



REVIEW ARTICLE

MiRNAs and lncRNAs in NK cell biology and NK/T-cell lymphoma

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Abstract The important role of lncRNAs and miRNAs in directing immune responses has become increasingly clear. Recent evidence confirms that miRNAs and lncRNAs are involved in NK cell biology and diseases through RNA–protein, RNA–RNA, or RNA–DNA interactions. In this view, we summarize the contribution of miRNAs and lncRNAs to NK cell lineage development, activation and function, highlight the biological significance of functional miRNAs or lncRNAs in NKTL and discuss the potential of these miRNAs and lncRNAs as innovative biomarkers/targets for NKTL early diagnosis, target treatment and prognostic evaluations.

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Introduction

Non-coding RNAs are an important family in human genome and are broadly classified as lncRNAs, miRNAs, snoRNAs, snRNAs and short non-coding RNAs according to the length of the nucleotide. According to the latest GENCODE release (version 33) or (version M24) (<http://www.genencodegenes.org>), it indicates the abundance of lncRNA and miRNA in human or mouse. (Fig. 1). For miRNAs, they are 23 nucleotides shorter, are best characterized to introduce mRNA degradation or block mRNA translation through

deadenylation and decapping methods. Vasudevan et al has confirmed that some miRNAs increase protein expression via binding to the 5'UTR, but it remains unclear whether this is widely applicable.¹ The molecular mechanism of miRNAs are clearer than before and there are some classified reviews of miRNAs.^{2–4} For lncRNAs, they are longer than 200 nucleotides and another important non-coding member. Compared with mRNA, lncRNAs are usually shorter in length, contain fewer exons and are less conservative—only about 12% of lncRNAs can be found in other organisms, other than humans.⁵ Meanwhile, lncRNAs have precise tissue specificity and developmental stage-specific manner.^{5,6} According to their genomic localization with respect to the neighboring protein coding gene, lncRNAs are classified into five types: intronic lncRNA; antisense lncRNA; long intergenic non-coding RNA (lincRNA); sense lncRNA; bidirectional lncRNA. In fact, some lncRNAs do not belong to any of the above classifications. They often have

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two or more characteristics, which makes them more difficult for the classification and identification of lncRNAs. It has been found that lncRNAs mediate gene activation through multiple mechanisms: in the nucleus, lncRNAs directly regulate gene expression via cis-/trans-action or as protein bait for indirect regulation; in the cytoplasm, lncRNAs regulate gene expression by affecting mRNA stability and translation process or involvement in miRNA regulation as competitive endogenous RNA or binding with transcription factors to affect gene function.^{7–9} At present, we know more about how miRNAs and lncRNAs work and further confirm that various functional miRNAs and lncRNA play key roles in the innate or adaptive immune system.^{5,7} However, various secrets in lncRNAs are still unclear, such as the number and species of functional lncRNAs, the function of immune-related lncRNAs *in vivo*, the role of lncRNAs in different kinds of immune cells, like T, B, NK cells and so on.

NK cells are an important kind of lymphocyte to defense against bacteria, viruses and tumors in human body. There are quite more activating and inhibitory receptors expression on NK cell surface. The balance of these two types of receptors regulates the activation of NK cells. Besides these, there are also some efficient molecules, such as granzyme B, perforin, IFN- γ , TNF- α in NK cells, which cause target cell lysis and death.^{10,11} For example, following activation by bacterial lipopolysaccharide (LPS), NK cells inhibit pathogen infection via the cytokines secretion to kill the cells infected with pathogen. Meanwhile, NK cells also secrete soluble factors such as IL-3, GM-CSF and M-CSF to recruit neutrophils, macrophages and dendritic cells to activate the adaptive immune response.^{12,13} Therefore, NK cells play an critical role in innate immunity or acquired immunity.

For NK cells, recent studies have focused on the function of receptors, cytotoxic molecules, transcriptional factors

involved in immune response. With the study of miRNA or lncRNAs, there is accumulating evidence shows that miRNA or lncRNAs are involved in various innate or adaptive immune response.^{14–17} For example, lnc-DC controls the development and differentiation of DCs by directly binding to STAT3 in the cytoplasm¹⁸; miRNA-17-92 cluster directly mediate the differentiation of the naïve CD4⁺ T cells into Th1, Th2, Th17, Treg and Tfh.¹⁹ In addition, increasing number of publications showed the critical effect of non-coding RNAs in NK cells, especially lncRNAs and miRNAs. Though the role of miRNAs in NK cells have been recently reviewed, new advance on the relationship between NK and miRNAs or lncRNA are rarely been summarized and reported. Here, we summarize NK cell related miRNAs and lncRNAs from the latest researches and discuss their critical roles in NK cell development, activation and function, with a focus on abnormal miRNAs and lncRNAs in NKTL. As our knowledge of the molecular programs, including miRNAs and lncRNAs, that regulate NK cells increases, this will lead to identification of novel molecules and pathways that may be manipulated to enhance or attenuate NK cell function and NKTL early diagnosis, target treatment and prognostic evaluations.

Regulation of lncRNAs and miRNAs in the development of NK cell

Murine & human NK cell development

In the last decades, there has been two major advanced researches in NK cells, including the diversity of NK cell receptors and the diversity of NK cell function. Both the activity and function of NK cells are close to the development and differentiation of NK cells. The maturation of murine NK cells is a continuous process; according to their

