Genes & Diseases (2026) 13, 101833

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.keaipublishing.com/en/journals/genes-diseases

REVIEW ARTICLE

The role of long non-coding RNAs in NK cell biology and diseases

Dan Zhang [a,d,*], Siqiao Wei [a,d], Qianqiu Wei [a], Zhansong Lin [c], Xiaoming Sun [a,b,]**

[a] *Zhejiang Key Laboratory of Medical Epigenetics, Department of Immunology and Pathogen Biology, School of Basic Medical Sciences, Hangzhou Normal University, Hangzhou, Zhejiang 311121, China*
[b] *State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, Zhejiang 310003, China*
[c] *Laboratory of Integrative Cancer Immunology, Center for Cancer Research, National Cancer Institute, Bethesda, MD 20892, USA*

Received 26 May 2025; received in revised form 21 July 2025; accepted 30 July 2025
Available online 25 August 2025

KEYWORDS
Cytotoxic activity;
Innate immune cells;
Long non-coding RNAs;
Multiple diseases;
NK cell

Abstract Long non-coding RNAs (lncRNAs) are pivotal regulators of gene expression, increasingly recognized for their roles in immune responses and disease progression. Natural killer (NK) cells, essential cytotoxic lymphocytes of the innate immune system, orchestrate immune responses through cytokine secretion and direct cytotoxicity. This review elucidates the immunomodulatory functions of lncRNAs in NK cell biology and their implications in pathological conditions. LncRNAs intricately govern key NK cell processes, including development, differentiation, activation, recruitment, cytotoxic function, and immune infiltration within the tumor microenvironment. These regulatory effects are mediated through diverse mechanisms, such as transcriptional control of effector molecules, miRNA sponging, metabolic reprogramming, protein ubiquitination, and epigenetic modifications. Focusing on NK cell infiltration in tumors, we classify lncRNAs into mechanistically defined and uncharacterized groups, highlighting their roles in tumor-associated competing endogenous RNA (ceRNA) networks, epigenetic regulation, and cell death pathways. By integrating these perspectives, this review enhances our understanding of lncRNA-mediated immune regulation and underscores their potential as therapeutic targets for diseases involving NK cell dysfunction.
© 2025 The Authors. Publishing services by Elsevier B.V. on behalf of KeAi Communications Co. Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

* Corresponding author.
** Corresponding author. Department of Immunology and Pathogen Biology, School of Basic Medical Sciences, Hangzhou Normal University, No. 2318, Yuhangtang Rd, Yuhang District, Hangzhou, Zhejiang 311121, China.
E-mail addresses: ddzhang@hznu.edu.cn (D. Zhang), xiaoming@hznu.edu.cn (X. Sun).
Peer review under the responsibility of Chongqing Medical University.
[d] These authors contributed equally to this work.

https://doi.org/10.1016/j.gendis.2025.101833
2352-3042/© 2025 The Authors. Publishing services by Elsevier B.V. on behalf of KeAi Communications Co. Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Introduction

Natural killer (NK) cells are crucial components of the innate immune system, capable of recognizing and eliminating infected cells or cancer cells through spontaneous cytotoxicity.[1] The ability to distinguish between self and non/missing-self is acquired during the developmental stage by NK cells.[2] A repertoire of diverse activating and inhibitory receptors is expressed on the surface of NK cells, and the activation of NK cells is regulated by the balance between these two types of receptors.[3] Upon activation, mature NK cells perform their effector functions through the production of cytotoxic granules, death receptor ligands, and cytokines.[4] Given their potent effector capabilities, NK cell-targeted immunotherapies have been extensively investigated across diverse pathological contexts, including malignancies, infectious diseases, autoimmune disorders, transplantation medicine, and aging-related diseases, revealing substantial therapeutic promise.[5,6]

Recent advances in whole-genome analytical tools, including high-throughput sequencing and microarrays, have enabled the systematic discovery of long non-coding RNAs (lncRNAs).[7] LncRNAs are transcripts exceeding 200 nucleotides in length with no protein-coding potential or short peptides.[8] The GENCODE database has systematically annotated over 20,000 lncRNA genes in the human genome, while emerging transcriptomic repositories suggest the potential existence of more than 100,000 lncRNA transcripts through advanced computational predictions expressed in a cell- or tissue-specific manner.[9–11] LncRNAs are predominantly localized in the cytoplasmic and/or nuclear compartments, with their differential expression across distinct cell types underscoring their critical involvement in cellular molecular processes.[12] These transcripts exhibit functional versatility across diverse biological processes, including protein biosynthesis, RNA maturation, and molecular signaling, act as decoy molecules or trafficking regulators, and mediate transcriptional gene silencing through chromatin structure modulation.[8,13] Accumulating evidence has revealed their multifaceted roles in immune regulation, epigenetic programming, disease pathogenesis, and cellular differentiation.[14,15] Despite the uncharacterized roles of many lncRNAs, their abundance suggests profound functional significance within the human transcriptome.

LncRNAs have emerged as critical regulatory molecules bridging a key gap in NK cell research, which has historically focused on receptor signaling, cytotoxic mechanisms, and transcription factor networks.[16,17] Although lacking protein-coding capacity, certain lncRNAs potently modulate essential NK cell functions, including development, differentiation, migration, and cytotoxicity. Recent reviews have summarized the changes in the expression levels and mechanisms of action of relevant ncRNAs or lncRNAs in various pathophysiological processes from the perspective of immune cells, including innate immune cells and adaptive immune cells.[15,18–23] Some articles have also introduced ncRNAs affecting NK cell activity based on the classification of human systemic diseases.[23–25] However, most of the above descriptions focus on miRNAs. In this review, we provide a comprehensive summary of lncRNAs in the immunoregulatory functions of NK cells (Fig. 1 and Table 1). We systematically catalog lncRNAs governing NK cell ontogeny, chemotactic recruitment, activation dynamics, cytotoxic effector mechanisms, and tumor immune infiltration programs, while elucidating their mechanistic underpinnings and therapeutic targetability. Further studies on the regulatory mechanisms and functional significance of these lncRNAs will deepen our understanding of NK cell biology and unlock novel immunotherapeutic strategies for diverse diseases.

LncRNAs in NK cell development and differentiation

Emerging evidence highlights the critical roles of specific lncRNAs in modulating NK cell development and differentiation (Table 1). Killer cell immunoglobulin-like receptors (KIRs) are a critical family of receptors distributed on NK cell surfaces.[26] They recognize HLA class I molecules bound with peptides presented on target cells and regulate NK cell activity through both inhibitory and activating functions.[3] KIR genes remain completely silenced in NK progenitor cells to ensure that they do not negatively impact NK cell differentiation.[27] A notable example of lncRNA involvement is the KIR antisense lncRNA, transcribed from the antisense orientation of KIR protein-coding genes and expressed exclusively in progenitor or pluripotent cell lineages.[28] The distal KIR antisense lncRNA, expressed exclusively at the earliest stages of cell differentiation, enforces epigenetic silencing of KIR loci in NK progenitors to impede the NK cell differentiation process.[28]

In addition to their role in differentiation, lncRNAs also contribute to NK cell development, particularly in regulating maturation markers. For instance, the NK-specific lncRNA lnc-CD56 exhibits a strong positive correlation with the surface expression of CD56, a hallmark maturation marker of human NK cell differentiation and functional ontogeny.[16,29] This implies that lnc-CD56 may function as a positive regulator of CD56 in primary human NK cells and differentiate NK cells from human $CD34^+$ hematopoietic progenitor cells. Together, these findings illustrate how lncRNAs serve as critical molecular orchestrators in NK cell development and differentiation. By modulating epigenetic landscapes and transcriptional networks, lncRNAs such as KIR antisense lncRNAs and lnc-CD56 fine-tune the molecular events that govern NK cell ontogeny, offering novel insights into their regulatory potential and therapeutic relevance in NK cell-based immunotherapies.

LncRNAs in NK cell recruitment and activation

During tumorigenesis, NK cells are recruited into the tumor microenvironment (TME) via chemokine signaling and achieve full activation following cancer cell recognition.[30] Unlike cytotoxic T lymphocytes, which rely on T cell receptor signaling, the activation state of NK cells is controlled by a combination of activating and inhibiting receptor signal transduction.[31,32] Several lncRNAs have been linked to the NK cell recruitment and activation in the

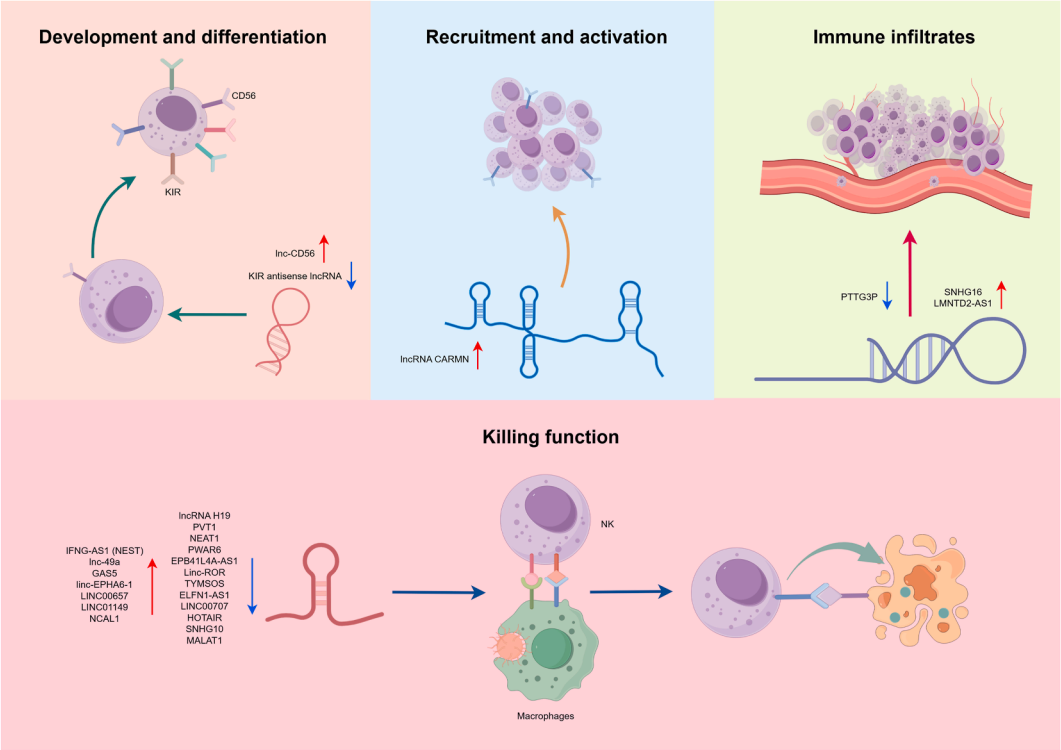

Figure 1 Overview of lncRNAs summarized in this study. The diagram shows lncRNAs and their role in the development, recruitment and activation, killing function and immune infiltration of NK cells. The red upward arrow represents positive regulation, the blue downward arrow represents negative regulation.

