocellular carcinoma progression via activating Wnt/$\beta$-catenin signaling. *Mol Oncol* 2020;**14**(2):462–83.
221. Zhou L, Tian Y, Guo F, *et al.* LincRNA-p21 knockdown reversed tumor-associated macrophages function by promoting MDM2 to antagonize* p53 activation and alleviate breast cancer development. *Cancer Immunol Immunother* 2020;**69**(5):835–46.
222. Cao J, Dong R, Jiang L, *et al.* LncRNA-MM2P identified as a modulator of macrophage M2 polarization. *Cancer Immunol Res* 2019;**7**(2):292–305.
223. Huang JK, Ma L, Song WH, *et al.* LncRNA-MALAT1 promotes angiogenesis of thyroid cancer by modulating tumor-associated macrophage FGF2 protein secretion. *J Cell Biochem* 2017;**118**(12):4821–30.
224. Zhou Y-X, Zhao W, Mao LW, *et al.* Long non-coding RNA NIFK-AS1 inhibits M2 polarization of macrophages in endometrial cancer through targeting miR-146a. *Int J Biochem Cell Biol* 2018;**104**:25–33.
225. Yang D, Liu K, Fan L, *et al.* LncRNA RP11-361F15.2 promotes osteosarcoma tumorigenesis by inhibiting M2-like polarization of tumor-associated macrophages of CPEB4. *Cancer Lett* 2020;**473**:33–49.
226. Liang ZX, Liu HS, Wang FW, *et al.* LncRNA RPPH1 promotes colorectal cancer metastasis by interacting with TUBB3 and by promoting exosomes-mediated macrophage M2 polarization. *Cell Death Dis* 2019;**10**(11):829.
227. Yin Z, Zhou Y, Ma T, *et al.* Down-regulated lncRNA SBF2-AS1 in M2 macrophage-derived exosomes elevates miR-122-5p to restrict XIAP, thereby limiting pancreatic cancer development. *J Cell Mol Med* 2020;**24**(9):5028–38.
228. Wang B, Li X, Hu W, *et al.* Silencing of lncRNA SNHG20 delays the progression of nonalcoholic fatty liver disease to hepatocellular carcinoma via regulating liver Kupffer cells polarization. *IUBMB Life* 2019;**71**(12):1952–61.
229. Li X, Lei Y, Wu M, *et al.* Regulation of macrophage activation and polarization by HCC-derived exosomal lncRNA TUC339. *Int J Mol Sci* 2018;**19**(10):2958.
230. Sun Y, Xu J. TCF-4 regulated lncRNA-XIST promotes M2 polarization of macrophages and is associated with lung cancer. *Onco Targets Ther* 2019;**12**:8055.
231. Tian X, Ma J, Wang T, *et al.* Long non-coding RNA HOXA transcript antisense RNA myeloid-specific 1-HOXA1 Axis down-regulates the immunosuppressive activity of myeloid-derived suppressor cells in lung cancer. *Front Immunol* 2018;**9**:473.
232. Gao Y, Sun W, Shang W, *et al.* Lnc-C/EBP$\beta$ negatively regulates the suppressive function of myeloid-derived suppressor cells. *Cancer Immunol Res* 2018;**6**(11):1352–63.
233. Gao Y, Wang T, Li Y, *et al.* Lnc-chop promotes immunosuppressive function of myeloid-derived suppressor cells in tumor and inflammatory environments. *J Immunol* 2018;**200**(8):2603–14.
234. Zhou Q, Tang X, Tian X, *et al.* LncRNA MALAT1 negatively regulates MDSCs in patients with lung cancer. *J Cancer* 2018;**9**(14):2436–42.
235. Shang W, Gao Y, Tang Z, *et al.* The pseudogene Olfr29-ps1 promotes the suppressive function and differentiation of monocytic MDSCs. *Cancer Immunol Res* 2019;**7**(5):813–27.
236. Zheng Y, Tian X, Wang T, *et al.* Long noncoding RNA Pvt1 regulates the immunosuppression activity of granulocytic myeloid-derived suppressor cells in tumor-bearing mice. *Mol Cancer* 2019;**18**(1):61.
237. Tian X, Ma J, Wang T, *et al.* Long non-coding RNA RUNXOR accelerates MDSC-mediated immunosuppression in lung cancer. *BMC Cancer* 2018;**18**(1):660.
