DOI: 10.1002/JLB.1RU0518-197RR

JLB JOURNAL OF LEUKOCYTE BIOLOGY

REVIEW

Noncoding RNA in NK cells

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Abstract

Noncoding RNAs (ncRNA) are important regulators that modulate cell proliferation, apoptosis, the cell cycle, and DNA methylation. NK cells mediate the immune response via the secretion of various cytokines and are important innate immune cells in the human immune system. Recent studies have found that ncRNA plays an important role in NK cell development and function. With recent advances in bioinformatics and next-generation sequencing, novel ncRNAs have been identified, allowing us to more fully appreciate its functions in NK cell biology. In this review, we summarize and discuss the latest studies on the functions and regulatory mechanisms of long noncoding RNA (lncRNA) and microRNA in NK cells from the viewpoint of epigenetic mechanisms to help us clearly understand ncRNA in NK cells.

KEYWORDS

cytokines, gene regulation mechanism, immune response, lncRNA, microRNA, NK cell

1 | INTRODUCTION

Long noncoding RNA (lncRNA) are defined as transcripts longer than 200 nucleotides in length, whereas microRNA are small RNA that ~23 nucleotides in length. It is now well recognized that genome consists of vast majority of noncoding genes with unidentified functions.[1,2] Noncoding RNA (ncRNA) is involved in many biologic processes, including cancer, inflammation, and neurologic diseases.[3] ncRNA has also been found to be involved in various immune responses. For example, NeST, also known as Tmevpg1, is the lncRNA that is expressed in the human and the mouse. NeST is located adjacent to the IFN-γ encoding gene. The transcript of NeST binds to the histone H3 lysine 4 methyltransferase complex WDR5, altering histone 3 methylation at the IFN-γ locus. Thus, this lncRNA regulates the expression of IFN-γ in T cells and microbial susceptibility to viral and bacterial infection, illustrating the potential regulation of lncRNA in the immune system.[4] MicroRNA are short ncRNA that act as gene expression regulators via interaction with the 3′untranslated region of target genes.[5] Increasing evidence shows that microRNA play crucial roles in diseases such as cancer.[6–8] The deletion of key enzymes, such as Dicer and Dgcr8 in the microRNA biosynthesis pathway, leads to defects in NK cells, indicating that miRNA play a crucial role in the biologic processes of NK cells.[9–11] These studies highlight the potential key roles of ncRNA in regulating NK cell development and function.

NK cells are a subpopulation of lymphocytes that are classified as CD56 positive and CD3 negative.[12] NK cells secrete perforin, IFN-γ, TNF, and GM-CSF,[13,14] and produce the beta chemokine MIP-1α,[15,16] which enhances NK cell-mediated cytotoxicity during the immune response. For example, following activation by IFN-α/β, NK cells inhibit viral infection via the secretion of perforin and lysis of the virus-infected cells.[17,18] In addition, NK cells can prevent tissue injury, regulate the outcome of pregnancy, and mediate immune cell homeostasis via cytotoxicity and cytokine-secretion effector functions.[19]

NK cells, together with monocytes/macrophages, dendritic cells (DCs), and granulocytes, are the first defense of the innate immune system. Recent studies have mainly focused on the functions of surface receptors, cytokines involved in the infection, and transcriptional factors, where increasing numbers of researchers are realizing the critical roles of ncRNA in NK cells.[20,21] To improve our understanding of the functions of ncRNA in NK cells, this review focused on the roles of ncRNA, mainly lncRNA and microRNA, in NK cell development and function. We also summarize the latest studies and discuss the potential regulation of NK cell biologic processes by lncRNA and microRNA.