context of carcinomas (Table 1). One prominent example is the lncRNA CARMN, whose expression positively correlates with the abundance of NK cells, T cells, and macrophages across various carcinomas.[33] This correlation suggests that CARMN may enhance NK cell recruitment or activation within the TME, potentially preventing NK cell exhaustion by modulating interactions with macrophages.[33] This suggests that CARMN may be a key regulator of the tumor immune microenvironment, with potential implications for immune activation, therapeutic targeting, and biomarker development in multiple cancer types.[33] Similarly, computational analyses have identified other lncRNAs with distinct roles in NK cell dynamics. For instance, N^6-methyladenosine (m^6A)-related lncRNAs in bladder cancer show a positive correlation with resting NK cells, whereas N^7-methylguanosine-related lncRNAs in colon adenocarcinoma and specific TF—mRNA—lncRNA networks in atopic dermatitis are negatively associated with resting NK cell populations.[34—36] These differential associations highlight the context-specific roles of lncRNAs in modulating NK cell states. Furthermore, the establishment of an immune-related lncRNA (IRL) classifier has enabled precise predictions of prognosis and immunotherapy responsiveness in patients with laryngeal squamous cell carcinoma (LSCC).[37] Consistent with computational predictions, this model demonstrated that low-risk patient cohorts exhibit significant enrichment of activated NK cells within the TME, underscoring the potential of lncRNAs to shape immune infiltration and effector function (29). Despite these promising insights, current studies primarily document correlative relationships between lncRNAs and NK cell recruitment or activation, with limited exploration of the underlying molecular mechanisms.[37]

LncRNAs in the killing function of NK cells

NK cells mediate target cell lysis through coordinated mechanisms involving perforin/granzyme exocytosis and Fas/Fas ligand (FasL) death receptor interactions, while simultaneously executing antibody-dependent cellular cytotoxicity (ADCC). Additionally, NK cells secrete immunomodulatory cytokines, such as IFN-γ, to orchestrate multifaceted cytotoxic responses.[38] Bioinformatics approaches, integrating differential gene expression profiling and functional enrichment analysis, have systematically identified lncRNAs associated with NK cell cytotoxicity in diverse disease models.[39—47] These lncRNAs play both autonomous regulatory roles and cooperative interactions within competing endogenous RNA (ceRNA) networks, engaging microRNAs, circular RNAs, and protein-coding transcripts. These interactions position lncRNAs as promising theranostic biomarkers within multi-omics frameworks for biomarker discovery.[39—47] Mechanistically, lncRNAs modulate NK cell killing functions through diverse pathways, including transcriptional regulation of cytotoxicity-related genes, miRNA sponging, metabolic reprogramming, protein ubiquitination, and epigenetic modifications (Table 1). These multifaceted regulatory roles underscore the complexity of lncRNA-mediated control over NK cell cytotoxicity.

Table 1 Summary of lncRNA type, location, pathways and functions of mechanistically characterized lncRNAs in NK cell regulation across various diseases.

lncRNA	LncRNA type	Species	Disease	RNA location	Affected signaling Molecules/Pathway	Function	Ref.
NK cell development and differentiation							
KIR antisense lncRNA	Antisense	H	Healthy	N/A	MZF-1/KIR signaling	Negative regulator of *KIR* gene expression early in development	28
lnc-CD56	Intronic, sense	H	Healthy	N/A	CD56 transcript	Positive regulator of CD56 expression	29
NK killing							
IFNG-AS1 (NEST)	Antisense	H	Healthy	Nucleus/ Cytoplasm	IFNG-AS1/IFN-γ	Positive regulator of IFN-γ	49
NeST	Antisense	H	$CD48^{+}$ tumors	Nucleus/ Cytoplasm	NeST/IFN-γ	Positive regulator of IFN-γ	50
IFNG-AS1	Antisense	M	MCMV infection	Nucleus/ Cytoplasm	IFNG-AS1/IFN-γ	Positive regulator of IFN-γ	51
lnc-49a	N/A	H	RSA	N/A	CD49a/perforin/IFN-γ/ Granzyme B	Positive regulator of CD49a and cytotoxicity of dNK	52
LINC00707	Intergenic	H	HCC	Cytoplasm/ Nucleus	YTHDF2 ubiquitination/ TNF-α/IFN-γ	Negative regulator of NK cell antitumour activity	53
HOTAIR	Antisense	M	Leukemia	N/A	Wnt/β-catenin signaling	Negative regulator of IFN-γ	54
SNHG10	N/A	H	CRC	Exosome	INHBC/perforin/ Granzyme B/NK1.1	Negative regulator of NK cell cytotoxicity	55
MALAT1	Intergenic	H	HBV infection	Nucleus/ Cytoplasm	hsa-miR-155-5p/HIF-1α/ IFN-γ	Negative regulator of IFN-γ transcription and secretion	57
GAS5	Sense	H	HCC	Nucleus/ Cytoplasm	miR-544/RUNX3/IFN-γ/ CD107a	Positive regulator of NK killing effect	58
GAS5	Sense	H	GC	Nucleus/ Cytoplasm	miR-18a/IFN-γ/TNF-α	Positive regulator of NK killing effect	59
linc-EPHA6-1	Intergenic	H	Zika infection	Cytoplasm/ Nucleus	hsa-miR-4485-5p/NKp46	Positive regulator of NK cytotoxicity	60
LINC00657	Intergenic	H	CC	N/A	miR-20a-5p/RUNX3/DR5	Positive regulator of NK cytotoxicity	61
MALAT-1	Intergenic	H	TNBC	Nucleus/ Cytoplasm	miR-34a/MICA/B/ perforin/Granzyme B/ IFN-γ	Negative regulator of NK cell cytotoxicity	62
LINC01149	Intergenic	H	HCC	N/A	miR-128-3p/MICA	Positive regulator of NK recruitment and cytotoxicity	63
lncRNA H19	Intergenic	H	BC	Nucleus/ Cytoplasm	miR-17-5p/STAT3/ULBP2	Negative regulator of NK cell cytotoxicity	64
PVT1	Intergenic	H	LSCC	Nucleus/ Cytoplasm	miR-1301-3p/MBNL1	Negative regulator of NK cell cytotoxicity	65
NEAT1	Intergenic	M	Sepsis	Cytoplasm/ Nucleus	miR-125/MCEMP1	Negative regulator of NK cell cytotoxicity	66
PWAR6	N/A	H	CRLM	Nucleus/ Cytoplasm	Keap1/NRF2/SLC38A2	Negative regulator of NK cell function by altering glutamine availability	68
EPB41L4A-AS1	Antisense	H	NB	N/A	Encapsulated in exosomes and transmitted from $CD56^{bright}$ NK to $CD56^{dim}$ NK cells	Negative regulator of NK cell function by inhibiting glycolysis	70

Table 1 (*continued*)

NK cell development and differentiation							
lncRNA	LncRNA type	Species	Disease	RNA location	Affected signaling Molecules/Pathway	Function	Ref.
Linc-ROR	Intergenic	H	GC	N/A	RXRA ubiquitination/ MICB	Negative regulator of NK cell killing activity	72
TYMSOS	N/A	H	BC	Cytoplasm/ Nucleus	CBX3/SYVN1/ULBP3 ubiquitination	Negative regulator of NK cell cytotoxicity	73
NCAL1	N/A	H	Healthy	Nucleus/ Cytoplasm	Gab2/H3K4me3/H3K27/ PI3K-AKT/CD107a	Positive regulator of NK cell cytotoxicity	74
ELFN1-AS1	Antisense	H	CRC	Cytoplasm/ Nucleus	GDF15/JNK/NKG2D/ GZMB	Negative regulator of NK cell NK surveillance and cytotoxicity	75
NK cell infiltration							
PTTG3P	N/A	H	CRC	Cytoplasm/ Nucleus	HIF1α/PTTG3P/YAP1	Negatively correlates with NK cell infiltration	82
SNHG16	Intergenic	H	SKCM	N/A	hsa-let-7b-5p-TUBB4A	Positively correlates with NK cell infiltration	83
LMNTD2-AS1	Antisense	H	PCa	N/A	NRF2/FUS	Positively correlates with $CD56^{bright}$ NK cell abundance	84

Footnotes:
LncRNA type: N/A, Not applicable; Species: H, Homo sapiens; M, Mice.
Disease: MCMV, murine cytomegalovirus; RSA, recurrent spontaneous abortion; HCC, hepatocellular carcinoma; CRC, colorectal cancer; HBV, hepatitis B virus; GC, gastric cancer; CC, cervical cancer; TNBC, triple negative breast cancer; BC, breast cancer; LSCC, laryngeal squamous cell carcinoma; CRLM, colorectal cancer liver metastases; NB, neuroblastoma; SKCM, skin cutaneous melanoma; PCa, prostate cancer.