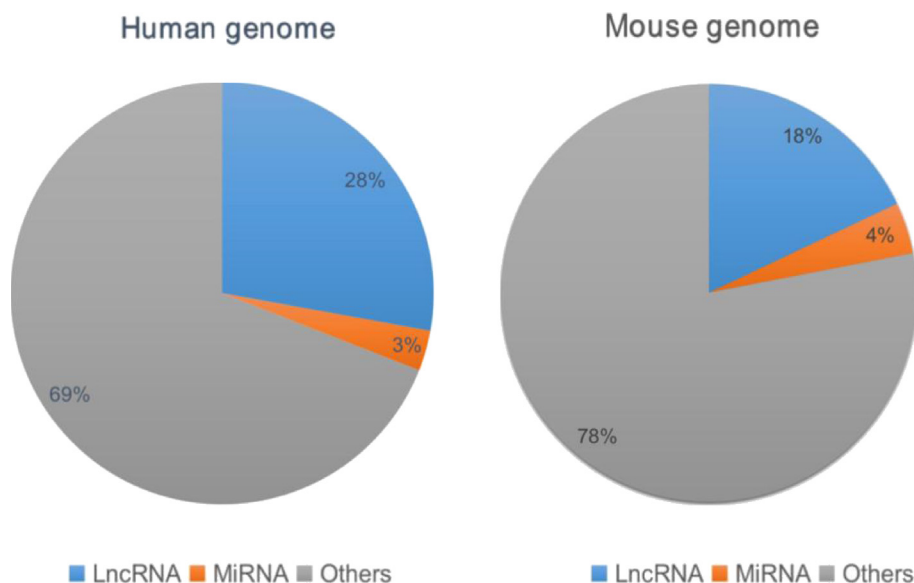


Figure 1 Abundance of lncRNA and miRNAs genes. The data respectively represents the latest GENCODE release (Human genome version 33 vs. Mouse genome version 24): the number of lncRNA gene:16,892(human) vs. 9959(mouse); the number of miRNA gene:1881 (human) vs. 2202 (mouse). (<http://www.genencodegenes.org>).

phenotypic and functional characteristics, NK cells into two different development stages, in first stage: hematopoietic stem cells (HSC) differentiated into common lymphoid precursors (CLP), and then differentiated into the earliest precursor of NK cells, namely pre-pro NK cells. During the process, some key transcription factor, such as PU.1,^{20,21} ETS-4²² are involved in the development of NK cells by regulating the generation of pre-pro NK cells. And next, pre-pro NK cells up-regulate the expression of CD122 (IL-2R β) and further develop into NK cell precursors (NKP), which is mainly regulated by transcription factor E4BP4.²³ In second stage: accepting IL-15 stimulus NKPs differentiate to immature NK cells (iNK), which relies on the expression of transcription factor TOX,²⁴ T-bet.²⁵ And then iNKs receive MHC-I domestication signals and finally develop into mature NK cells (mNK), this needs various transcription factor, such as Id2,²⁶ Blimp-1,^{27,28} Eomes,²⁹ Aiolos,³⁰ Rfx7.³¹ Generally, the traditional development of NK cells is quite clear as introduced above. However, the emergence of innate lymphoid cells (ILC) presents a new challenge to the definition of traditional NK cells and their precursors. The new study suggests that CLPs will further differentiate into the common ILC precursors (CILP). And CILPs further develops into the common helper-like ILC precursors (CHILP) and NKPs.³² Since then, the relationship between pre-pro NK cells and CILPs becomes more complicated, and that between ILC and traditional NK cell development intermediates, which need to be confirmed and differentiated by further study. (Fig. 2A).

However, the developmental path of murine NK cells does not fully explain the development of human NK cells. Human NK cells have been reported to mature in the BM and secondary lymphoid organs such as lymph nodes, spleen.³³ HSCs firstly transit into CD45RA⁺ lymphoid-primed multipotential progenitor (LMPP).³⁴ By expressing CD38,³⁵ CD7,³⁶ CD10³⁷ and IL-7R α ,³⁸ LMPPs next differentiate into CLPs with potential to make lineage commitments into Pro-B, Pre-T and NKPs. Expression of CD122 further marks the irreversible fate decision of NKPs into iNKs. The appearance of CD56 (NCAM) indicates a final transition of iNKs into mNK. According to the different expression densities of CD56, human NK cells are divided into two sub-populations: CD56^{bright} NK cells and CD56^{dim} NK cells. CD56^{bright} NK cells are considered less mature and CD56^{dim} NK cells probably differentiation from CD56^{bright} NK cells.³⁹ Distinct stages through which human NK cells develop are less understood compared to that of the murine counterparts. (Fig. 2B).

Regulation of lncRNAs in NK cells development

During hematopoietic stem cells (HSC) differentiated to ST-HSCs (Short Time Hematopoietic Stem Cells), Monnier P et al found that H19 lncRNA can regulate maternal imprinting during embryo formation by binding to MBD1 (methyl-CpG-binding-domain)1 protein and recruiting histone–lysine–methyltransferase complexes. The deficiency of H19 expression in male parent of hematopoietic system *in vivo* will decrease the number of LT-HSCs (Long Time Hematopoietic Stem Cells) and increase the number of ST-HSCs.⁴⁰ (Fig. 4A).

NK cells are classified to Group 1 innate lymphoid and play a “cytotoxic” role. Mowel WK et al firstly found in mouse that a nuclear lncRNA-Rroid that highly and specially expressed in ILC1s, but not ILC2s or CD4⁺ILC3s by gene browser tracks of ATAC sequence and RNA sequence from mouse indicated cell populations—CLP, ILC1, ILC2, CD4⁺ILC3.⁴¹ As mentioned earlier, lncRNAs regulate target gene expression by direct or indirect molecular mechanism. Similarly, Rroid can repress the expression of E-protein target genes, promote ILC1 lineage identity, sustain ILC1 homeostasis and function by indirectly promoting the activity of Id2, a key transcription factor for mNKs.⁴¹ This indicates lncRNAs are distinctive among different kinds of immune cells and act as crucial roles in the development and identity homeostasis of immune cells. (Fig. 4B).

NK cells are a group of innate immune cell which specifically express adhesion molecule CD56. In order to identify NK cell-specific lncRNAs, Zhang et al first broadly analyzed lncRNA expression in three different human NK cell samples. They detected various novel lncRNAs related to NK cell development, differentiation and function by analyzing human primary lymphocyte lncRNA expression profiles.⁴² Among these lncRNAs, they found the lnc-CD56 is positively correlated with the expression of adhesion molecule CD56. Interestingly, catRAPID predicted the interactions between lnc-CD56 and critical transcription factors of NK cell—TBX21, IRF2, IKZF2, ELF4, EMOES.⁴² Thus, additional studies of lnc-CD56 in human NK cells will be required to confirm its roles in NK cell biology.