Abbreviations: dNK cell, Decidual NK cell; EOMES, Eomesodermin; H3K27me3, H3 lysine-27 trimethylation; H3K4me3, Histone H3 lysine-4 trimethylation; ILCs1, Group1 innate lymphocytes cells; lincRNA, Long intergenic noncoding RNA; lncRNA, Long noncoding RNA; MICA/B, Major histocompatibility complex class I chain-related proteins A and B; ncRNA, Noncoding RNA; NLK, Nemo-like kinase; PRC2, Polycomb repressive complex 2; pre-microRNA, precursor microRNA; pri-microRNA, long primary transcripts; SPFQ, splicing factor proline/glutamine-rich; TBET, T-box-related TBX21; ULBP1-6, Unique long 16 binding proteins 1–6; URSA, Unexplained recurrent spontaneous abortion; VSMC, Vascular smooth muscle cell; Xist, Inactive X-specific transcript

Received: 16 May 2018 | Revised: 5 September 2018 | Accepted: 9 September 2018

2 | MECHANISMS OF GENE EXPRESSION REGULATION BY LNCRNA

lncRNAs are emerging as important regulators of gene expression, which act at the level of transcription, post-transcription, and at the epigenetic level. These regulatory mechanisms influence important cellular processes, and their deregulation is observed during the immune response and in many diseases. lncRNA can further be divided into long intergenic noncoding RNA (lincRNA), intronic lncRNA, antisense lncRNA, and enhancer ncRNA.[22] The majority of lncRNA are located in the nucleus, whereas some are exported from the nucleus to the cytoplasm and function as important regulators.[23] lncRNA act as regulators of gene expression via lncRNA-DNA interaction and lncRNA-protein interaction. The function of lncRNA is becoming clearer, with the reporting of more detailed studies in every aspect of the biologic field. The lncRNA involved in NK cell gene regulation are shown in Table 1.

2.1 | CIS/TRANS Regulation

lncRNA have been reported to modulate gene expression in cis or in trans by binding to genomic DNA targets or recruiting chromatin modifiers. When lncRNA exerts its influence on a neighboring gene on the same allele from which it is transcribed, lncRNA act in cis[24] (Fig. 1A). An example of typical cis regulation is the lncRNA HOTTIP that is expressed in the HOXA cluster, which binds to WDR5 in the MLL histone modifier complex, enhancing gene expression by bringing histone H3 lysine-4 trimethylation (H3K4me3) to the promoter of flanking genes.[24–26] lncRNA mediation of trans regulation involves distantly located genes[24] (Fig. 1B). One example of trans regulation is the lncRNA called HOTAIR that is expressed from the HOXC cluster. HOTAIR interacts with polycomb repressive complex 2 (PRC2) and is required for PRC occupancy and activation of H3K27me3 of the HOXD locus, thereby repressing the transcription of the HOXD cluster.[27]

2.2 | LNCRNA-Protein Interaction

Interaction between lncRNA and proteins has been demonstrated to be an important mechanism in the lncRNA regulation network. lncRNA can contain functional domains that bind chromatin-modifying proteins, which mediate gene regulation via the chemical modification of histones.[22,28] For example, one well-studied lncRNA, inactive X-specific transcript (Xist), is involved in the silencing of the entire X chromosome in females.[29] The lncRNA XIST specifically binds to genomic DNA and recruits PRC2, leading to the establishment of H3 lysine-27 trimethylation (H3K27me3) histone modification, rendering an entire X chromosome in mammalian female tissues transcriptionally inactive.[30,31] This situation results in a dosage equivalence between females who have two X chromosomes and males who have one X chromosome, indicating the importance of lncRNA in human cell development. lncRNA can also act as scaffolds, binding proteins that regulate gene expression. For example, when the lncRNA VL30 binds to the RNA binding domain of the splicing factor proline/glutamine-rich (SPFQ) protein, the promoter of the proto-oncogene rab23 (which regulates cell proliferation) is released from the DNA binding domain of SFPQ and expression of the rab23 gene is activated (Fig. 1D).[32] Similarly, the lncRNA NEAT1 is an essential lncRNA for the formation of nuclear body paraspeckles. NEAT1 facilitates the expression of IL-8 by binding to SFPQ, thus relocating SFPQ from the IL-8 promoter to the paraspeckles, leading to transcriptional activation of IL-8.[33]