LncRNA-driven transcriptional regulation of cytolytic effectors

NK cells eliminate target cells through the secretion of cytotoxic mediators, including IFN-γ, granzyme B, and perforin.[48] A well-documented example is lncRNA IFNG-AS1 (also known as NEST), which is rapidly induced upon NK cell activation and enhances IFN-γ secretion when overexpressed.[49] Similarly, in a murine immunotherapy combining NK cell-mediated tumor targeting and lncRNA, lncRNA NeST overexpression in YTS cells was observed to enhance interferon secretion upon encountering $CD48^{+}$ tumor cells, thereby augmenting cytotoxic efficacy.[50] Conversely, impaired lncRNA regulation can compromise NK cell maturation and function. For instance, in neonatal mice infected with murine cytomegalovirus (MCMV), downregulated expression of lncRNA IFNG-AS1 in NK cells severely reduces IFN-γ production, leading to defective maturation and diminished cytotoxic capacity.[51] These findings highlight the critical role of lncRNAs in sustaining IFN-γ-mediated effector functions. Beyond IFN-γ, lncRNAs regulate other cytotoxic mediators in NK cells. For example, lnc-49a acts as a positive regulator of CD49a in primary human decidual NK cells from patients with recurrent spontaneous abortions. Knockdown of lnc-49a via siRNA significantly reduces the production of perforin, IFN-γ, and granzyme B, underscoring its role in maintaining NK cell cytotoxicity.[52] Similarly, LINC00707 enhances the cytotoxicity of NK-92MI cells against hepatocellular carcinoma (HCC) cells by interacting with YTH N6-methyladenosine RNA-binding protein 2 (YTHDF2).[53] In contrast, certain lncRNAs exert immunosuppressive effects. Upregulation of the lncRNA HOTAIR through mimic transfection in murine models reduces IFN-γ levels in peripheral blood and diminishes NK cell activity by activating the Wnt/β-catenin signaling pathway, thereby promoting immune evasion in leukemia.[54] Likewise, the exosomal lncRNA SNHG10, which is upregulated in colorectal cancer cells, suppresses perforin, granzyme B, and NK1.1 expression in NK cells by activating the TGF-β signaling pathway via inhibin subunit beta C (INHBC), facilitating tumor immune escape.[55]

LncRNAs as ceRNAs modulating NK cytotoxicity

Certain lncRNAs can function as "miRNA sponges" through competitive miRNA binding. Consequently, these lncRNAs located on NK cells act as ceRNAs to regulate the function of miRNAs and thus affect NK cytotoxicity[56] (Fig. 2 and Table 1). For example, in NK cells from tenofovir-treated pregnant women with hepatitis B virus infection, lncRNA MALAT1 expression is significantly down-regulated, which consequently suppresses IFN-γ transcription and

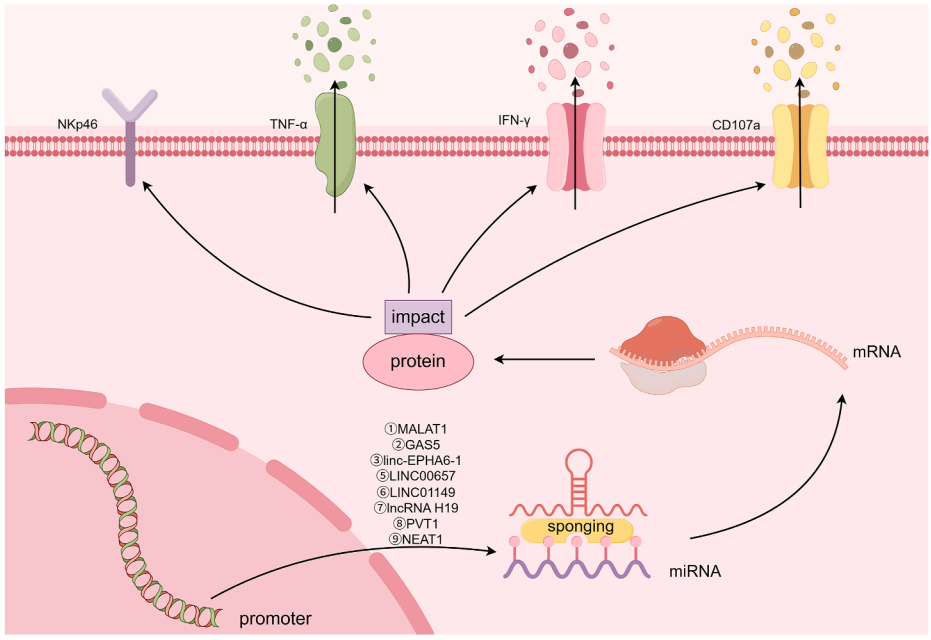

Figure 2 LncRNAs as ceRNA. LncRNAs act as miRNA sponges to regulate NK cell toxicity.

production.[57] Mechanistically, MALAT1 functions as a ceRNA by sponging hsa-miR-155-5p to up-regulate HIF-1a, promoting NK cell immune recovery.[57] Similarly, the lncRNA GAS5 is significantly downregulated in NK cells from HCC patients.[58] The overexpression of GAS5 enhances RUNX3 expression, IFN-γ secretion, and NK cell cytotoxic activity by targeting the miR-544/RUNX3 axis, which is an effect reversed by miR-544 mimic.[58] In gastric cancer (GC), NK cells show decreased lncRNA GAS5 and increased miR-18a expression. GAS5 deficiency suppresses IFN-γ/TNF-α secretion and cytotoxicity in NK cells, while miR-18a inhibition rescues cytotoxic activity, indicating that GAS5 enhances NK-mediated antitumor effects by sponging miR-18a.[59] Additionally, linc-EPHA6-1 in IFNβ-induced exosomes enhances NK cell cytolytic activity by sponging hsa-miR-4485-5p, up-regulating the natural cytotoxicity receptor NKp46 in both NK92 cells and primary NK cells.[60]

In addition to acting as ceRNAs in NK cells, there are several lncRNAs located in tumor cells or T cells that can regulate the killing toxicity of NK cells to target cells. In cervical cancer (CC), miR-20a-5p was confirmed as a target of LINC00657. LINC00657 has been demonstrated to promote the cytotoxic activity of NK cells by inducing the miR-20a-5p/RUNX3/DR5 axis, where DR5 is a downstream target of RUNX3.[61] In triple negative breast cancer (TNBC) patients, the up-regulated lncRNA MALAT-1 inhibits NK cell cytotoxicity, but silencing MALAT-1 enhances NK cell activity, potentially via the miR-34a or miR-17-5p pathway.[62] In HCC, the LINC01149 variant rs2844512 acts as a ceRNA by sponging miR-128-3p to induce MHC class I chain-related protein A (MICA) expression, which recruits NK cells.[63] While this mechanism potentially recruits NK cells to lyse infected cells, concomitant shedding of highly soluble MICA paradoxically promotes NK cell exhaustion and tumor immune evasion through sustained receptor—ligand interactions.[63] In young breast cancer (BC) patients, lncRNA H19 functions as a ceRNA by sequestering miR-17-5p, thereby counteracting its suppressive activity and blocking the miR-17-5p-mediated down-regulation of STAT3.[64] The ectopic expression of miR-17-5p in MDA-MB-231 cells significantly inhibited the expression levels of STAT3 and lncRNA H19, and induced the expression of ULBP2, a NKG2D ligand, in TNBC cell lines.[64] In LSCC, the up-regulated lncRNA, PVT1, promotes tumor cell proliferation and resistance to NK cell lysis by sponging miR-1301-3p to up-regulate MBNL1.[65] Similarly, in T cells from sepsis patients, the lncRNA NEAT1 acts as a ceRNA for miR-125 to up-regulate its target gene MCEMP1, inhibiting NK cell activity and accelerating the pathological progression of sepsis.[66]

LncRNAs orchestrate metabolic reprogramming in NK cell cytotoxicity

LncRNAs modulate NK cell cytotoxicity through diverse mechanisms, with metabolic reprogramming emerging as a critical, yet underexplored, regulatory pathway (Fig. 3 and Table 1). Metabolic reprogramming critically drives tumor progression and metastasis, with glutamine serving as a vital substrate for the tricarboxylic acid (TCA) cycle and precursor for lipid, nucleotide, and hexosamine biosynthesis.[67] In colorectal cancer (CRC) liver metastases, exosomal lncRNA PWAR6, derived from myofibroblastic cancer-associated fibroblasts (myCAFs), is markedly up-regulated.[68] PWAR6 competes with Keap1 to stabilize NRF2 and up-regulate SLC38A2 expression, thereby increasing glutamine uptake in CRC cells.[68] This metabolic competition depletes extracellular glutamine, a critical resource for NK cell activation, resulting in impaired cytotoxicity due to substrate deprivation.[68] Glucose metabolism also serves as a primary bioenergetic source for NK cell activation.[69] Similarly, in neuroblastoma, NK cells exhibit glycolytic arrest, which is mediated by the transfer of the elevated exosome lncRNA EPB41L4A-AS1 from the $CD56^{bright}$ NK subset to $CD56^{dim}$ NK subset.[70]

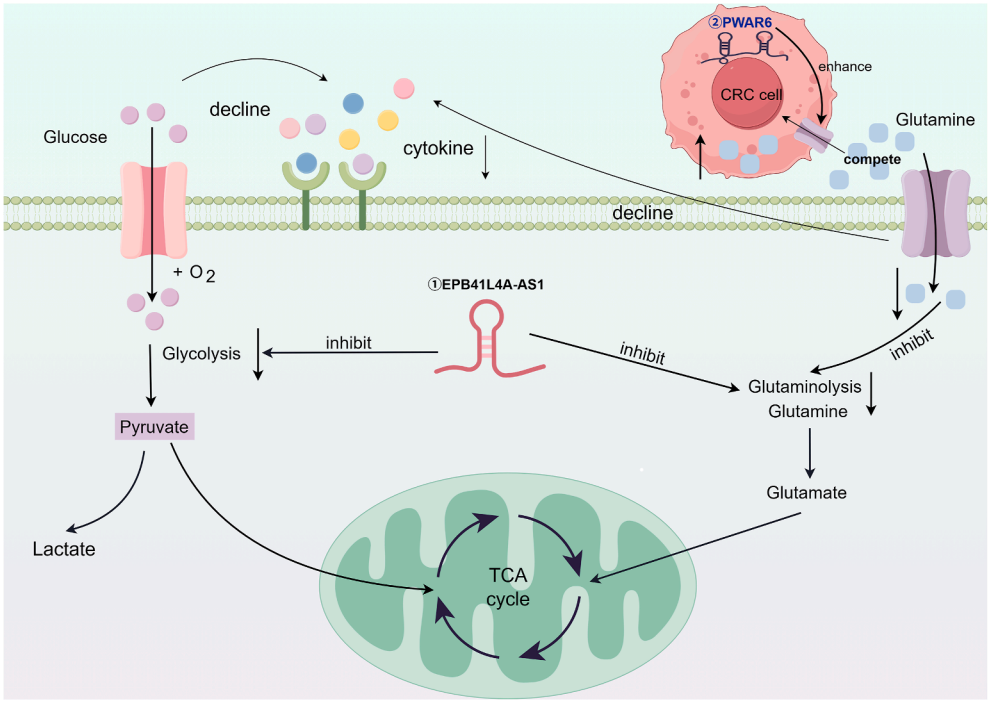

Figure 3 LncRNAs orchestrate metabolic reprogramming. LncRNAs regulate the killing function of NK cells by participating in the tricarboxylic acid cycle and glucose glycolysis.