238. Zhang W, Yang M, Yu L, *et al.* Long non-coding RNA lnc-DC in dendritic cells regulates trophoblast invasion via p-STAT3-mediated TIMP/MMP expression. *Am J Reprod Immunol* 2020;**83**(6):e13239.
239. Liu J, Zhang X, Chen K, *et al.* CCR7 chemokine receptor-inducible lnc-Dpf3 restrains dendritic cell migration by inhibiting HIF-1$\alpha$-mediated glycolysis. *Immunity* 2019;**50**(3):600–615.e15.
240. Fang P, Xiang L, Chen W, *et al.* LncRNA GAS5 enhanced the killing effect of NK cell on liver cancer through regulating miR-544/RUNX3. *Innate Immun* 2019;**25**(2):99–109.
241. Li S, Zhu A, Ren K, *et al.* IFN$\beta$-induced exosomal linc-EPHA6-1 promotes cytotoxicity of NK cells by acting as a ceRNA for hsa-miR-4485-5p to up-regulate NKp46 expression. *Life Sci* 2020;**257**:118064.
242. Ji J, Yin Y, Ju H, *et al.* Long non-coding RNA Lnc-Tim3 exacerbates CD8 T cell exhaustion via binding to Tim-3 and inducing nuclear translocation of Bat3 in HCC. *Cell Death Dis* 2018;**9**(5):478.
243. Yan K, Fu Y, Zhu N, *et al.* Repression of lncRNA NEAT1 enhances the antitumor activity of CD8(+)T cells against hepatocellular carcinoma via regulating miR-155/Tim-3. *Int J Biochem Cell Biol* 2019;**110**:1–8.
244. Brajic A, Franckaert D, Burton O, *et al.* The long non-coding RNA Flatr anticipates Foxp3 expression in regulatory T cells. *Front Immunol* 2018;**9**:1989.
245. Jiang R, Tang J, Chen Y, *et al.* The long noncoding RNA lnc-EGFR stimulates T-regulatory cells differentiation thus promoting hepatocellular carcinoma immune evasion. *Nat Commun* 2017;**8**(1):1–15.
246. Xiong G, Yang L, Chen Y, *et al.* Linc-POU3F3 promotes cell proliferation in gastric cancer via increasing T-reg distribution. *Am J Transl Res* 2015;**7**(11):2262–9.
247. Pei X, Wang X, Li H. LncRNA SNHG1 regulates the differentiation of Treg cells and affects the immune escape of breast cancer via regulating miR-448/IDO. *Int J Biol Macromol* 2018;**118**(Pt A):24–30.
248. Yu Z, Zhao H, Feng X, *et al.* Long non-coding RNA FENDRR acts as a miR-423-5p sponge to suppress the Treg-mediated immune escape of hepatocellular carcinoma cells. *Mol Ther Nucleic Acids* 2019;**17**:516–29.
249. Ma H, Chang H, Yang W, *et al.* A novel IFN$\alpha$-induced long noncoding RNA negatively regulates immunosuppression by interrupting H3K27 acetylation in head and neck squamous cell carcinoma. *Mol Cancer* 2020;**19**(1):4.
250. Takahashi K, Yan IK, Kogure T, *et al.* Extracellular vesicle-mediated transfer of long non-coding RNA ROR modulates chemosensitivity in human hepatocellular cancer. *FEBS Open Bio* 2014;**4**(1):458–67.
251. Wu K, Zhao Z, Liu K, *et al.* Long noncoding RNA lnc-sox5 modulates CRC tumorigenesis by unbalancing tumor microenvironment. *Cell Cycle* 2017;**16**(13):1295–301.
252. Takahashi K, Yan IK, Wood J, *et al.* Involvement of extracellular vesicle long noncoding RNA (linc-VLDLR) in tumor cell responses to chemotherapy. *Mol Cancer Res* 2014;**12**(10):1377–87.
253. Wang QM, Lian GY, Song Y, *et al.* LncRNA MALAT1 promotes tumorigenesis and immune escape of diffuse large B cell lymphoma by sponging miR-195. *Life Sci* 2019;**231**:116335.
254. Wang J, Huang F, Shi Y, *et al.* RP11-323N12.5 promotes the malignancy and immunosuppression of human gastric cancer by increasing YAP1 transcription. *Gastric Cancer* 2021;**24**(1):85–102.