3 | MECHANISMS OF GENE EXPRESSION REGULATED BY MICRORNA

MicroRNAs are a large family of small noncoding, endogenous, single-stranded RNA molecules that play crucial roles as post-transcriptional factors that negatively regulate mRNA translation. RNase III Drosha cleaved long primary transcripts (pri-microRNA) to release precursor microRNA (pre-microRNA). Pre-microRNA are exported from the nucleus to the cytoplasm and processed to the mature microRNA by the RNase III Dicer.[34–36] The mature microRNA interact with target mRNA, potentially leading to mRNA degradation or translational blockade.[37,38] MicroRNA with similar sequences are classified into the same family, and the nucleotides situated at positions 2–7 from the microRNA 5′-end are called the "seed" sequence. The seed sequence is important for the specific function of the microRNA.[9] MicroRNA regulate gene transcription through binding with the complementary sequence located in the 3′-untranslated region of target mRNA, thereby repressing target protein expression (Fig. 1C).[39] MicroRNA has been found to widely regulate NK cell development and function. The microRNAs involved in this regulation are summarized in Table 1.

4 | GENE REGULATION BY LNCRNA IN NK CELLS

NK cells are a type of group 1 innate lymphoid cells (ILCs1) and are key members in the response to infection by viruses, parasites, and bacteria.[40] lncRNA regulates target gene expression by direct and indirect mechanisms.[23,41,42] Many types of studies have focused on the direct interaction between lncRNA and chromatin in modulating gene transcription[43]; however, the locus marked by lncRNA also shows potential for modulation of flanking genes.[41] Transcriptional regulator inhibitor of DNA binding 2, which is encoded by gene Id2, modulates T and B cell-specific gene expression through down-regulating key transcription factors from the E-protein family. Mowel et al. found that in response to the cytokine IL-15, the locus marked by the lncRNA Rroid controls the function and lineage identity of group 1 ILCs via up-regulating the expression of the transcriptional regulator Id2. These findings demonstrate that the lncRNA loci play a critical role as regulatory elements to determine the function and identity of NK cells and group1 ILCs. This indicates that epigenetic elements such as lncRNA are unique to each immune cell and are crucial regulators that determine immune cell function and identity.[20]

An example of typical cis regulator in the NK cell is lnc-CD56, which is involved in the regulation of CD56 expression. CD56 is a neural cell-adhesion molecule isoform expressed in NK cells. It is

TABLE 1 Genes regulated by lncRNA and microRNA in NK cells

Noncoding RNA	Target gene	Function	Pathways
lnc-CD56	CD56	Enhance CD56 expression[46]	-
MEG3	-	Inhibit VSMC proliferation, promote VSMC migration and induce VSMC apoptosis[48]	-
Rroid locus	Id2	Regulate NK cell identity[20]	-
miR-155	SOCS1/SHIP1	Regulate INF-γ expression[73]	JAK-STAT
miR-155	Tim3	Regulate INF-γ expression[21]	
miR-146a	IRAK1/TRAF6	Regulate INF-γ expression[71]	NK-κB
miR-146a	STAT1	Regulate INF-γ expression[72]	-
miR-30c, miR-20c, miR-10b	MICA/B (NKG2DL)	Regulate NK cell cytotoxicity[77,88,89]	-
miR-27a-5p	CX_3CR1	Migration of NK cell[62]	-
miR-182	NKG2A/NKG2D (predicted)	cytotoxicity[80]	-
miR-181a/b	Nemo-like kinase (NLK)	Regulate maturation of NK cell[54]	Notch
miR-29b	TBET/EOMES	Regulate maturation of NK cell[61]	-
miR-378	Granzyme B	Regulate GrzB production[81,82]	-
miR-17-92	MICA/B (NKG2L)	Regulate NLG2L and NK cell-mediated cytotoxicity[78]	-
miR-34a-3p/5p, miR-141-3p/5p, and miR-24	-	May associated with URSA[84]	-
miR-615-5p	-	Depress NK cell cytotoxicity via repress IGF-1R[90]	-
miR-15/16	Myb	Regulate NK cell maturation[51]	
miR-362-5p	Cylindromatosis	Regulate IFN-γ, perforin, granzyme-B, and CD107a expression[67]	NK-κB
miR-583	IL2Rγ	Regulate NK cell differentiation[91]	-
miR-17/20a	Mekk2	Modulate NK cell antitumor activity[92]	-
miR-150, MiR-30e	Perforin-1	Regulate NK cell cytotoxicity[81,93]	-
miR-483-3p	IGF-1	Decrease NK cell cytotoxicity[94]	-
miR-1245	NKG2D	Regulate NKG2D-mediated cytotoxicity in NK cells[97]	
MiR-30c-1*	HMBOX1	Promote NK cell cytotoxicity[95]	
miR-27a*	Perforin1, Granzyme B	Regulate NK cell cytotoxicity[96]	