LncRNA-mediated control of ubiquitination in NK cell cytotoxicity

Ubiquitination is a process of post-translational modification that degrades target proteins and facilitates protein interactions, cell localization, and signal transduction.[71] LncRNAs have also been found to influence NK cytotoxicity by regulating ubiquitination (Fig. 4 and Table 1). For instance, the linc-ROR promotes the ubiquitination and degradation of retinoid X receptor alpha (RXRA) in gastric cancer cells, leading to reduced MHC class I chain-related protein B (MICB) expression and thereby suppressing NK cell cytotoxic activity in gastric cancer patients.[72] Similarly, in breast cancer cells, the lncRNA TYMSOS promotes chromobox protein homolog 3 (CBX3)-mediated transcriptional repression and synoviolin 1 (SYVN1)-driven ubiquitin–proteasomal degradation of UL16 binding protein 3 (ULBP3), suppressing NK cell cytotoxicity to facilitate tumor metastasis and immune escape.[73] These findings highlight the critical role of lncRNAs in fine-tuning ubiquitination to modulate NK cell function and tumor progression.

LncRNA-mediated epigenetic regulation in NK cell cytotoxicity

In NK cells, the nuclear lncRNA NCAL1 epigenetically regulates NK cell function by binding to the Gab2 promoter, reducing its methylation while increasing H3K4me3 and H3K27 levels, thereby enhancing NK cell cytotoxicity against tumor cells via the PI3K-AKT pathway.[74] Conversely, the lncRNA ELFN1-AS1 enhances the ability of CRC cells to evade NK cell surveillance both *in vitro* and *in vivo*.[75] Mechanistically, ELFN1-AS1 down-regulates NKG2D and GZMB expression via the GDF15/JNK pathway. Concurrently, it strengthens the interaction between the GCN5 and SND1 proteins, reducing H3K9ac enrichment at the GDF15 promoter to up-regulate GDF15 production in CRC cells.[75] Collectively, these studies provide compelling evidence for the regulatory role of lncRNAs in NK function via epigenetic regulation (Fig. 5 and Table 1).

LncRNA regulates NK cell infiltration in the TME

The TME is a complex system comprising diverse cell types, cytokines, and extracellular components.[76–78] The type and abundance of tumor-infiltrating immune cells critically influence tumor progression.[79,80] Specific lncRNAs critically regulate NK cell infiltration, influencing tumor immune dynamics via diverse mechanisms.

Mechanistically defined lncRNAs in NK immune infiltration

In colorectal cancer, the lncRNA PTTG3P enhances tumor cell proliferation and glycolysis via the HIF1α/PTTG3P/YAP1 axis and exhibits a negative correlation with NK, CD8 T, and other immune cell infiltrations.[81] Similarly, the lncRNA SNHG16 in skin cutaneous melanoma (SKCM) regulates the hsa-let-7b-5p-TUBB4A axis, potentially linked to NK cell immune infiltration.[82] In prostate cancer patients, the lncRNA LMNTD2-AS1 is the only lncRNA associated with both overall survival (OS) and progression-free interval (PFI).[83] Its elevated expression correlates positively with

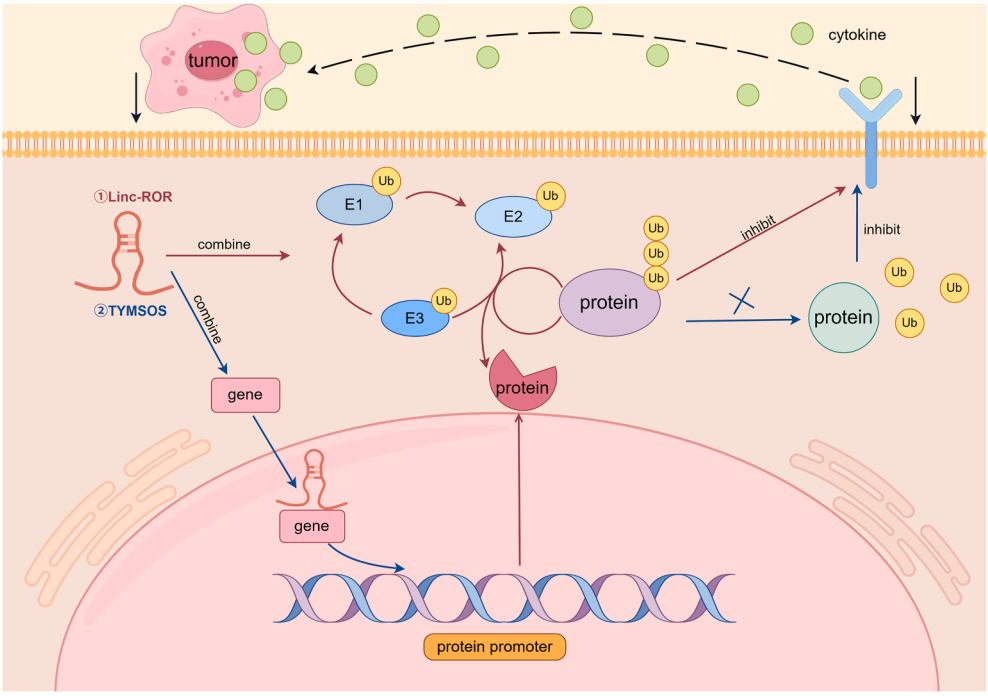

Figure 4 LncRNA-mediated control of ubiquitination. Linc-ROR and the lncRNA TYMSOS alter the cytotoxicity of NK cells against tumor cells by participating in protein ubiquitination and degradation. The red line indicates the linc-ROR pathway, and the blue line indicates the TYMSOS pathway.

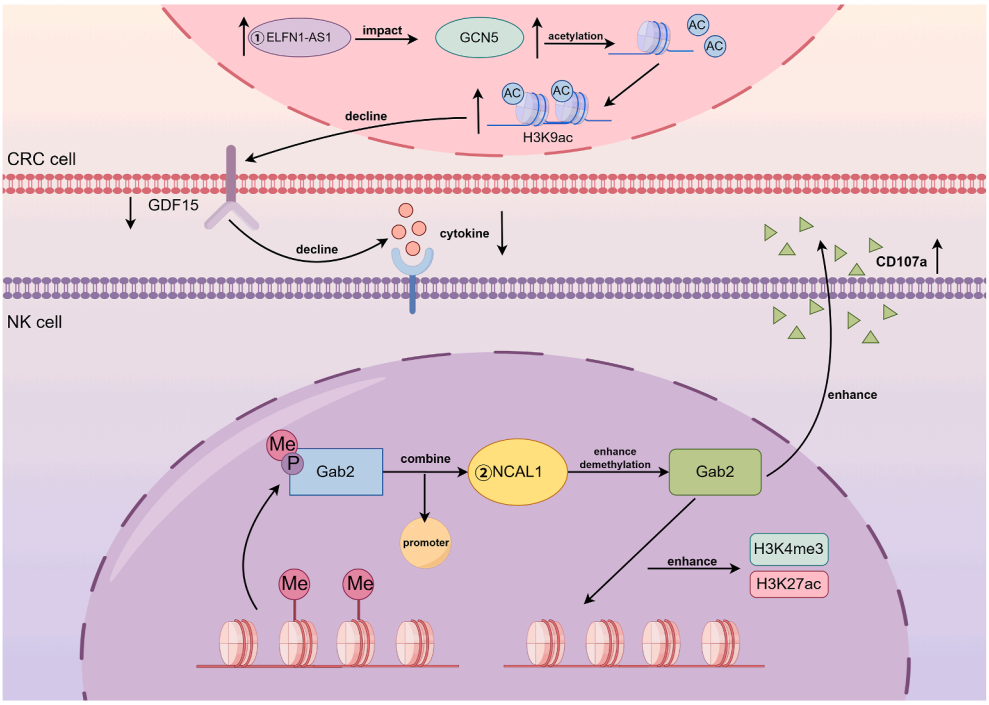

Figure 5 LncRNA-mediated epigenetic regulation. The LncRNAs NCAL1 and ELFN1-AS1 affect NK cell toxicity by regulating epigenetic modifications and the PI3K-AKT and GDF15/JNK signaling pathways.

CD56^{bright} NK cell abundance by regulating the NRF2 signaling pathway through targeting FUS.[83]

Mechanistically unexplored lncRNAs in NK immune infiltration

Furthermore, although certain lncRNAs have been shown to be significantly associated with NK cell infiltration in the TME, their mechanisms remain unexplored. In this section, we summarized lncRNAs associated with CD56^{bright}, CD56^{dim}, or total NK cell populations across diverse tumor microenvironments. Although mechanistic elucidation is lacking, these findings suggest functional disparities of such lncRNAs within distinct NK cell subsets within the tumor microenvironment. In lung adenocarcinoma (LUAD), the expression of the lncRNA NPSR1-AS1 was negatively associated with CD56^{dim} NK cells but positively correlated with CD56^{bright} NK cells, suggesting that NPSR1-AS1 may have different functions in different NK subgroups.[84] Similarly, lncRNA ITGB1-DT levels positively correlate with CD56^{dim} NK cell abundance, suggesting its potential role in modulating NK cell infiltration.[85] The expression of the LncRNA HAND2-AS1 positively correlates with NK cell infiltration in the TME, a pan-cancer association suggesting its potential as a tumor suppressor.[86] Conversely, the lncRNA PRR7-AS1 inversely correlates with CD56^{bright} NK cell abundance and serves as a prognostic biomarker.[87] In gastric cancer patients with peritoneal metastasis, elevated LINC00924 expression predicts poor survival and increased NK cell infiltration.[88] In HCC patients, the lncRNA INKA2-AS1 is recognized as an independent prognostic factor for overall survival.[89] Its expression positively correlates with immune cells such as CD56^{bright} NK cells, helper T cells, Th2 cells, and macrophages, suggesting its role as a critical immune response modulator in HCC.[89] In cholangiocarcinoma (CCA), the expression of the lncRNA AL161431.1 is significantly upregulated.[90] Its high expression positively correlates with increased infiltration of CD56^{dim} NK cells, T cells, and helper T cells, while AL161431.1 knockdown in CCA cells suppresses tumor cell invasion, migration, and proliferation, highlighting its potential as a therapeutic target for CCA.[90] In addition, LINC01589 in uterine corpus endometrial carcinoma (UCEC)[91] and MSC-AS1 in gastric cancer[92] are positively related to NK cell abundance, while the lncRNA MIAT in breast cancer (BC),[93] the lncRNA ZFHX4-AS1 in ovarian cancer,[94] and PCBP1-AS1 in cervical cancer[95] are negatively related to NK cell abundance, suggesting diverse roles in NK cell modulation. The discovery of lncRNAs linked to NK cell infiltration opens new possibilities for current conventional therapies, but mechanistic studies need to be further explored.