In summary, lncRNAs are a key regulator of NK cell lineage. Presently, there are less functional lncRNAs which have been found in the development of NK cells. Mowel WK et al. provided a convenient and effective method for screening conditional lncRNAs nearby Id2 in NK cells.⁴¹ Besides, with the popularity of mass spectrometry flow cytometry and single-cell analysis techniques, single-cell tracking from HSC to mNK may simplify the study of NK cell development and help to discover more functional lncRNAs involved in NK development. Besides lncRNAs, miRNAs are crucial for NK cell development. There are more functional miRNAs in the development of NK cell which can be divided into positive or negative functional regulation.

Regulation of miRNAs in NK cells development

MiRNAs positively regulate the development of NK cells. The expression of miR-15/16 in NK cells is relatively high and promotes NK cell differentiation and development. Hence, there are a large number of immature NK cells in miR-15/16 knockout mice. When miR-15/16 and c-Myb gene are both knocked out, the number of immature NK cells gets less. It has seen that miR-15/16 promotes NK cell maturation by inhibiting c-Myb.⁴³ Similarly, for miR-150, some animal experiments proved that miR-150 could promote NK cell development through the inhibition of c-Myb.⁴⁴ MiR-181 can regulate CD34⁺ HSC to differentiate into mature NK cells. One paper shows that nemo-like kinase (NLK) mRNA is the miR-181 target gene. NLK blocks NK cell maturation by inhibiting Notch signaling pathway, while miR-181 can inhibit NLK gene expression. Thus miR-181 positively regulate NK cell development.⁴⁵

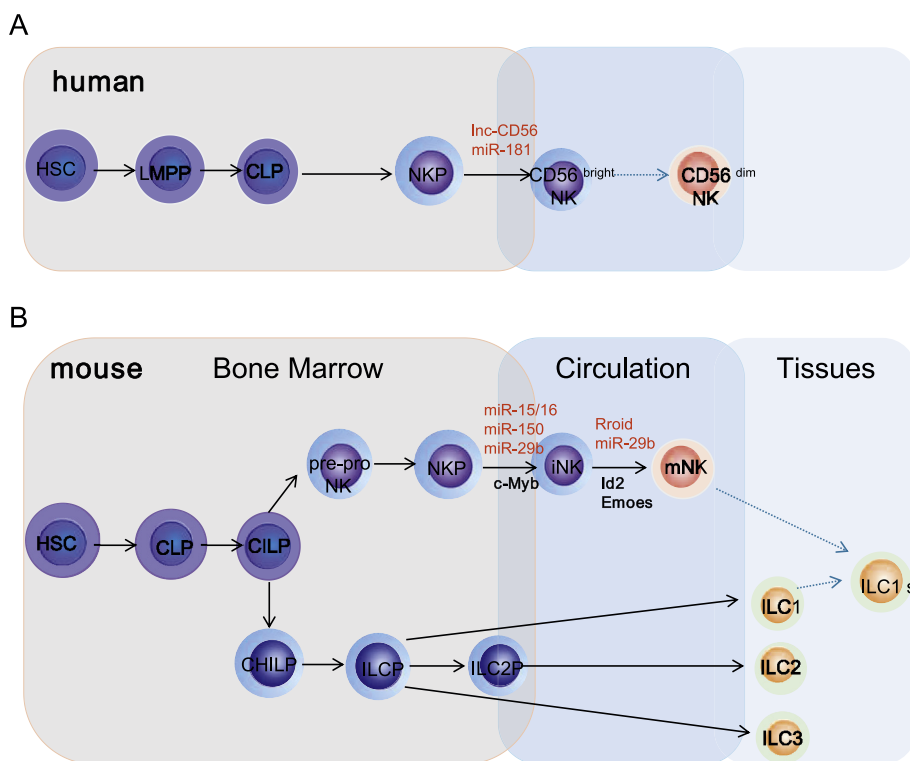


Figure 2 The key lncRNA and miRNA involved in developmental origin of murine and human NK cells. A. In human, HSCs firstly transit into CD45RA⁺ LMPPs. By expressing CD38, CD7, CD10 and IL-7R α , LMPPs next differentiate into CLPs with potential to make lineage commitments into NKPs. Expression of CD122 further marks NKPs transit into immature NK cells (iNK). The appearance of CD56 indicates a final transition of iNK cells into mNK cells. CD56^{bright} NK cells are considered less mature and CD56^{dim} NK cells probably differentiate from CD56^{bright} NK cells (dotted arrow) that is yet to be validated. B. In murine, HSCs firstly transit into CLPs and then differentiate into the CILPs. CILPs further develop into the common helper-like ILC precursors (CHILP) and earliest precursor of NK cells, namely pre-pro NK cells. Pre-pro NK cells up-regulate the expression of CD122 and further develop into NKPs. Accepting IL-15 stimulus, NKPs differentiate to iNK. iNKs receive MHC-I domestication signals and finally develop into mature NK cells. CHILPs further differentiate into ILCPs and finally transit into ILC1, ILC2, ILC3.

MiRNAs negatively regulate the development of NK cells. During the process of NK cell maturation, miR-583 is a miRNA which changes the most. Over-expression of miR-583 can inhibit NK cell differentiation. If IL-2R- γ 3'-UTR basic group mutated, the inhibitory function of miR-583 will disappear. Therefore, miR-583, as a negative regulatory factor, acts on IL-2R- γ 3'-UTR to inhibit NK cell differentiation.⁴⁶ TBET and EOMES are both key transcription factors taking part in the differentiation and development of NK cells. It has been found in mouse that TBET and EOMES can be meaningfully decreased by miRNA-29b to inhibit NK cell maturation.⁴⁷ In addition, Over-expression of miRNA-29b induces NK cell depletion, indicating a potential mechanism of miRNA-mediated in immune escape.⁴⁷ (Table 1).