widely known that the function of $CD56^{bright}$ NK cells is mainly to produce pro-inflammatory cytokines, whereas $CD56^{dim}$ NK cells are described as the cytotoxic group.[44,45] The Lnc-CD56, located in the first intron of the CD56 gene, is the lncRNA that is highly expressed in human decidual NK cells (dNK cells). The lnc-CD56 was shown to positively regulate CD56 expression via epigenetic modification. This study described that knockdown of lnc-CD56 decreased CD56 expression, suggesting that lnc-CD56 may function as a regulator of CD56. lnc-CD56 in human NK cells could be essential for acquisition and maintenance of the CD56 marker during NK cell differentiation,[46] which gives a deeper understanding of the molecular regulation of NK cell development.

Previous studies have been focused on the noncoding regulation of NK cells, and thus the exploration of effects on NK cell function and differentiation. NK cells can also regulate the expression of certain lncRNA via cell-cell interaction. dNK cells are the main immune cells in the maternal-fetal interface, and are involved in tissue building and remodeling via secretion of angiogenic factors.[47] Vascular smooth muscle cell (VSMC) loss and separation, involving cell migration and apoptosis, plays an important role in appropriate spiral artery remodeling, which is important for fetal development and pregnancy outcomes.[48] Co-culture of dNK cells and VSMC can positively regulate expression of the lncRNA MEG3 in VSMC, inhibiting VSMC proliferation, promoting VSMC migration, and inducing VSMC apoptosis.[48] Thus, dNK cells facilitate the creation of the appropriate microenvironment for placental and fetal development, which is important for a successful pregnancy.

5 | GENE REGULATION BY MICRORNA IN NK CELLS

5.1 | MicroRNA Regulate NK Cell Development

Derived from the bone marrow, NK cells undergo additional differentiation and maturation in peripheral organs.[49,50] The miR-15/16 family, which regulates key biologic processes, is abundantly expressed in NK cells. The transcriptional factor Myb is a direct target of miR-15/16, which is preferentially expressed in immature NK cells. miR-15/16 knockout in a mouse model increased the expression of Myb. Importantly, maturation of miR-15/16 knockout NK cells was rescued by silencing of Myb expression. Myb overexpression in wild type NK