NK infiltration-associated lncRNAs in tumor ceRNA networks

Bioinformatics analyses have identified additional lncRNAs potentially linked to NK cell infiltration, though experimental validation or mechanistic exploration remains lacking. Notably, ceRNA networks, particularly lncRNA-miRNA-mRNA regulatory axes, are increasingly implicated in tumorigenesis and prognosis across cancers, offering frameworks for dissecting oncogenic mechanisms.[96] Differentially expressed lncRNAs (DElncRNAs) were identified through computational screening using algorithms like CIBERSORT. Intriguingly, DElncRNAs in radiation-induced esophageal injury,[97] hepatocellular carcinoma,[98] and thyroid cancer[99] showed positive correlations with NK cell infiltration levels, whereas those in idiopathic pulmonary fibrosis[100] and diabetic kidney disease[101] exhibited negative correlations.

Epigenetic modification-linked lncRNAs in the TME

The main RNA methylation modifications, including m^{6}A, 5-methylcytosine (m^{5}C), and N1-methyladenosine (m^{1}A) in mRNAs and ncRNAs, play critical regulatory roles in tumor RNA modifications.[102,103] In gastric cancer, m^{6}A-related lncRNAs were identified to construct a risk model stratifying patients into high- and low-risk groups. The risk score demonstrated negative correlations with activated NK cells[104] or with resting NK cells[105] across studies. In colorectal cancer,[105] bladder cancer,[106,107] and pancreatic ductal adenocarcinoma,[108] tumor immune profiling of risk models constructed from m^{6}A-related lncRNAs revealed significantly elevated resting NK cell infiltration levels in high-risk groups. In lung squamous cell carcinoma (LUSC), prognostic models based on m^{5}C-related lncRNAs showed a negative correlation between risk scores and activated NK cells,[109] whereas in head and neck squamous cell carcinoma (HNSCC), m^{6}A/m^{5}C/m^{1}A-related lncRNA models positively correlate with resting NK cells.[110] These findings highlight the significance of epigenetic modification-associated lncRNAs in tumor prognosis and NK cell infiltration, providing a framework for further functional and mechanistic exploration.

Cell death mechanism-linked lncRNAs in tumors

Cuproptosis, ferroptosis, and pyroptosis are emerging as novel regulatory cell death mechanisms, with mounting evidence linking them to tumorigenesis and cancer progression.[111–113] Cuproptosis-related lncRNA risk models in HCC, gastric cancer, colon cancer, HNSCC, and ovarian serous cystadenocarcinoma show negative correlations with NK cell activation.[114–118] In gliomas, patients stratified by ferroptosis-related lncRNA expression into high- and low-risk groups showed elevated levels of both activated and resting NK cells in high-risk cohorts.[119] In contrast, stratification based on pyroptosis-related lncRNAs revealed a positive correlation between risk score and activated NK cells only.[120] In Wilms tumor, ferroptosis-related lncRNAs were identified and used for patient stratification. Analysis revealed significantly elevated tumor NK cell levels in high-risk groups.[121] These findings suggest that lncRNAs linked to cell death-regulatory mechanisms may serve as promising molecular therapeutic targets.

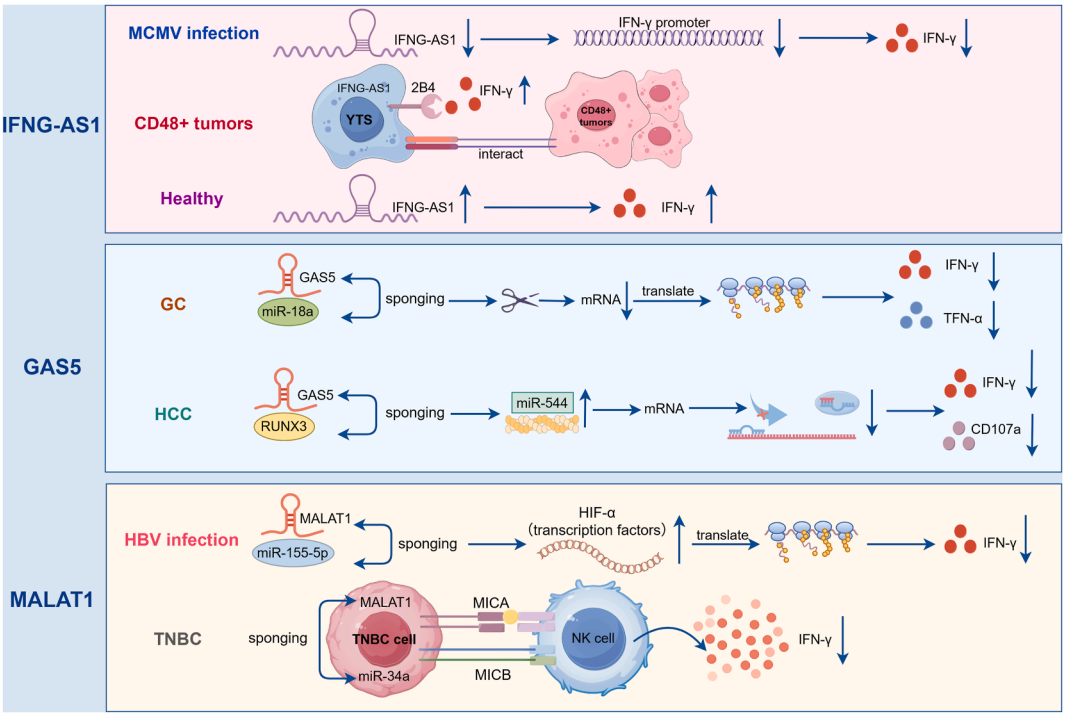

Figure 6 Common lncRNAs in different diseases. Some lncRNAs affect the function of NK cells through different pathways, such as IFNG-AS1 (NEST) in healthy individuals, CD48$^+$ tumors, and MCMV infections; GAS5 in HCC and GC; and MALAT-1 in HBV infection and TNBC.

Bioinformatics identified lncRNAs associated with NK infiltration

Furthermore, lncRNAs are implicated across multiple cancer types, where they correlate with the infiltration of activated or resting NK cells in the tumor immune microenvironment and serve as prognostic and diagnostic biomarkers.[85,122–139] Shao et al constructed a pan-cancer immune co-regulatory network of lncRNAs, revealing that these immune-cooperative lncRNAs (IC-lncRNAs) are predominantly enriched in immune cell populations and exhibit significant correlations with heterogeneous immune infiltration patterns, thereby uncovering conserved immunomodulatory mechanisms across malignancies.[140] These bioinformatics-derived findings necessitate further functional dissection, particularly exploration of context-specific molecular mechanisms, to advance the mechanistic understanding of disease pathogenesis.

Therapeutic strategies targeting lncRNAs in NK cells

The clinical significance of lncRNA dysregulation is underscored by its potential as diagnostic biomarkers and therapeutic targets.[141] For example, urinary lncRNA PCA3 is an FDA-approved biomarker for prostate cancer diagnosis.[142] In the H19-targeted therapy program for bladder cancer (NCT04234216), intravesical administration of BC-819 achieves maximal local exposure to targeted bladder cancer cells, and the program has now entered Phase II clinical trials.[143] Class inhibitors of the lncRNA MALAT1-FTX-001 are undergoing preclinical validation, with potential progression to Phase I trials upon safety clearance.[144] As previously mentioned, MALAT-1 functions as a ceRNA to regulate NK cell cytotoxicity, highlighting its significant therapeutic potential in NK cells. Other lncRNA-targeted strategies, including those against HOTAIR and NEAT1, are in preclinical testing.[145,146] Upon optimization of their stability and targeted delivery technologies, therapies based on these lncRNAs are poised to enter clinical trials. Considering HOTAIR's transcriptional regulation of cytotoxic factors and NEAT1's role as a ceRNA in modulating NK cell cytotoxicity, further mechanistic exploration will help address the gap in targeted therapies for immune-related lncRNAs across multiple diseases.

Conclusion and future perspectives

Growing evidence highlights the critical roles of lncRNAs as regulators of NK cell biology. LncRNAs regulate the levels of translatable mRNAs in response to specific developmental or stimulus cues, which provides the possibility of controlling the cytotoxicity and cytokine secretion of NK cells. These findings deepen our understanding of immune regulation and its implications in diverse diseases. In this review, we comprehensively summarize the reported lncRNAs and their functions across various diseases, focusing on four key aspects of NK cell biology: development/differentiation, recruitment/activation, killing function, and tumor infiltration. Notably, lncRNAs regulate the transcription of NK cell cytotoxic molecules through direct or indirect mechanisms, with their role as miRNA sponges being widely

studied. This underscores the complexity of lncRNA-mediated immune regulation.

To date, numerous lncRNA-related studies in the immune system have focused on characterizing lncRNA functions in murine and human primary cells or cell lines. Nevertheless, emerging evidence has demonstrated that specific lncRNAs influence disease pathogenesis and progression across diverse pathologies by modulating NK cell activity, such as IFNG-AS1 in healthy individuals, $CD48^{+}$ tumors, and MCMV infection; GAS5 in HCC and GC; MALAT1 in HBV infection and TNBC. All of these play pivotal roles in mediating protection against or susceptibility to inflammatory diseases by regulating NK cell functions. The same lncRNA has been proven to adopt different molecular mechanisms in different diseases (Fig. 6).

Nevertheless, the mechanisms of action of these lncRNAs remain incompletely elucidated. As highlighted in this review, numerous functional lncRNAs with potential diagnostic and prognostic utility have been identified. Future research should prioritize comprehensive mechanistic studies to uncover how lncRNAs govern NK cell functionality from multiple perspectives. Such efforts will strengthen their potential as innovative therapeutic targets, paving the way for novel immunotherapies in cancer and beyond.

CRediT authorship contribution statement

Dan Zhang: Writing — review & editing, Writing — original draft, Visualization, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Siqiao Wei:** Software, Investigation. **Qianqiu Wei:** Methodology, Investigation. **Zhansong Lin:** Writing — review & editing, Supervision. **Xiaoming Sun:** Writing — review & editing, Funding acquisition, Conceptualization.

Conflict of interests

The authors declare no conflicts of interest in any form.

Acknowledgements

X.S. is supported by grants from the National Natural Science Foundation of China (No. 82271791), the Medical Health Science and Technology Project of Zhejiang Provincial Health Commission (China) (No. 2023KY1007), the Natural Science Foundation of Hangzhou, China (No. 2024SZRYBC080003), the Interdisciplinary Research Project of Hangzhou Normal University (China) (No. 2024JCXK07), the Hangzhou Youth Innovation Team Project (China) (No. TD2023020) and Hangzhou Normal University grant (China) (No. 4255C50222204027). D.Z. is supported by grants from the Natural Science Foundation of Zhejiang Province, China (No. LQN25H100002), a project supported by Scientific Research Fund of Zhejiang Provincial Education Department (China) (No. Y202351669), and Hangzhou Normal University grant (China) (No. 4255C50222204139). The funding agencies had no role in the study design; in the collection, analysis, and interpretation of the data; in the writing of the report; and in the decision to submit the paper for publication. The figures were generated by Figdraw 2.0.