255. Zhang C, Jiang F, Su C, *et al.* Upregulation of long noncoding RNA SNHG20 promotes cell growth and metastasis in esophageal squamous cell carcinoma via modulating

ATM-JAK-PD-L1 pathway. *J Cell Biochem* 2019;**120**(7): 11642–50.
256. Wang CJ, Zhu CC, Xu J, *et al.* The lncRNA UCA1 promotes proliferation, migration, immune escape and inhibits apoptosis in gastric cancer by sponging anti-tumor miRNAs. *Mol Cancer* 2019;**18**(1):115.
257. Su J, Zhang E, Han L, *et al.* Long noncoding RNA BLACAT1 indicates a poor prognosis of colorectal cancer and affects cell proliferation by epigenetically silencing of p15. *Cell Death Dis* 2017;**8**(3):e2665.
258. Petti AA, Williams SR, Miller CA, *et al.* A general approach for detecting expressed mutations in AML cells using single cell RNA-sequencing. *Nat Commun* 2019;**10**(1):3660.
259. Bhaduri A, di Lullo E, Jung D, *et al.* Outer radial glia-like cancer stem cells contribute to heterogeneity of glioblastoma. *Cell Stem Cell* 2020;**26**(1):48–63.e6.
260. Losic B, Craig AJ, Villacorta-Martin C, *et al.* Intratumoral heterogeneity and clonal evolution in liver cancer. *Nat Commun* 2020;**11**(1):291.
261. Lee HO, Hong Y, Etlioglu HE, *et al.* Lineage-dependent gene expression programs influence the immune landscape of colorectal cancer. *Nat Genet* 2020;**52**(6):594–603.
262. Qian J, Olbrecht S, Boeckx B, *et al.* A pan-cancer blueprint of the heterogeneous tumor microenvironment revealed by single-cell profiling. *Cell Res* 2020;**30**(9):745–62.
263. Ma L, Hernandez MO, Zhao Y, *et al.* Tumor cell biodiversity drives microenvironmental reprogramming in liver cancer. *Cancer Cell* 2019;**36**(4):418–30.e6.
264. Witkowski MT, Dolgalev I, Evensen NA, *et al.* Extensive remodeling of the immune microenvironment in B cell acute lymphoblastic leukemia. *Cancer Cell* 2020;**37**(6):867–82.e12.
265. Durante MA, Rodriguez DA, Kurtenbach S, *et al.* Single-cell analysis reveals new evolutionary complexity in uveal melanoma. *Nat Commun* 2020;**11**(1):496.
266. Kim N, Kim HK, Lee K, *et al.* Single-cell RNA sequencing demonstrates the molecular and cellular reprogramming of metastatic lung adenocarcinoma. *Nat Commun* 2020;**11**(1): 2285.
267. Zhang P, Yang M, Zhang Y, *et al.* Dissecting the single-cell transcriptome network underlying gastric premalignant lesions and early gastric cancer. *Cell Rep* 2019;**27**(6):1934–47.e5.
268. Puram SV, Tirosh I, Parikh AS, *et al.* Single-cell transcriptomic analysis of primary and metastatic tumor ecosystems in head and neck cancer. *Cell* 2017;**171**(7):1611–24.e24.
269. Tirosh I, Izar B, Prakadan SM, *et al.* Dissecting the multicellular ecosystem of metastatic melanoma by single-cell RNA-seq. *Science* 2016;**352**(6282):189–96.
270. Sade-Feldman M, Yizhak K, Bjorgaard SL, *et al.* Defining T cell states associated with response to checkpoint immunotherapy in melanoma. *Cell* 2018;**175**(4):998–1013.e20.
271. Tirosh I, Venteicher AS, Hebert C, *et al.* Single-cell RNA-seq supports a developmental hierarchy in human oligodendroglioma. *Nature* 2016;**539**(7628):309–13.
272. Olalekan S, Xie B, Back R, *et al.* Characterizing the tumor microenvironment of metastatic ovarian cancer by single-cell transcriptomics. *Cell Rep* 2021;**35**(8):109165.
273. Chung W, Eum HH, Lee HO, *et al.* Single-cell RNA-seq enables comprehensive tumour and immune cell profiling in primary breast cancer. *Nat Commun* 2017;**8**(1):15081.
274. van Galen P, Hovestadt V, Wadsworth II MH, *et al.* Single-cell RNA-seq reveals AML hierarchies relevant to disease progression and immunity. *Cell* 2019;**176**(6):1265–1281.e24.