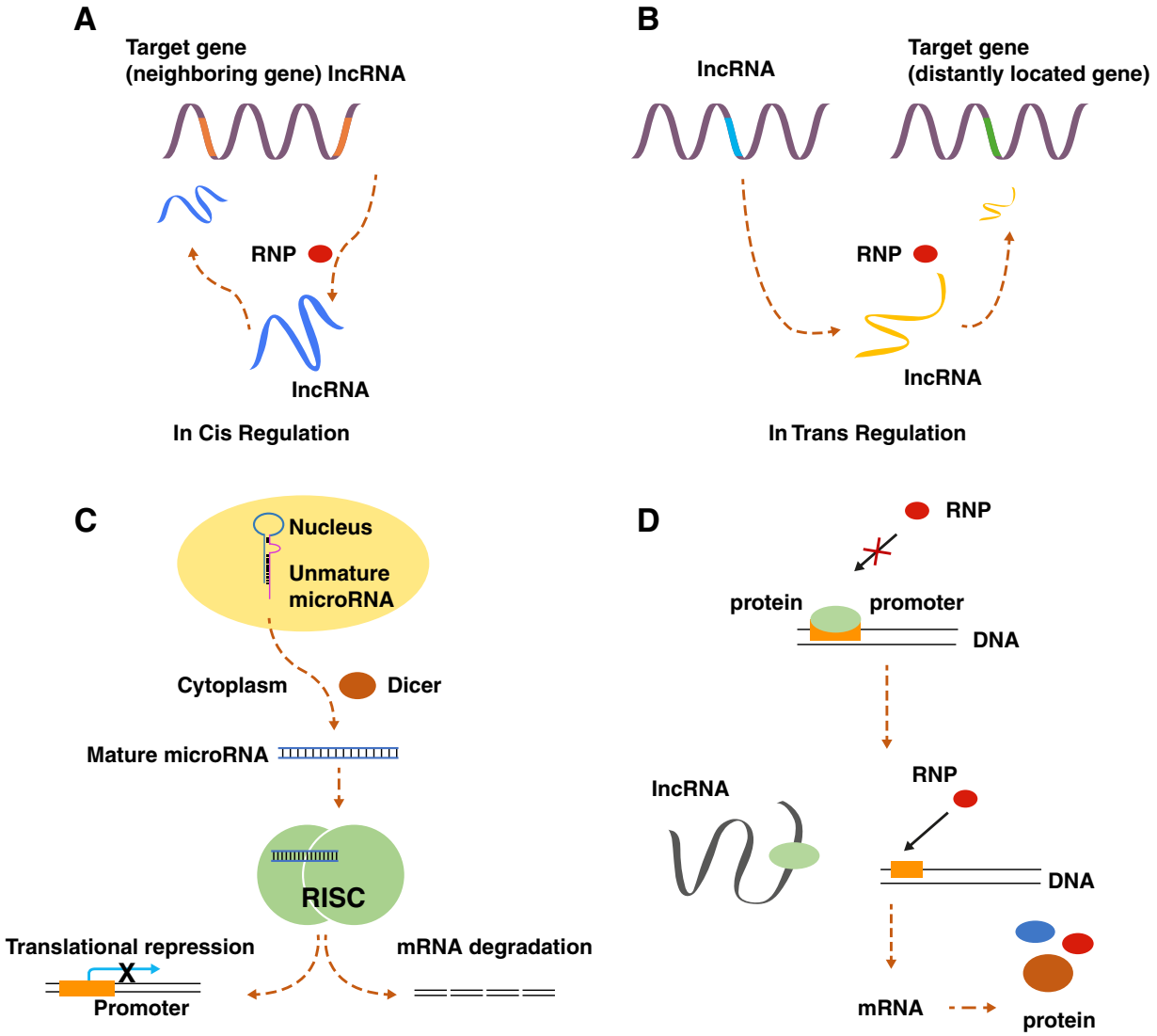

FIGURE 1 A, B: Regulation of lncRNA in trans or cis. When regulation is restricted in the same chromosome from which they are transcribed, lncRNAs act in cis (A), or in trans (B). C: Mature microRNA specifically binds to target mRNA and induces translational repression or mRNA degradation. D: Interaction of lncRNA with protein. When protein binds to lncRNA, the promoter of the gene is released from the DNA binding domain of the protein and transcription of the target gene is activated

cells led to a defective NK cell maturation phenotype, which had the same effect in miR-15/16 knockout NK cells,[51] indicating that miR-15/16 negatively regulates Myb expression during NK cell development. NK cells are known to secrete cytokines like granzyme B and perforin to lyse target cells.[52,53] However, these functions depend on appropriate NK cell maturation, indicating that miR-15/16 is a key regulator in NK cell development.

miR-181a and miR-181b, located on chromosome 1 and 9, respectively, are the most well-studied members of the miR-181 family.[54] The expression of miR-181 has a significant impact on the maturation of $CD34^+$ hematopoietic progenitor cells to human NK cells, as well as IFN-γ secretion in primary $CD56^+$ NK cells. Interestingly, Nemo-like kinase (NLK) negatively regulates Notch-dependent transcriptional activation via down-regulating the formation of its ternary complex. Further, NLK is regulated by miR-181 specifically through sites on the 3′-untranslated region.[54] Overexpression of miR-181 down-regulates NLK expressio;n[55,56] thus, miR-181 promotes NK cell development via the Notch signaling pathway.[54]