References

1. Vivier E, Raulet DH, Moretta A, et al. Innate or adaptive immunity? The example of natural killer cells. *Science*. 2011;331(6013):44—49.
2. Perera Molligoda Arachchige AS. Human NK cells: from development to effector functions. *Innate Immun*. 2021;27(3):212—229.
3. Sivori S, Vacca P, Del Zotto G, Munari E, Mingari MC, Moretta L. Human NK cells: surface receptors, inhibitory checkpoints, and translational applications. *Cell Mol Immunol*. 2019;16(5):430—441.
4. Crinier A, Narni-Mancinelli E, Ugolini S, Vivier E. SnapShot: natural killer cells. *Cell*. 2020;180(6):1280—1280.e1.
5. Liu S, Galat V, Galat Y, Lee YKA, Wainwright D, Wu J. NK cell-based cancer immunotherapy: from basic biology to clinical development. *J Hematol Oncol*. 2021;14(1):7.
6. Cichocki F, van der Stegen SJC, Miller JS. Engineered and banked iPSCs for advanced NK- and T-cell immunotherapies. *Blood*. 2023;141(8):846—855.
7. Chen LL, Kim VN. Small and long non-coding RNAs: past, present, and future. *Cell*. 2024;187(23):6451—6485.
8. Rinn JL, Chang HY. Genome regulation by long noncoding RNAs. *Annu Rev Biochem*. 2012;81:145—166.
9. Zhao L, Wang J, Li Y, et al. NONCODEV6: an updated database dedicated to long non-coding RNA annotation in both animals and plants. *Nucleic Acids Res*. 2021;49(D1):D165—D171.
10. Uszczynska-Ratajczak B, Lagarde J, Frankish A, Guigó R, Johnson R. Towards a complete map of the human long non-coding RNA transcriptome. *Nat Rev Genet*. 2018;19(9):535—548.
11. Fang S, Zhang L, Guo J, et al. NONCODEV5: a comprehensive annotation database for long non-coding RNAs. *Nucleic Acids Res*. 2018;46(D1):D308—D314.
12. Bridges MC, Daulagala AC, Kourtidis A. LNCcation: lncRNA localization and function. *J Cell Biol*. 2021;220(2):e202009045.
13. Herman AB, Tsitsipatis D, Gorospe M. Integrated lncRNA function upon genomic and epigenomic regulation. *Mol Cell*. 2022;82(12):2252—2266.
14. Statello L, Guo CJ, Chen LL, Huarte M. Gene regulation by long non-coding RNAs and its biological functions. *Nat Rev Mol Cell Biol*. 2021;22(2):96—118.
15. Zhang D, Zhang M, Zhang L, et al. Long non-coding RNAs and immune cells: unveiling the role in viral infections. *Biomed Pharmacother*. 2024;170:115978.
16. Mace EM, Gunesch JT, Dixon A, Orange JS. Human NK cell development requires CD56-mediated motility and formation of the developmental synapse. *Nat Commun*. 2016;7:12171.
17. Wu SY, Fu T, Jiang YZ, Shao ZM. Natural killer cells in cancer biology and therapy. *Mol Cancer*. 2020;19(1):120.
18. Sigdel KR, Cheng A, Wang Y, Duan L, Zhang Y. The emerging functions of long noncoding RNA in immune cells: autoimmune diseases. *J Immunol Res*. 2015;2015:848790.
19. Hur K, Kim SH, Kim JM. Potential implications of long non-coding RNAs in autoimmune diseases. *Immune Netw*. 2019;19(1):e4.
20. Ahmad I, Valverde A, Ahmad F, Naqvi AR. Long noncoding RNA in myeloid and lymphoid cell differentiation, polarization and function. *Cells*. 2020;9(2):269.
21. Khan S, Masood M, Gaur H, Ahmad S, Syed MA. Long non-coding RNA: an immune cells perspective. *Life Sci*. 2021;271:119152.