Regulation of lncRNAs and miRNAs in NK cell activation

NK cells express a series of activating and inhibitory receptors on their surface. Whether NK cells are activated relied on the balance between these activating and inhibitory signal of NK cells. Broadly speaking, the currently recognized activating receptors are NKP30,⁴⁸ NKG2D,⁴⁹

NKP44,⁵⁰ NKP46,⁵¹ CD244/2B4,⁵¹ NKP46,⁵¹ CD16a,⁵² CD226,⁵² while inhibitory receptors are CD94/NKG2A,⁵³ CD158b.⁵⁴ Among these receptors, NKG2D is the most famous receptor. Its high expression promotes NK cell activation and increases their killing activity against target cells.⁴⁹ However, many miRNAs have been found that they can positively or negatively regulate NKG2D signaling.^{55,56} A high level of miR-34a can up-regulate NKG2D ligand expression in hepatocytes of HCC patients.⁵⁵ In addition, miR-182 also enhances NK cell cytotoxicity which leads to HCC (hepatocellular carcinoma cells) by regulating NKG2D expression. Furthermore, over-expression of miR-182 increases NK cell cytotoxicity against liver carcinoma via modulating NKG2D expression.⁵⁶ Moreover, miR-30c augment the cytotoxicity of NK cells (an human NK cell line) by up-regulating NKG2D expression. Further study found that only 40% of NK cells from freshly isolated PBMC (Peripheral Blood Mononuclear Cell) express a high level of NKG2D after miR-30c over-expression, suggesting that miRNA may show a perplexing and synergistic effect in NK cell-mediated immune response.⁵⁷ In the latest research, miRNA-186 also can promote NKG2D-mediated cytotoxicity by directly inhibiting MYCN, AURKA, TGFRB1 and TGFRB2 expression.⁵⁸ NKG2DLs are the ligand of NKG2D, including MHC class I-related chain A/B (MICA/B), and usually

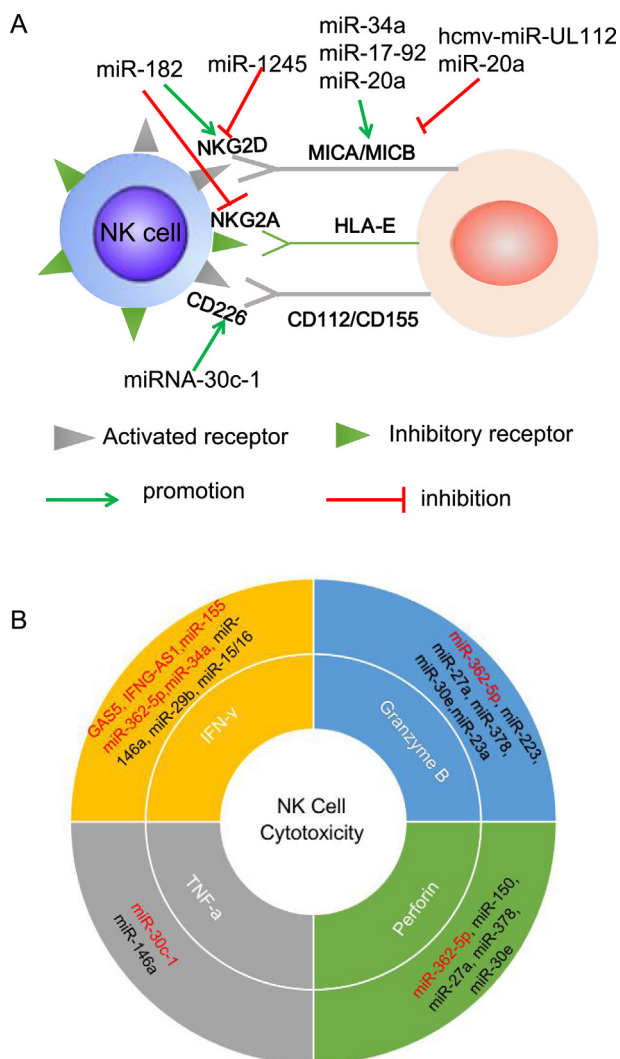


Figure 3 The key lncRNAs and miRNAs involved in activation and function of NK cells. **(A)** NKG2D, CD226 represented by gray triangle are activating receptors of NK cells; NKG2A represented by green triangle is inhibitory receptors of NK cells. MICA/MICB, HLA-E and CD112 are the ligands of NKG2D, NKG2A and CD225, respectively. Green arrow represents the promotion of receptors or ligands expression. Red arrow indicates the inhibition of receptors or ligands expression. **(B)** The key lncRNAs and miRNAs involved in function of NK cells. IFN- γ , TNF- α , Perforin and Granzyme B are molecules via which NK cells play a cytotoxic role. Red coloured words represent the promotion of corresponding molecule expression. Black coloured words indicate the inhibition of corresponding molecule expression.

expressed on the surface of some tumor cells or pathogen-infected cells, such as breast cancer, cervical cancer and leukaemia.^{49,59,60} It has been reported in breast cancer that miR-17-92 can specifically bind to the 3'UTR of MICA/B.⁶⁰ Thus, silencing miR-17-92 can enhance NK cell-mediated cytotoxicity by up-regulating NKG2DLs expression.

MiRNAs can not only positively regulate the NKG2D or NKG2DL expression, some miRNAs also can negatively mediate the activation of NKG2D signaling. TGF β 1 is a major negative regulator of NKG2D expression.⁶¹ MiRNA-

1245 can down-regulate NKG2D expression and impair NKG2D-mediated immune responses in NK cells though up-regulating TGF β 1 expression from post-transcription level.⁶² Similarly, Tang P et al. found that increased levels of miR-20a in cancer cells may functionally inhibit NKG2D-mediated cytotoxicity of NK cell by down-regulating MICA/B expression of colorectal cancer cells.⁶³ These studies also provide a potential evidence between cancer cells and immune escape from NK cells.

Except NKG2D, CD226 is also an important activating receptor. The activity of CD226 signal can increase the cytotoxicity of NK cells. Research showed that miRNA-30c-1 promoted NK cells cytotoxicity against human liver cancer cells by binding to the transcription factor hmbox1, a direct target gene of miR-30c-1.⁶⁴ Further study found that miRNA-30c-1 acts on CD226 to promote the production of TNF- α and enhance the killing effect of NK cells.⁶⁴ (Table 2). NK cells are different from other immune cells and not dominated by any single receptor. Presently, except for the NKG2D and CD226 receptors, the relationship between other receptors and lncRNA or miRNA have been rarely reported. Therefore, more researches are urgently needed to investigate the role of lncRNAs or miRNAs on NK cell activity.⁶¹ The regulatory network diagram of miRNA or lncRNA on the receptor-ligand signal axis of NK cells is shown in Fig. 3A. In summary, the function of NK cells depends on the balance of signals transmitted by the activating receptors and inhibitory receptors after recognizing the corresponding ligands on the target cell surface. Although NK cells express a variety of activating or inhibitory receptors, studies have found that miRNAs are mainly involved in the expression of CD226 and NKG2D. Therefore, the regulatory relationship between miRNAs and other receptors is still unclear, which is worth more researches to focus on.