T-box-related TBX21(TBET) and eomesodermin (EOMES) control the final stage of NK cell differentiation in both humans and mice, and are key transcriptional factors that are involved in NK cell development.[57,58] The impact of miR-29b on TBET and EOMES has been studied in T cells.[59,60] A high level of miR-29b in NK cells was identified in a *de novo* acute myeloid leukemia mouse model. In this model, miR-29b specifically down-regulated TEBT and EOMES expression, inhibiting maturation of NK cells in this mouse model. NK cells play an important role in the death of tumor cells; interestingly, a high level of miR-29b induced the depletion of NK cells, indicating a potential mechanism of microRNA-mediated immune-escape in cancer.[61]

5.2 | MicroRNAs Regulate the Function of NK Cells

NK cells migrate to infected tissues in response to various infections. The distribution of NK cells in physiologic and pathologic conditions is dictated by chemokine receptors.[62] CX_3CR1 is an important surface chemokine receptor that mediates the migration of $CD56^{dim}$ NK cells.[63] As an immunomodulatory cytokine, TGF-beta1 suppressed the anti-tumor activity of NK cells. The expression of miR-27a-5p is increased in NK cells responding to TGF-beta1 stimulation, and negatively modulates the expression of CX_3CR1 in NK cells. Hence, miR-27a-5p acts as a pivotal TGF-β1-induced regulator of CX_3CR1 expression that affects the migration of NK cells to peripheral tissues, including tumor sites.[62]

Studying the microRNA in human NK cell biology contributes to a better understanding of microRNA regulation in NK cells at the molecular level. miR-362-5p was found to be highly expressed in peripheral blood. It is known that NF-κB signaling is involved in NK cell activity and cytokine production.[64–66] Cylindromatosis (CYLD), a negative regulator of NF-κB signaling and the target of miR-362-5p, is down-regulated in miR-362-5p overexpressed cells, which leads to the up-regulation of IFN-γ, perforin, granzyme-B, and CD107a in human primary NK cells. These phenotypes arise with the silencing of CYLD in human primary NK cells,[67] suggesting that miR-362-5p promotes the effector function of human NK cells by targeting CYLD.

IFN-γ is a critical type II interferon cytokine that plays an important role in the immune response, such as responding to infectious pathogens in NK cells, and is also important to the maturation, activation, and functions of monocytes.[19,68–70] Hongwei Wang et al. found that miR-146a directly targeted IRAK1 and TRAF6, the upstream components of the NK-κB pathway, down-regulating NF-κB p65 phosphorylation.[71] Thus, IFN-γ expression was decreased. Another clinical study in chronic hepatitis B (CHB) and hepatocellular carcinoma (HCC) also showed the correlation between miR-146a and IFN-γ. A high expression level of miR-146a was found in CHB and HCC patients compared with healthy donors. Forced expression of miR-146a reduced NK cell cytotoxicity and IFN-γ production via targeting STAT1.[72] This may explain the reduction of IFN-γ and the inhibition of the cytotoxicity of NK cells in CHB and HCC patients. Furthermore, the multiple targets of miR-146a suggest that microRNA regulation is complex and may target different mRNA in different physiologic processes. miR-155 was previously reported to up-regulate IFN-γ production via down-regulating SHIP1 in NK cells.[73] A recent study of immune-active patients among those with hepatitis B virus (HBV) infection found the miR-155, a positive regulator of IFN-γ in NK cells, was expressed much lower in patients than in healthy controls. In response to HBV infection in patients, down-regulation of miR-155 impaired IFN-γ secretion through targeting suppressor of cytokine signaling 1 (SOCS1) in the JAK/STAT signaling pathway.[74] Positive regulators of IFN-γ, such as miR-181[54] and miR-155,[73] together with the negative regulator miR-146, balance the expression of IFN-γ in NK cells during the immune response.