22. Luaibi AR, Al-Saffar M, Jalil AT, et al. Long non-coding RNAs: the modulators of innate and adaptive immune cells. *Pathol Res Pract*. 2023;241:154295.
23. Gao F, He S, Jin A. MiRNAs and lncRNAs in NK cell biology and NK/T-cell lymphoma. *Genes Dis*. 2020;8(5):590—602.
24. Yang C, Shen C, Feng T, Li H. Noncoding RNA in NK cells. *J Leukoc Biol*. 2019;105(1):63—71.
25. Ghafouri-Fard S, Askari A, Zangooie A, Shoorei H, Pourmoshtagh H, Taheri M. Non-coding RNA profile for natural killer cell activity. *Mol Cell Probes*. 2023;72:101935.
26. Höglund P, Brodin P. Current perspectives of natural killer cell education by MHC class I molecules. *Nat Rev Immunol*. 2010;10(10):724—734.
27. Björkström NK, Riese P, Heuts F, et al. Expression patterns of NKG2A, KIR, and CD57 define a process of CD56dim NK-cell differentiation uncoupled from NK-cell education. *Blood*. 2010;116(19):3853—3864.
28. Wright PW, Huehn A, Cichocki F, et al. Identification of a KIR antisense lncRNA expressed by progenitor cells. *Gene Immun*. 2013;14(7):427—433.
29. 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—72558.
30. Laskowski TJ, Biederstädt A, Rezvani K. Natural killer cells in antitumour adoptive cell immunotherapy. *Nat Rev Cancer*. 2022;22(10):557—575.
31. Bryceson YT, March ME, Ljunggren HG, Long EO. Activation, coactivation, and costimulation of resting human natural killer cells. *Immunol Rev*. 2006;214:73—91.
32. Möbus L, Rodriguez E, Harder I, et al. Elevated NK-cell transcriptional signature and dysbalance of resting and activated NK cells in atopic dermatitis. *J Allergy Clin Immunol*. 2021;147(5):1959—1965.e2.
33. Liu H, Liu X, Lu Y. The roles of LncRNA CARMN in cancers: biomarker potential, therapeutic targeting, and immune response. *Discov Oncol*. 2024;15(1):776.
34. Ma X, Yang B, Yang Y, et al. Identification of N^7-methylguanosine-related lncRNA signature as a potential predictive biomarker for colon adenocarcinoma. *Front Genet*. 2022;13:946845.
35. Lin Y, Xiong G, Xia X, et al. Authentication and validation of key genes in the treatment of atopic dermatitis with Runfuzhiyang powder: combined RNA-seq, bioinformatics analysis, and experimental research. *Front Genet*. 2024;15:1335093.
36. Xue MQ, Wang YL, Wang JC, Wang XD, Wang XJ, Zhang YQ. Comprehensive analysis of the PD-L1 and immune infiltrates of N6-methyladenosine related long non-coding RNAs in bladder cancer. *Sci Rep*. 2022;12(1):10082.
37. Wang X, Pan Y, Ou Y, Duan T, Zou Y, Zhou X. Construction and validation of immune-related LncRNAs classifier to predict prognosis and immunotherapy response in laryngeal squamous cell carcinoma. *World J Surg Oncol*. 2022;20(1):164.
38. Vivier E, Tomasello E, Baratin M, Walzer T, Ugolini S. Functions of natural killer cells. *Nat Immunol*. 2008;9(5):503—510.
39. Guo Y, Xie Y, Luo Y. The role of long non-coding RNAs in the tumor immune microenvironment. *Front Immunol*. 2022;13:851004.
40. Afra F, Mahboobipour AA, Salehi Farid A, Ala M. Recent progress in the immunotherapy of hepatocellular carcinoma: non-coding RNA-based immunotherapy may improve the outcome. *Biomed Pharmacother*. 2023;165:115104.
41. Cheng Q, Chen M, Chen X, et al. Novel long non-coding RNA expression profile of peripheral blood mononuclear cells reveals potential biomarkers and regulatory mechanisms in systemic lupus erythematosus. *Front Cell Dev Biol*. 2021;9:639321.
42. Yang X, Kuang S, Wang L, Wei Y. MHC class I chain-related A: polymorphism, regulation and therapeutic value in cancer. *Biomed Pharmacother*. 2018;103:111—117.
43. Maruyama SR, Fuzo CA, Oliveira AER, et al. Insight into the long noncoding RNA and mRNA coexpression profile in the human blood transcriptome upon *Leishmania infantum* infection. *Front Immunol*. 2022;13:784463.
44. Zhu X, Du M, Gu H, et al. Integrated analysis of lncRNA and mRNA expression profiles in patients with unexplained recurrent spontaneous abortion. *Am J Reprod Immunol*. 2023;89(6):e13691.
45. Chattopadhyay P, Mehta P, Soni J, Tardalkar K, Joshi M, Pandey R. Cell-specific housekeeping role of lncRNAs in COVID-19-infected and recovered patients. *NAR Genom Bioinform*. 2024;6(1):lqae023.
46. Lin H, Xie Y, Kong Y, Yang L, Li M. Identification of two molecular subtypes of hepatocellular carcinoma based on dysregulated immune LncRNAs. *Front Mol Biosci*. 2021;8:625858.
47. He Y, Zhou Y, Wang H, et al. Identifying potential biomarkers in hepatitis B virus infection and its response to the antiviral therapy by integrated bioinformatic analysis. *J Cell Mol Med*. 2021;25(14):6558—6572.
48. Vivier E, Rebuffet L, Narni-Mancinelli E, Cornen S, Igarashi RY, Fantin VR. Natural killer cell therapies. *Nature*. 2024;626(8000):727—736.
49. Stein N, Berhani O, Schmiedel D, et al. IFNG-AS1 enhances interferon gamma production in human natural killer cells. *iScience*. 2019;11:466—473.
50. Kotzur R, Stein N, Kahlon S, Berhani O, Isaacson B, Mandelboim O. Eradication of CD48-positive tumors by selectively enhanced YTS cells harnessing the lncRNA NeST. *iScience*. 2023;26(8):107284.
51. Rožmanić C, Lisnić B, Pribanić Matešić M, et al. Perinatal murine cytomegalovirus infection reshapes the transcriptional profile and functionality of NK cells. *Nat Commun*. 2023;14(1):6412.
52. Li H, Hou Y, Zhang S, et al. CD49a regulates the function of human decidual natural killer cells. *Am J Reprod Immunol*. 2019;81(4):e13101.
53. Wei M, Lu L, Ma J, Luo Z, Tan X, Wang J. LINC00707 impairs the Natural Killer cell antitumour activity in hepatocellular carcinoma through decreasing YTHDF2 stability. *J Cell Mol Med*. 2024;28(5):e18106.
54. Li GJ, Ding H, Miao D. Long-noncoding RNA HOTAIR inhibits immunologic rejection of mouse leukemia cells through activating the Wnt/β-catenin signaling pathway in a mouse model of leukemia. *J Cell Physiol*. 2019;234(7):10386—10396.
55. Huang Y, Luo Y, Ou W, et al. Exosomal lncRNA SNHG10 derived from colorectal cancer cells suppresses natural killer cell cytotoxicity by upregulating INHBC. *Cancer Cell Int*. 2021;21(1):528.
56. Venkatesh J, Wasson MD, Brown JM, Fernando W, Marcato P. LncRNA-miRNA axes in breast cancer: novel points of interaction for strategic attack. *Cancer Lett*. 2021;509:81—88.
57. Guo F, Yuan Y, Chen Z, et al. Downregulation of the long noncoding RNA MALAT1 in tenofovir-treated pregnant women with hepatitis B virus infection promotes immune recovery of natural killer cells *via* the has-miR-155-5p/HIF-1α axis. *Int Immunopharmacol*. 2022;107:108701.
58. 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.
59. Wei MF, Gu ZS, Zheng LL, Zhao MX, Wang XJ. Long non-coding RNA GAS5 promotes natural killer cell cytotoxicity against gastric cancer by regulating miR-18a. *Neoplasma*. 2020;67(5):1085—1093.
60. Li S, Zhu A, Ren K, Li S, Chen L. IFNβ-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.
61. Qin X, Zhou M, Lv H, et al. Long noncoding RNA LINC00657 inhibits cervical cancer development by sponging miR-20a-5p and targeting RUNX3. *Cancer Lett*. 2021;498:130—141.
62. Mekky RY, Ragab MF, Manie T, Attia AA, Youness RA. MALAT-1: immunomodulatory lncRNA hampering the innate and the adaptive immune arms in triple negative breast cancer. *Transl Oncol*. 2023;31:101653.
63. Zhong R, Tian J, Fu M, et al. LINC01149 variant modulates *MICA* expression that facilitates hepatitis B virus spontaneous recovery but increases hepatocellular carcinoma risk. *Oncogene*. 2020;39(9):1944—1956.
64. Abdelhamid AM, Zeinelabdeen Y, Manie T, Khallaf E, Assal RA, Youness RA. miR-17-5p/STAT3/H19: a novel regulatory axis tuning ULBP2 expression in young breast cancer patients. *Pathol Res Pract*. 2024;263:155638.
65. Tang T, Zeng F. NFIB-mediated lncRNA PVT1 aggravates laryngeal squamous cell carcinoma progression *via* the miR-1301-3p/MBNL1 axis. *J Immunol Res*. 2021;2021:8675123.
66. Chen JX, Xu X, Zhang S. Silence of long noncoding RNA NEAT1 exerts suppressive effects on immunity during sepsis by promoting microRNA-125-dependent MCEMP1 downregulation. *IUBMB Life*. 2019;71(7):956—968.
67. Kodama M, Oshikawa K, Shimizu H, et al. A shift in glutamine nitrogen metabolism contributes to the malignant progression of cancer. *Nat Commun*. 2020;11(1):1320.
68. Fang H, Dai W, Gu R, et al. myCAF-derived exosomal PWAR6 accelerates CRC liver metastasis *via* altering glutamine availability and NK cell function in the tumor microenvironment. *J Hematol Oncol*. 2024;17(1):126.
69. Poznanski SM, Singh K, Ritchie TM, et al. Metabolic flexibility determines human NK cell functional fate in the tumor microenvironment. *Cell Metab*. 2021;33(6):1205—1220.e5.
70. Chai W, Wang X, Lu Z, et al. Elevated exosome-transferrable lncRNA EPB41L4A-AS1 in CD56^{bright} NK cells is responsible for the impaired NK function in neuroblastoma patients by suppressing cell glycolysis. *Clin Immunol*. 2023;250:109322.
71. Dikic I, Schulman BA. An expanded lexicon for the ubiquitin code. *Nat Rev Mol Cell Biol*. 2023;24(4):273—287.
72. Niu Q, Li Z, Jiang H, Hu B. Linc-ROR inhibits NK cell-killing activity by promoting RXRA ubiquitination and reducing MICB expression in gastric cancer patients. *J Cell Biochem*. 2024;125(2):e30516.
73. Zhang KJ, Tan XL, Guo L. LncRNA TYMSOS facilitates breast cancer metastasis and immune escape through downregulating ULBP3. *iScience*. 2023;26(9):107556.
74. Niu C, Li M, Chen Y, et al. LncRNA NCAL1 potentiates natural killer cell cytotoxicity through the Gab2-PI3K-AKT pathway. *Front Immunol*. 2022;13:970195.
75. Han B, He J, Chen Q, et al. ELFN1-AS1 promotes GDF15-mediated immune escape of colorectal cancer from NK cells by facilitating GCN5 and SND1 association. *Discov Oncol*. 2023;14(1):56.
76. Bejarano L, Jordão MJC, Joyce JA. Therapeutic targeting of the tumor microenvironment. *Cancer Discov*. 2021;11(4):933—959.
77. Zhou Z, Lv Y, Zuo A, et al. Interactions between microbiota and innate immunity in tumor microenvironment: novel insights into cancer progression and immunotherapy. *hLife*. 2025;3(10):462—493.
78. Verma SK, Khare R, Singh D. Current perspectives on neuroendocrine tumors. *hLife*. 2024;2(11):563—575.
79. Khosravi GR, Mostafavi S, Bastan S, Ebrahimi N, Gharibvand RS, Eskandari N. Immunologic tumor microenvironment modulators for turning cold tumors hot. *Cancer Commun*. 2024;44(5):521—553.
80. Wang L, Chen Z, Liu G, Pan Y. Functional crosstalk and regulation of natural killer cells in tumor microenvironment: significance and potential therapeutic strategies. *Genes Dis*. 2022;10(3):990—1004.
81. Wang Y, Yu G, Liu Y, et al. Hypoxia-induced PTTG3P contributes to colorectal cancer glycolysis and M2 phenotype of macrophage. *Biosci Rep*. 2021;41(7):BSR20210764.
82. Chen G, Yan J. Dysregulation of SNHG16(lncRNA)-Hsa-Let-7b-5p(miRNA)-TUBB4A (mRNA) pathway fuels progression of skin cutaneous melanoma. *Curr Protein Pept Sci*. 2022;23(11):791—809.
83. Wu H, Liu N, He A, et al. LMNTD2-AS1 regulates immune cell infiltration and promotes prostate cancer progression by targeting FUS to regulate NRF2 signal pathway. *Am J Cancer Res*. 2023;13(8):3384—3400.
84. Zhang H, Yuan J, Xiang Y, Liu Y. Comprehensive analysis of NPSR1-AS1 as a novel diagnostic and prognostic biomarker involved in immune infiltrates in lung adenocarcinoma. *J Oncol*. 2022;2022:2099327.
85. Li D, Liu X, Jiang N, et al. Interfering with ITGB1-DT expression delays cancer progression and promotes cell sensitivity of NSCLC to cisplatin by inhibiting the MAPK/ERK pathway. *Am J Cancer Res*. 2022;12(7):2966—2988.
86. Samadi P, Shahnazari M, Shekari A, Maghool F, Jalali A. A pan-cancer analysis indicates long noncoding RNA HAND2-AS1 as a potential prognostic, immunomodulatory and therapeutic biomarker in various cancers including colorectal adenocarcinoma. *Cancer Cell Int*. 2023;23(1):307.
87. Lu Y, Chen S, Wang Q, Zhang J, Pei X. PRR7-AS1 correlates with immune cell infiltration and is a diagnostic and prognostic marker for hepatocellular carcinoma. *J Oncol*. 2022;2022:1939368.
88. Fang Y, Huang S, Han L, Wang S, Xiong B. Comprehensive analysis of peritoneal metastasis sequencing data to identify LINC00924 as a prognostic biomarker in gastric cancer. *Cancer Manag Res*. 2021;13:5599—5611.
89. Li W, Hong G, Lai X. INKA2-AS1 is a potential promising prognostic-related biomarker and correlated with immune infiltrates in hepatocellular carcinoma. *Mediat Inflamm*. 2023;2023:7057236.
90. Bai Z, Tian N, Ding Z, et al. Knockdown of long noncoding RNA AL161431.1 inhibits malignant progression of cholangiocarcinoma. *Aging (Albany NY)*. 2024;16(15):11501—11512.
91. Chen R, An J, Wang Y, Yang L, Lin Q, Wang Y. LINC01589 serves as a potential tumor-suppressor and immune-related biomarker in endometrial cancer: a review. *Medicine (Baltimore)*. 2023;102(15):e33536.
92. Yang W, Ge F, Lu S, et al. LncRNA MSC-AS1 is a diagnostic biomarker and predicts poor prognosis in patients with gastric cancer by integrated bioinformatics analysis. *Front Med*. 2021;8:795427.
93. Ye T, Feng J, Cui M, et al. LncRNA MIAT services as a noninvasive biomarker for diagnosis and correlated with immune infiltrates in breast cancer. *Int J Womens Health*. 2021;13:991—1004.
94. Wang X, Wang Y, Sun F, et al. Novel LncRNA ZFHX4-AS1 as a potential prognostic biomarker that affects the immune microenvironment in ovarian cancer. *Front Oncol*. 2022;12:945518.
95. Li L, Peng Q, Gong M, Ling L, Xu Y, Liu Q. Using lncRNA sequencing to reveal a putative lncRNA-mRNA correlation network and the potential role of PCBP1-AS1 in the pathogenesis of cervical cancer. *Front Oncol*. 2021;11:634732.
96. Nejadi Orang F, Abdoli Shadbad M. Competing endogenous RNA networks and ferroptosis in cancer: novel therapeutic targets. *Cell Death Dis*. 2024;15(5):357.
97. Wu F, Zhang X, Zhang S, et al. Construction of an immune-related lncRNA-miRNA-mRNA regulatory network in radiation-