Regulation of lncRNAs and miRNAs in NK cell function

Activation of NK cells is the foundation for them to be effective to anti-infection, anti-virus and anti-tumor. As mentioned earlier, the activation of inhibitory receptors on the surface of NK cells can inhibit the activation of NK cells by inhibiting intracellular calcium signaling through SHP-1, SHP-2 and inhibiting phosphorylation level of critical factors in NK cells. However, if the ligand binds to the activating receptors of NK cell surface, tyrosine activating motif of intracellular receptors activates the downstream PTKs, which will increase the secretion of IFN- γ , granzyme B and perforin to play NK cell cytotoxicity.⁶⁵

lncRNAs are involved in the regulation of many cellular processes. Stein N et al. found that lncRNA IFNG-AS1 can sharply increase IFN- γ secretion and strongly inhibit pathogens infection in mice after IFNG-AS1 over-expression in primary NK cells or an NK cell line.⁶⁶ In addition, Fang P et al. also found that knockdown of GAS5 in activated NK cells will reduce the clearance ratio of NK cells against liver cancer cells through decreasing IFN- γ secretion and the percentage of CD107⁺ NK cells. On the contrary, lncRNA GAS5 over-expression can increase the cytotoxic effect of NK cell on liver cancer cell by down-regulating the

Table 1 Gene regulated by lncRNAs and miRNAs in NK cell development.

LncRNA/MiRNA	Target gene	Model	Biological significance	Reference
lnc-CD56	CD56	human	enhances the expression of CD56	42
miR-583	IL-2R γ	human	acts as a negative regulator of NK cell differentiation by silencing IL2R γ	46
miR-181	Nemo-like kinase	human	promotes NK cell development through the suppression of Nemo-like-kinase	45
Rroid	Id2	mouse	regulates the function and lineage identity of NK cells	41
miR-29b	TBET, EOMES	mouse	deletion of miR-29b in NK cells reverses the depletion of NK cell subset in leukemic mice	47
miR-150	c-Myb	mouse	differentially controls the development of NK cell lineages by targeting c-Myb	44
miR-15/16	c-Myb	mouse	miR-15/16 regulation of Myb controls the NK cell maturation program	43

expression of miR-544, suggesting that lncRNAs have an important effect on the release of IFN- γ ⁶⁷ (Fig. 4).

Apart from IFN- γ , NK cells mainly secrete perforin and granzymes to kill target cell. At present, lncRNAs are mainly found to be involved in the regulation of IFN- γ secretion. MiRNAs are main regulator in the expression of perforin or granzymes B. It has been reported Ni F et al. found NK cells in human peripheral blood highly expressed miR-362-5p.⁶⁸ The miRNA can up-regulate CD107a expression in NK cells, promote perforin and granzyme B secretion, and increase NK cell cytotoxicity by targeting the tumor suppressor factor -CYLD (cylindromatosis).⁶⁸ After NK cells are activated by IL-15, miRNA-27a-5p also can positively regulated perforin and granzyme B mRNA expression by directly combining to 3'-UTR of them. In order to prevent NK cells from excessive activation when miR-27a-5p is over-expression, granzyme B and perforin expression are decreased.⁶⁹

Being contrary with the effect of miRNA-362-5p, miRNA-223 and miRNA-27a both negatively regulate NK cell cytotoxicity.^{70,71} MiRNA-223 directly inhibits granzyme B mRNA translation in NK cells.⁷⁰ MiRNA-27a also inhibit NK cell cytotoxic effect by simultaneously inhibiting granzyme B and perforin mRNA translation in NK cells.⁷¹ MiRNA-378 is a negative regulated factor of NK cell cytotoxicity. Research

showed that miRNA-378 expresses less in NK cells of DENV (Dengue virus) infected patients. When adding miRNA-378 agomir to mice infected with DENV, the expression of granzyme B was inhibited and DENV replication increased.⁷² Moreover, besides miRNA-378, miRNA-30e is also involved in the negative regulation in the expression of granzyme B and perforin.⁷³ If miRNA-378 or miRNA-30e was inhibited in NK-92 nucleus, the cytotoxicity and tumor killing ability of NK-92 cells sharply increase. Interestingly, in the NK cells of miRNA-233 knockout mice, the secretion of granzyme B and NK cell cytotoxicity are different from those of normal wild mice.⁷⁴ It suggests that miRNA-233 does not work alone, and there may be other factors or miRNAs involved in this process. All-trans retinoic acid (ATRA) can inhibit NK cell killing ability by inhibiting target gene expression. It has been confirmed that miRNA-23a express less after NK cells are activated and is a negative regulator of cathepsin C (CTSC). CTSC is a downstream target gene of miRNA-23a.⁷⁵ After CTSC was activated, granzyme B secretion can increase. However, ATRA can induce miRNA-23a up-regulation, thus inhibiting CTSC expression, and result in impaired NK cell killing function. (Table 3). In summary, miRNAs can be specifically paired with the 3'-UTR of granzyme B and perforin mRNA to cause degradation of the mRNA. It reduces the

Table 2 Gene regulated by lncRNAs and miRNAs in NK cell activation.