NKG2D, which is expressed on the surface of NK cells, is an important receptor that activates the function of NK cells.[75,76] miR-30c increased the cytotoxicity of NKL cells by up-regulating the expression of NKG2D. In addition, the expression of FasL is increased in NKL cells and peripheral blood NK cells. However, only 40% of freshly isolated peripheral blood NK cells express high levels of NKG2D after overexpression of miR-30c, suggesting that microRNA may have a complicated and delicate balance in the immune system.[77] Ligands of NKG2D (NKG2DL) include the major histocompatibility complex class I chain-related proteins A and B (MICA/B), and the unique long 16 binding proteins 1–6 (ULBP1-6). A recent study showed that in breast cancer, the miR-17-92 cluster specifically targeted the 3′UTR of MICA/B. Thus, up-regulating NKG2DL expression by silencing the microRNA could enhance NK cell-mediated cytotoxicity.[78] miR-182 expression was found to be dysregulated in the NK cells of patients with hepatitis C virus (HCV)-induced HCC, compared with healthy controls.[79] *In silico* analysis showed that miR-182 may bind to the 5′UTR and 3′UTR of NKG2A and NKG2D, respectively. Further study showed that overexpression of miR-182 in HCC NK cells could increase the expression of NKG2A and NKG2D, suggesting that miR-182 may augment NK-cell cytotoxicity against liver cancer via modulating NKG2D and NKG2A expression.[80] MicroRNA in NK cells may be an effective approach to activating NK cell-mediated clearance of tumor cells and may enhance NK cell-based immunotherapy against various cancers.

GrzB plays an important role during viral infection in NK cell-mediated cytotoxicity. It is known that miR-378 directly targets perforin in the cord and peripheral blood in response to IFN-α stimulation.[81] In addition, another study demonstrated that miR-378 is down-regulated in NK cells during dengue viral infection, thus increasing GrzB production in NK cells.[82] Taken together with the previous study,[81] this indicates that miR-378 is a negative regulator of human NK cell cytotoxicity

The decidual immune cells are important to the maintenance of pregnancy. Decidua invades the uterine mucosa during the first trimester of pregnancy and is crucial for controlling the depth of invasion of trophoblasts. dNK cells secrete regulatory molecules, cytokines, and chemokines to mediate trophoblast invasion and vascular remodeling.[83] These functions suggest a potential role of NK cells in unexplained recurrent spontaneous abortion (URSA). Li et al. found that the abnormal expression of microRNA like miR-34a-3p/5p, miR-141-3p/5p, and miR-24 in dNK cells could be associated with URSA, showing that microRNA might be important to the diagnosis of URSA and may facilitate the development of gene therapies targeted against URSA.[84] The maternal-fetal interface supplies the appropriate microenvironment for a normal pregnancy. There are various immune cells located in the maternal-fetal interface, and NK cells account for approximately 70% of all immune cells, indicating that NK cells in the maternal-fetal interface are crucial for defenses against infection, immune tolerance, and placental development.[85] The deregulated expression of ncRNAs involved in the regulation of immune cells may directly regulate the expression of cytokines and placental development, which may affect the outcomes of pregnancy. Hence, ncRNAs also can act as a marker to indicate the outcomes of pregnancy, which may useful for prenatal diagnosis.