induced esophageal injury in rats. *Int Immunopharmacol*. 2023;122:110606.
98. Chen W, Chen F, Gong M, et al. Comprehensive analysis of lncRNA-mediated *CeRNA* networkfor hepatocellular carcinoma. *Front Oncol*. 2022;12:1042928.
99. Li X, Wang K, Liu J, Li Y. A comprehensive analysis to reveal the underlying molecular mechanisms of natural killer cell in thyroid carcinoma based on single-cell RNA sequencing data. *Discov Oncol*. 2025;16(1):44.
100. Wang Z, Qu S, Zhu J, Chen F, Ma L. Comprehensive analysis of lncRNA-associated competing endogenous RNA network and immune infiltration in idiopathic pulmonary fibrosis. *J Thorac Dis*. 2020;12(5):1856—1865.
101. Lan F, Zhao J, Liang D, Mo C, Shi W. Comprehensive analysis of cuproptosis-related *CeRNA* network and immune infiltration in diabetic kidney disease. *Heliyon*. 2024;10(16):e35700.
102. Hu L, Liu S, Peng Y, et al. m^6A RNA modifications are measured at single-base resolution across the mammalian transcriptome. *Nat Biotechnol*. 2022;40(8):1210—1219.
103. Pomaville MM, He C. Advances in targeting RNA modifications for anticancer therapy. *Trends Cancer*. 2023;9(7):528—542.
104. Huang J, Song J, Li X, et al. Analysis and prognostic significance of tumour immune infiltrates and immune microenvironment of m6A-related lncRNAs in patients with gastric cancer. *BMC Med Genomics*. 2022;15(1):164.
105. Xu S, Chen W, Wang Y, et al. N6-methyladenosine-related lncRNAs identified as potential biomarkers for predicting the overall survival of Asian gastric cancer patients. *BMC Cancer*. 2022;22(1):721.
106. Li Z, Li Y, Zhong W, Huang P. m6A-related lncRNA to develop prognostic signature and predict the immune landscape in bladder cancer. *J Oncol*. 2021;2021:7488188.
107. Huang Z, Wang G, Wu Y, et al. N6-methyladenosine-related lncRNAs in combination with computational histopathology and radiomics predict the prognosis of bladder cancer. *Transl Oncol*. 2023;27:101581.
108. Hu Y, Chen Y. N6-methylandenosine-related lncRNAs play an important role in the prognosis and immune microenvironment of pancreatic ductal adenocarcinoma. *Sci Rep*. 2021;11(1):17844.
109. Xu R, Zhang W. Prognostic value and immune landscapes of m5C-related lncRNAs in lung squamous cell carcinoma. *Front Genet*. 2022;13:960229.
110. Wang E, Li Y, Ming R, et al. The prognostic value and immune landscapes of a $m^6A/m^5C/m^1A$-Related LncRNAs signature in head and neck squamous cell carcinoma. *Front Cell Dev Biol*. 2021;9:718974.
111. Tsvetkov P, Coy S, Petrova B, et al. Copper induces cell death by targeting lipoylated TCA cycle proteins. *Science*. 2022;375(6586):1254—1261.
112. Cui K, Wang K, Huang Z. Ferroptosis and the tumor microenvironment. *J Exp Clin Cancer Res*. 2024;43(1):315.
113. Wang H, Wang T, Yan S, et al. Crosstalk of pyroptosis and cytokine in the tumor microenvironment: from mechanisms to clinical implication. *Mol Cancer*. 2024;23(1):268.
114. Huang EM, Ma N, Ma T, et al. Cuproptosis-related long noncoding RNAs model that effectively predicts prognosis in hepatocellular carcinoma. *World J Gastrointest Oncol*. 2022;14(10):1981—2003.
115. Wang Y, Liu K, Shen K, et al. A novel risk model construction and immune landscape analysis of gastric cancer based on cuproptosis-related long noncoding RNAs. *Front Oncol*. 2022;12:1015235.
116. Song J, Xie D, Wei X, Liu B, Yao F, Ye W. A cuproptosis-related lncRNAs signature predicts prognosis and reveals pivotal interactions between immune cells in colon cancer. *Heliyon*. 2024;10(14):e34586.
117. Li YJ, Li HY, Zhang Q, Wei SL. The prognostic value and immune landscape of a cuproptosis-related lncRNA signature in head and neck squamous cell carcinoma. *Front Genet*. 2022;13:942785.
118. Guo J, Zhou M, Li J, et al. The prognosis and immunotherapy prediction model of ovarian serous cystadenocarcinoma patient was constructed based on cuproptosis-related LncRNA. *Tohoku J Exp Med*. 2024;262(2):63—74.
119. Huang L, Zhang J, Gong F, et al. Identification and validation of ferroptosis-related lncRNA signatures as a novel prognostic model for glioma. *Front Genet*. 2022;13:927142.
120. Tanzhu G, Li N, Li Z, Zhou R, Shen L. Molecular subtypes and prognostic signature of pyroptosis-related lncRNAs in glioma patients. *Front Oncol*. 2022;12:779168.
121. Liu H, Zhang M, Zhang T, et al. Identification of a ferroptosis-related lncRNA signature with prognosis for Wilms tumor. *Transl Pediatr*. 2021;10(10):2418—2431.
122. Zhu L, Zhang XP, Xu S, et al. Identification of a $CD4^+$ conventional T cells-related lncRNAs signature associated with hepatocellular carcinoma prognosis, therapy, and tumor microenvironment. *Front Immunol*. 2023;13:1111246.
123. Huang F, Zhang C, Yang W, et al. Identification of a DNA damage repair-related LncRNA signature for predicting the prognosis and immunotherapy response of hepatocellular carcinoma. *BMC Genom*. 2024;25(1):155.
124. Yuan M, Wang Y, Sun Q, et al. Identification of a nine immune-related lncRNA signature as a novel diagnostic biomarker for hepatocellular carcinoma. *Biomed Res Int*. 2021;2021:9798231.
125. Sun X, Li L, Yang X, et al. Identification of a novel prognostic cuproptosis-associated LncRNA signature for predicting prognosis and immunotherapy response in patients with esophageal cancer. *Heliyon*. 2024;10(9):e30277.
126. Zhang M, Sun Q, Han Z, et al. Construction of a novel disulfidptosis-related lncRNAs signature for prognosis prediction and anti-tumor immunity in laryngeal squamous cell carcinoma. *Heliyon*. 2024;10(10):e30877.
127. Yang Y, Feng M, Bai L, et al. The effects of autophagy-related genes and lncRNAs in therapy and prognosis of colorectal cancer. *Front Oncol*. 2021;11:582040.
128. Zhang B, Cheng Y, Li R, Lian M, Guo S, Liang C. Development of a novel angiogenesis-related lncRNA signature to predict the prognosis and immunotherapy of glioblastoma multiforme. *Transl Cancer Res*. 2023;12(1):13—30.
129. Zhang K, Lu S, Jiang M, et al. Development of a risk model and genotyping patterns based on disulfidptosis-related lncRNAs to predict prognosis and immune landscape in osteosarcoma. *Front Biosci (Landmark Ed)*. 2024;29(5):193.
130. Xu X, Zou R, Liu X, Liu J, Su Q. Epithelial-mesenchymal transition-related genes in coronary artery disease. *Open Med*. 2022;17(1):781—800.
131. Qing L, Gu P, Liu M, et al. Extracellular matrix-related six-lncRNA signature as a novel prognostic biomarker for bladder cancer. *Onco Targets Ther*. 2020;13:12521—12538.
132. Mu L, Ding K, Tu R, Yang W. Identification of 4 immune cells and a 5-lncRNA risk signature with prognosis for early-stage lung adenocarcinoma. *J Transl Med*. 2021;19(1):127.
133. Liang P, Li J, Chen J, et al. Immunoprognostic model of lung adenocarcinoma and screening of sensitive drugs. *Sci Rep*. 2022;12(1):7162.
134. Wang X, Cao K, Guo E, et al. Identification of immune-related LncRNA pairs for predicting prognosis and immunotherapeutic response in head and neck squamous cell carcinoma. *Front Immunol*. 2021;12:658631.
135. Li L, Xiao Z, He P, et al. Molecular subtyping based on TRP family and prognostic assessment for TRP-associated lncRNAs in pancreatic adenocarcinoma. *BMC Gastroenterol*. 2022;22(1):454.

136. Huang G, Cao H, Liu G, Chen J. Role of androgen receptor signaling pathway-related lncRNAs in the prognosis and immune infiltration of breast cancer. *Sci Rep*. 2022;12(1):20631.
137. Esmeray Sönmez E, Hatipoğlu T, Kurşun D, et al. Whole transcriptome sequencing reveals cancer-related, prognostically significant transcripts and tumor-infiltrating immunocytes in mantle cell lymphoma. *Cells*. 2022;11(21):3394.
138. Li J, Xia C, Li Y, Liu H, Gong C, Liang D. Effects of NK cell-related lncRNA on the immune microenvironment and molecular subtyping for pancreatic ductal adenocarcinoma. *Front Immunol*. 2025;15:1514259.
139. Zhang Q, Wang Z, Yu X, et al. Immune subtypes based on immune-related lncRNA: differential prognostic mechanism of pancreatic cancer. *Front Cell Dev Biol*. 2021;9:698296.
140. Shao T, Xie Y, Shi J, et al. Surveying lncRNA-lncRNA co-operations reveals dominant effect on tumor immunity cross cancers. *Commun Biol*. 2022;5(1):1324.
141. Ahadi A. Functional roles of lncRNAs in the pathogenesis and progression of cancer. *Genes Dis*. 2020;8(4):424—437.
142. Lemos AEG, Matos ADR, Ferreira LB, Gimba ERP. The long non-coding RNA *PCA3*: an update of its functions and clinical applications as a biomarker in prostate cancer. *Oncotarget*. 2019;10(61):6589—6603.
143. Halachmi S, Leibovitch I, Zisman A, et al. Phase II trial of BC-819 intravesical gene therapy in combination with BCG in patients with non-muscle invasive bladder cancer (NMIBC). *J Clin Oncol*. 2018;36(6_suppl):499.
144. Neveu MC, Ravenko A, Kim TW, et al. Abstract 450: preclinical development of FTX-001: first in class inhibitor of the long non-coding RNA MALAT1. *Cancer Res*. 2023;83(7_Supplement):450.
145. Raju GSR, Pavitra E, Bandaru SS, et al. HOTAIR: a potential metastatic, drug-resistant and prognostic regulator of breast cancer. *Mol Cancer*. 2023;22(1):65.
146. Toker J, Iorgulescu JB, Ling AL, et al. Clinical importance of the lncRNA NEAT1 in cancer patients treated with immune checkpoint inhibitors. *Clin Cancer Res*. 2023;29(12):2226—2238.