Receptor	LncRNA/MiRNA	Target gene	Biological significance	Reference
NKG2D	miR-34a	/	increases their susceptibility to NK cell-mediated cytolysis in non-transformed liver cells	55
	miR-17-92	MICA/B	regulates NLG2L and NK cell-mediated cytotoxicity	60
	hcmv-miR-UL112	MICB	down-regulates MICB expression during viral infection, leading to decreased binding of NKG2D and reduced killing by NK cells	61
	miR-182	NKG2D/NKG2A	augments NK cell cytotoxicity against liver cancer via modulating NKG2D and NKG2A expressions	56
	miR-20a	MICA	regulates sensitivity of CRC cells to NK cells by targeting MICA	63
	miR-1245	NKG2D	microRNA-1245 down-regulation significantly increases the expression of NKG2D expression in NK cells	62
CD226	miRNA-30c-1	hm-box1	promotes NK cell cytotoxicity against hepatoma cells by targeting HMBOX1	64

stability of target gene mRNA or inhibits protein translation, regulates the secretion of granzyme and perforin of NK cells, thereby regulate NK cytotoxicity. The regulatory effect of miRNA or lncRNA on the function of NK cells is shown in Fig. 3B. Though miRNAs largely participate in the regulation of NK cell cytotoxic molecules, especially IFN- γ , lncRNAs related to NK cell function are rarely reported, which is related to the difficulty in finding functional lncRNAs. However, lncRNAs have an absolute advantage in non-coding RNAs, and their modes of action and mechanisms are more complex compared with miRNAs. Therefore, more researches are needed to reveal the relationship between the NK cell function and lncRNAs, which will provide a theoretical basis for the application of miRNAs or lncRNAs in NK cells.

The role of lncRNAs and miRNAs in NK/T cell lymphoma

Extranodal nasal-type natural killer/T-cell lymphoma (NKTL), an Epstein–Barr virus (EBV) associated lymphoma, is mostly derived from cytotoxic NK cells and a small part is derived from NK-like T cells. Study has reported that the EBV infection rate in NKTL patients is up to 90%.⁷⁶ Normally, though cytotoxic NK cells will eradicate viral infections, it is interesting to investigate how the EBV evades and transforms NK cells in NKTL. IFN- γ is an important cytotoxic cytokine of NK cells and main transcribed by transcription factor T-bet. The EBV-encoded miR-BART20-5p inhibits both T-bet and IFNG in NKTL, which allows the survival of EBV inside NK cells.^{77,78} Apart from miR-BART20-5p, there are also some other EBV-encoded miRNA help NKTL tumorigenesis and progression as mentioned below: BART9 is involved in NKTL proliferation by regulating LMP-1 expression;⁷⁹ miR-BART8 cause progression of NKTL through inhibition of the IFN- γ -STAT1 pathway.⁷⁸ The more information of abnormal EBV-encoded miRNAs in NKTL is summarized in Table 4. Though miR-142-3p and miR-205 may not EBV-encoded miRNA, they are down-regulated in the EBV-positive vs EBV-negative lymphomas.⁸⁰ Down-

regulated miR-142-3p and miR-205 can contribute to lymphomas tumorigenesis through up-regulating the oncogenic BCL6 and the proinflammatory cytokine interleukin 1 alpha (IL1A) expression. Clearly, the EBV encodes at least 44 miRNAs, but the pathogenesis of most EBV-encoded miRNAs in NKTL remain to be explored.

MiRNA deregulation in NKTL

Mention to the pathogenesis of NKTL, besides EBV infection, like p53, C-kit, K-ras, C-MYC et al gene mutations and abnormal activation of JAK-STAT, NF- κ B, Wnt/ β -catenin are also important factors. These deregulated single genes and deregulated signaling pathways mainly cause the increasing of tumor cell proliferation or the inhibition of tumor cell apoptosis.⁸¹ To understand the pathogenetic role of miRNA deregulation in NKTL, Ng et al performed a comprehensive genome-wide miRNA expression profiling of NKTL tissues and NK cell lines compared with normal NK cells and found differentially expressed miRNAs in NKTL are predominantly down-regulated. Re-expression of down-regulated miRNAs, such as miR-101, miR-26a, miR26b, miR-28-5, and miR-363, may reduce the growth of the NK cell line and modulated the expression of their predicted target genes, suggesting the potential functional role of the deregulated miRNAs in the oncogenesis of NKTL.⁸² On the other hand, there are also some microRNAs, such as miR-21 and miR-155 have been shown to be over-expressed in ENKTL (Extranodal NK/T cell lymphoma), with pro-oncogenic consequences. All above these suggest the potential functional role of the deregulated miRNAs in the oncogenesis of NKTL.⁸²

Mechanically, abnormal miRNAs usually promote or inhibit the expression of key genes and key signaling pathway to help NKTL tumorigenesis and progression. In NKTL, the activation of AKT signal, NF- κ B, STAT3 can promote cancer cell proliferation, inhibit cell apoptosis and induce tumorigenesis. In NKTL, there are some abnormal miRNAs can activate these signaling passway by acting on the targets. For example, Aberrant over-expression of miR-21,⁸³ miR-155,⁸⁴ miR-494-3p⁸⁵ and down-regulation of miR-

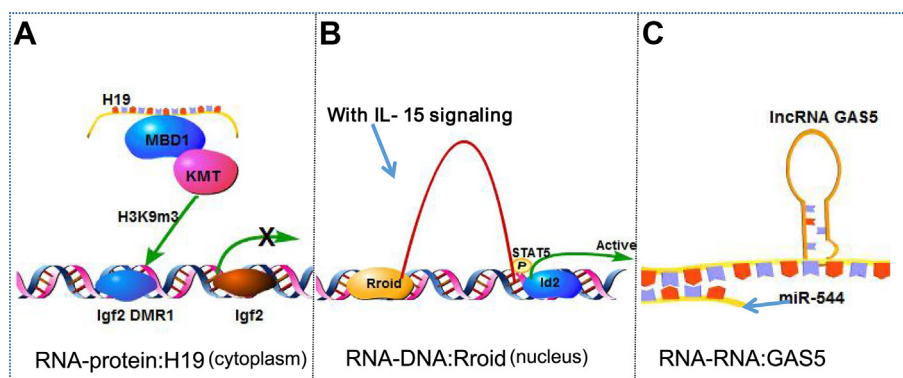


Figure 4 The molecular mechanism of lncRNA in NK cells or NKTL. (A) The H19 RNA is required for the recruitment of MBD1 to inhibit *Igf2* gene. The H19 lncRNA–MBD1 complex through its interaction with histone lysine methyltransferases KMT, and then acts by bringing repressive H3K9me3 marks on the differentially methylated region of *Igf2* DMR1. (B) With IL15 signaling, Roid promotes the deposition of phosphorylated STAT5 at the *Id2* promoter region through long–range interaction and finally increases the activity of *Id2*. (C) lncRNA GAS5 increase the cytotoxic effect of NK cell via binding to miR-544 and down-regulating the expression of miR-544.