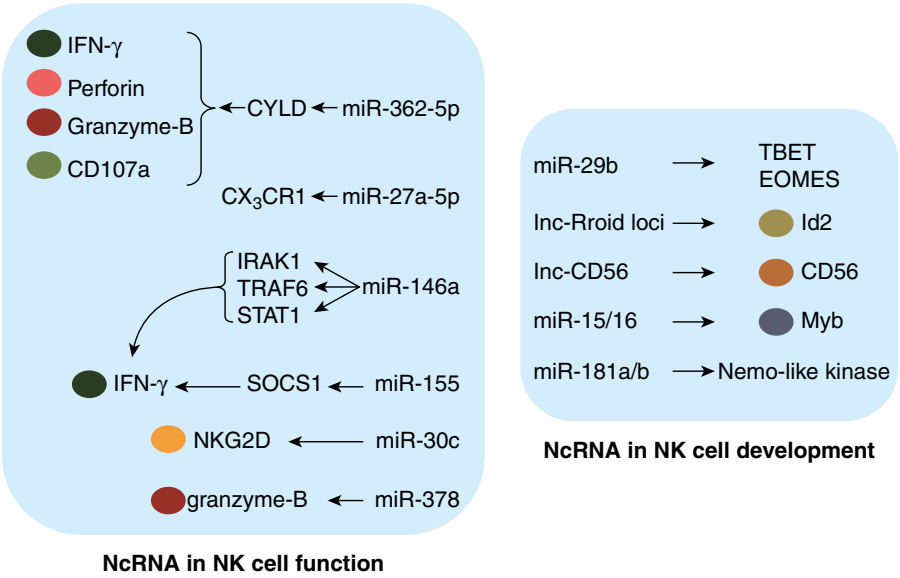

FIGURE 2 Key noncoding RNA involved in NK cell biology

6 | CONCLUDING REMARKS

As important regulators in biologic process, ncRNA are involved in many aspects of NK cell biology (Fig. 2). In response to the different immune conditions, ncRNA modulate the expression of various cytokines. lncRNA, such as lnc-CD56[46] and Rroid locus,[20] regulate NK cell development. Receptors, such as NKG2D[77] and its ligand NKG2L,[78] are regulated by microRNA. Cytokines, such as IFN-γ, are regulated by several microRNA to balance expression levels, illustrating the complexity of ncRNA regulation in the immune response. These studies strongly suggest that ncRNA has roles in the various physiologic process of NK cells.

Viruses such as HBV and HCV regulate cytokine expression via the induction of aberrant microRNA expression. This suggests that viral infection may affect the expression of microRNA or lncRNA. Hence, pathogen-induced abnormal expression of ncRNA in NK cells may play a key role in infection, which may also be a new aspect of NK cell biology for future study. Another emerging area of investigation is the role of lncRNA in immune escape. MicroRNA was found to be involved in the regulation of tumor cell escape from NK cell clearance.[61] It is essential to explore whether lncRNA are involved in immune escape in NK cells. Human NK cells from different tissues have different functions and phenotypes. Tissue-specific ncRNA may influence NK cell function in different peripheral lymphoid organs, and exploring the lncRNA and microRNA profiles of NK cells from different tissues would help us to clearly understand specific ncRNA expression. Through silencing or forced expression techniques, we can determine the various functions of tissue specific ncRNA in NK cells.

However, there are fewer studies focused on lncRNA than there are on microRNA in NK cells. Nonetheless, this does not mean that lncRNA is not as important as microRNA. There are various functional lncRNA in different immune cells, for example, NeST regulates IFN-γ expression in T cells,[4] lnc-DC regulates human DC differentiation,[86] and lincRNA-EPS controls H3K4me3, chromatin accessibility, and nucleosome positioning in macrophages.[22,87] These findings highlight the fact that lncRNA may also play crucial roles in NK cell biology. MicroRNA has been a research topic in the study of immune cell for many years, where lncRNA may be the next focus due to its increasing relevance.

To date, only a small number of ncRNA, especially lncRNA, have been identified in NK cells. The functional roles of the majority ncRNA are still unknown, and there is growing evidence that ncRNA play key roles in regulating the differentiation, activation, and function of NK cells. The role of ncRNA in NK cells in the innate and adaptive immune responses is complex but deserves attention. With the development of whole transcriptome sequencing and bioinformatics analysis, novel lncRNAs and microRNAs and their functions will be determined in NK cells.

AUTHORSHIP

C.Y. wrote the review and drew the figures; C.S. and T.F. made the table; and H.L. edited the review.

ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (Nos. 81671497, 81471848).

DISCLOSURES

The authors declare no conflicts of interest.

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How to cite this article: Yang C, Shen C, Feng T, Li H. Noncoding RNA in NK cells. *J Leukoc Biol*. 2019;105:63–71. https://doi.org/10.1002/JLB.1RU0518-197RR