Table 3 Gene regulated by lncRNAs and miRNAs in NK cell function.

Cytotoxic molecules	LncRNA/MiRNA	Target gene	Biological significance	References
Granzyme B	miR-362–5p	CYLD	enhances the expression of granzyme-B via NK- κ B pathway	68
	miR-223	GzmB	contributes to control of GzmB translation in resting NK cells	74
	miR-27a	GzmB	suppresses NK-cell cytotoxicity by silencing GzmB expression	71
	miR-378	GzmB	suppresses GrzB expression in NK cells	72
	miR-30e	GzmB	suppresses GrzB expression in NK cells	73
	miR-23a	CTSC	decreases CTSC expression and granzyme B activity	75
Perforin	miR-362–5p	CYLD	enhances the expression of perforin via NK- κ B pathway	68
	miR-27a	Prf1	silences Prf1 expression in NK cells	71
	miR-30e	Prf1	suppresses Prf1 expression in NK cells	73
	miR-150	Prf1	represses NK cell lytic activity by targeting perforin-1	44
	miR-378	miR-378	inhibites GrzB expression in DENV-infected patients	74
TNF- α	miR-146a	STAT1	negatively regulates TNF- α expression via STAT1 signaling	87
	miR-30c-1	hmbx1	enhances NKL cell cytotoxicity through up-regulation of TNF- α	64
IFN- γ	lncRNA GAS5	miR-544/RUNX3	increases RUNX3 expression and IFN- γ secretion	69
	lncRNA IFNG-AS1	/	induces upon NK cell activation and increases IFN γ secretion	66
	miR-155	SHIP-1/Noxa	increase IFN- γ production in HCV-infected patients	95
	miR-155	Tim-3	regulates IFN- γ production in NK cells via Tim-3 signalling	96
	miR-146a	STAT1	negatively regulates IFN- γ expression via STAT1 signaling	98
	miR-362–5p	CYLD	enhances the expression of IFN- γ via NK- κ B pathway	68
	miR-34a	/	enhances cytolysis and interferon- γ production by NK-92MI cells	55
	miRNA-29b	DNMTs	regulates INF- γ expression via decreasing methylation of IFN- γ	99
miR-15/16	c-Myb	enhances the expression of granzyme-B in NK cells	43	

150⁸⁶ in NKTL lead to activation of the PI3K-AKT pathway; aberrant down-regulation of miRNA-146a in NKTL lead to activation of the NF- κ B pathway.⁸⁷ Over-expressed miR-155 also can activate STAT3/VEGFC signaling and promoted lymphangiogenesis.⁸⁴ In addition, miR-34a and miR-181c may be involved in the oncogenic progression of NKTL through the regulation of STAT3 pathway,⁸⁸ miRNA-342-3p may contribute to the development of NKTL via the TIAM1 pathway.⁸⁰ Other abnormal miRNAs participate in the pathogenesis of NKTL by inhibiting or promoting key genes that regulate growth, development, proliferation, and apoptosis of cells. For example, miR-181c and miR-34a may be involved in the oncogenic progression of NKTL by targeting PDGFR α and K-RAS;⁸⁸ abnormal upregulation of miR-155 may be associated with regulation of FOXO3a gene can promote the proliferation of SNK-6 lymphoma cells and

inhibit their apoptosis.⁸⁹ This table summarizes the mechanisms by which miRNA deregulation contributes to lymphomagenesis in NKTL (Table 4).

Clinical value of lncRNA and miRNA dysregulation in NKTL

Presently, the studies of lncRNA and miRNA mainly focused on cancer and an increasing number of researches showed that nc-RNAs can be defined as new biomarkers for disease diagnosis and new targets for drug treatment. For example, lncRNA-PCA3 in urine, has been identified as the most specific biomarker for proadenocarcinoma and it will be used in clinical soon.⁹⁰ There are also some new miRNA or lncRNA biomarkers involved in NKTL. It has been found in

Table 4 The role of lncRNAs and miRNAs in NKTL.

Noncoding RNA	Encoded by EBV (Yes/No)	Target gene	Underexpressed Overexpressed in NKTL	Biological significance	References
BART9	Yes	LMP-1	Overexpressed	BART9 is involved in NKTL proliferation by regulating LMP-1 levels	79
miR-BART20-5p	Yes	T-bet(TBX21)	—	promotes NKTL progress via the PTEN-AKT-mTOR/RICTOR pathway	85
miR-BART20-5p	Yes	—	—	promotes the development of NKTL through inhibition of the IFN- γ -STAT1 pathway	78
miR-BART8	Yes	—	—	causes progression of NKTL through inhibition of the IFN- γ -STAT1 pathway	78
miR-142-3p	No	IL1-a	Underexpressed	regulates the expression of IL1A	85
lncRNA MALAT1	No	ZH2, SUZ12	Overexpressed	MALAT1 is related to poor prognosis	91
miR-21,miR155	No	—	Overexpressed	leads to activation of the PI3K-AKT pathway	82
miR-150	No	AKT2, DCK1	Underexpressed	induces continuous activation of the PI3K-AKT pathway	86
miRNA-146a	No	TRAF6	Underexpressed	downregulates NF- κ B activity and is related to prognosis	87
miR-15a	No	Myb, cyclin D1	Underexpressed	promotes cell proliferation and predicts poor prognosis in NKTL	94
miR-223	No	PRDM1	Overexpressed	The downregulation of the tumour suppressor PRDM1 is mediated by miR-223 and that PRDM1-positive staining might have prognostic value for NKT patients	92
miR-155	No	BRG1	Overexpressed	activates STAT3/VEGFC signaling, promotes lymphangiogenesis and controlled the viability of NKTL cells	84
miR-155	No	Foxo3a	—	Reduction in miRNA-155 expression can inhibit the proliferation of SNK-6 lymphoma cells and promote their apoptosis	89
miR-494-3p	No	PTEN	Overexpressed	promotes NKTL progress through the PTEN-AKT-mTOR/RICTOR pathway	85
miR-142-3p	No	RICTOR	Overexpressed	inhibites RICTOR, with secondary suppression of AKT in YT cells	80
circulating miR-221	No	—	—	a reverse correlation with performance status and the overall survival after treatment	101
miR-16	No	Bmi1	Underexpressed	enhances p21 expression via downregulation of Bmi1, thereby inducing cellular senescence	102
miR-205	No	BCL6	Underexpressed	regulates the expression of the oncogenic BCL6	80
miR-34a,miR-181c	No	PDGFR α	—	are involved in the oncogenic progression of NKTL through the regulation of PDGFR α , STAT3, and K-RAS	88
miR-143,miR-20b, miR34a	No	—	—	miR-20b, miR34a, miR-143 expression showed inverse correlations with STAT3 mRNA expression in NKTL tissues	99

NKTL that MALAT1 is most highly expressed in lncRNAs connected to the polycomb repressive complex (PRC) and is related to poor prognosis of NK cell lymphoma patients by directly binding to EZH2 an SUZ1285.^{91,92} Except lncRNAs, more miRNAs also are involved in NK cell lymphoma. For example, the down-regulation of the tumor suppressor-PRDM1 in NKTL samples is mediated by miR-223 and the PRDM1-positive staining might have prognostic value for evaluating the clinical outcome of NKTL patients.⁹² PRDM1 is an tumor suppressor gene and indirect target gene of miR-223. There are several publications showed PRDM1 might be a favorable predictor of overall survival and failure-free survival in EN-NK patients.^{87,93} Except contribution to prognosis, miRNAs also can be used as a target of disease treatment. Lin J et al found that miR-BART20-5p will inhibit the translation of T-bet, the master transcription factor for cytotoxic NK cells, and decrease p53 expression, a tumor suppressor gene. Therefore, an antagonist for miR-BART20-5p might be an effective therapeutic agent through inducing the expression of T-bet and p53. In addition, Komabayashi found over-expression of miR-15a can decrease MYB and cyclin D1 levels thereby blocking G1-S transition and cell proliferation.⁹⁴ Further study also found in NK/T cell lymphoma tissues, reduced miR-15a expression, was associated with poor prognosis of NK/T cell lymphoma patients.⁹⁴ Therefore, miR-15a may be a potential target for anti-tumor therapy and a prognostic predictor for NKTL.^{55,95–101} (Table 4.)

Mechanisms of miRNA dysregulation in NKTL

Deregulated miRNA patterns are frequently linked to a variety of human cancers including lymphomas. The mechanisms of dysfunctional miRNAs in NKTL are beginning to be delineated. MYC, a key transcriptional regulator known to cause extensive repression of miRNA, has been reported to be over-expressed in NKTL and may cause the widespread down-regulation of miRNAs in NKTL.^{82,102} Moreover, the oncogenic EBV is strongly associated with the pathogenesis of NKTL and expresses 44 mature miRNAs and two noncoding EBV-encoded RNAs (EBERs). It has been confirmed that EBV promotes the deregulation of miRNAs since down-regulation of miR-142–3p,⁸⁵ MiR-205⁸⁰ and up-regulation of miR-155⁸⁴ in NKTL. Besides, epigenetic deregulation has been shown to result in the deregulation of miRNAs in NKTL, such as miR-146a.⁸⁷ Paik JK et al. found that promoter methylation of miR-146a gene was observed in SNK6 and YT cells, as well as in NKTL tissues with low miR-146a expression, and miR-146a expression was induced by the conversion of methylation status with a demethylating agent in SNK6 and YT cells, which suggests promoter methylation of miRNA has contributed to the deregulation of miRNAs in NKTL.⁸⁷

Summary and future outlook

Mounting evidence underscores the critical role of miRNAs and lncRNA as regulators of NK cell biology and carcinogenesis and progress of NKTL. MiRNAs or lncRNA finely tune the level of translatable mRNAs in response to specific developmental or stimulatory cues and change cellular requirements, which provides the possibility to control the

cytotoxicity and cytokine secretion of NK cells. Meanwhile, lncRNA or miRNA has various target genes, which increases uncertainty and difficulty for directionally modifying the biological function of NK cells or curing diseases by regulating miRNAs or lncRNAs.

NKTL is a malignant tumor caused by the aberrant development NK cells. Abnormally expressed miRNAs and lncRNAs of NK cells contribute to the occurrence and progression of NKTL. Restoring key miRNAs and lncRNAs with abnormal expression may provide the possibility for the treatment of NKTL. Presently, lncRNA and miRNA related to NK cell biological activity and NKTL still have a certain distance in practical application. On one hand, compared with miRNAs, lncRNAs are much less studied in NK cell but they are the most component of non-coding RNA. To realize lncRNA application value in NK cell function and NKTL rapid diagnosis, treatment and prognosis evaluation, it is necessary to discover and study more functional lncRNAs in physiological or pathological NK cells. On the other hand, technically, transfection of NK cell is more difficult. Improving the transfection efficiency of miRNA mimics or miRNA antagomir in NK cells will help to verify the function of key functional miRNAs in NK cells and realize the application value of miRNAs in NK cell-related diseases, such as NKTL.

Although this review has focus on how miRNAs or lncRNAs participates in the development, activation, function of NK cells and NKTL occurrence from a relatively comprehensive and detailed perspective, the mechanism of how they works is not sufficiently elaborated. In summary, there has been discovered more functional miRNAs and lncRNAs with potential NKTL diagnosis and prognostic evaluation as introduced in this review. In order to realize the clinical application of miRNAs and lncRNAs in NKTL, more researches from different dimensions are needed to support the feasibility of miRNAs and lncRNAs as new NKTL diagnostic markers, indicators of patients' prognostic and the targets of the therapeutic drugs.

Authors contribution

FengXia Gao performed the selection of literature, drafted the manuscript, and prepared the figures. SiRong He participated in the design and discussion. AiShun Jin carried out the design of this review and revised the manuscript. All authors contributed to this manuscript. All authors read and approved the final manuscript.

Conflict of Interests

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