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ABSTRACT

Natural killer cells (NK cells) are a type of cytotoxic lymphocytes which are involved in innate immunity, alongside with assisting with adaptive immune response. Since they have cytotoxic effects, disruptions in their functionality and development leads to a variety of conditions, whether malignant or non-malignant. The profile and interaction of these non-coding RNAs and NK cells in different conditions is extensively studied, and it is now approved that if dysregulated, non-coding RNAs have detrimental effects on NK cell activity and can contribute to the pathogenesis of diverse disorders. In this review, we aim at a thorough inspection on the role of different non-coding RNAs on the activity and development of NK cells, in a broad spectrum of conditions, including blood-related disorders, viral infections, neurological diseases, gastrointestinal disorders, lung disorders, reproductive system conditions and other types of maladies, alongside with providing insight to the future non-coding RNA-NK cell studies.

1. Introduction

Natural killer cells (NK) are cytotoxic immune cells that actively counteract effects of stressed cells like viral infected cells or cancer cells [1]. NK cells are originated from hematopoietic stem cells (HSCs) and their lineage can be traced back to the common lymphoid progenitor cells (CLPs) which are responsible for producing Pro-B, Pre-T and early NK cell progenitor (NKP) cells [2]. Despite being generally considered as cells of innate immune system, the ability of NK cells to exhibit memory activity and adapting to their environment has led to the understanding that these cells are somewhere between innate and adaptive immunity [3]. NK cells are identified by expression of Clusters of Differentiation (CD) 56 and CD16, and lack of CD3 on their surface ($CD56^+$, $CD3^-$) [4]. Morphologically, a NK cell consists of large granules, and eliminates cancerous cells similar to T cells, by secreting perforin and granzyme, or by inducing death receptor mediated apoptosis [5]. It is worth mentioning that NK cells not only act directly against pathogens, but they are also capable of modulating other immune cells like macrophages and dendritic cells via secreting different substances such as interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α) and interleukins 10, 5, and 13 [1]. As a rule of thumb, any type of cell that is capable of regulating, can also be regulated, and NK cells are not exception. These NK cells regulators could be "non-coding RNAs" (6).

The first established non-coding was a tRNA which transfers Ala amino acid for translation process. This tRNA was extracted from yeast [7]. Non-coding RNAs are types of RNA that are not translated into proteins. Despite of not contributing to protein production, these RNAs have functional and crucial roles through different mechanisms. For a long time, different types of non-coding RNAs such as long non-coding RNAs (lncRNAs), microRNAs (miRNAs) and circular RNAs were considered as "junk" byproducts of cells [8]. However, with recent advances in functional studies and high throughput techniques, pivotal roles of non-coding RNAs in different regulatory mechanisms have now been determined [9–11]. Briefly, lncRNAs are longer than 200 bp in

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length, and are transcribed by RNA pol II. They undergo capping and poly adenylation, and have diverse pivotal roles in different regulatory mechanisms. LncRNAs regulate gene expression at different levels, including the regulation of gene expression through miRNA sponging. By absorbing miRNAs, lncRNAs ultimately regulate downstream targets [12]. On the other hand, miRNAs are relatively short molecules with average length of 22 bp, and similar to lncRNA, they have diverse roles in cellular mechanism. Their mechanism of action mainly occurs through targeting 3′ untranslated region (3′ UTR) of an mRNA and degradation of it. However, miRNAs are not always inhibitory molecules, and they are also capable of activating downstream genes [13]. Circular RNAs are another group of non-coding RNAs, and they are formed through back-splicing or exon skipping of pre-mRNAs [14]. All three types of mentioned non-coding RNAs play important roles in the pathology of different disorders, whether malignant or non-malignant in nature [15–17].

Interactions between non-coding RNAs and NK cells are studied to a great extent [6]. Different types of non-coding RNAs have different effects on NK cells, and they exert these effects at distinct stages. In this review, we aim at discussing different interactions and the mechanisms by which non-coding RNAs regulate NK cells activity.

1.1. Non-coding RNA profile for NK cells activity in blood-related diseases

Since NK cells constitute 10–15% of circulating mononuclear cells [4], there is no surprise that their interactions with non-coding RNAs are critical and any disruptions in these interactions could have adverse effects. Natural killer/T Cell Lymphoma (NKTCL) is a subtype of non-Hodgkin lymphoma with highly invasive attributes. This malignancy is related to Epstein–Barr virus carcinogenesis, and despite implementing novel therapies such as immunotherapy, prognosis is still poor and many patients experience relapse [18]. In a 2021 study, downregulated levels of a miRNA, namely miR-188–5p was seen in NKTCL patients. Upon forced upregulation in a subset of NK cell lines, it was shown that miR-188–5p down-regulates XRCC5, and subsequently reduces tumorigenesis process [19]. XRCC5 (also known as Ku80) exerts oncogenic roles in various cancers, and the main function of it is repairing double-strand DNA breaks [20]. Additionally, a number of polymorphisms in XRCC5 gene are associated with different cancers [21], so it might be wise to perform SNP analysis on NKTCL patients as well.

With regard to biomarker capability, a study has shown that miR-155 is upregulated in the serum of NKTCL patients (20 NKTCL patients compared to 10 healthy individuals) [22]. Additionally, it was shown that FOXO3a serves as the target gene of miR-155. In this study, flow-cytometry analysis showed that if YTS and SNK-6 cells are infected with Lenti-*anti*-miR-155, apoptosis rate of cells increases. Overall, miR-155 could be a potential target for future studies on NKTCL patients, with an especial focus on the molecular basis of it.

A combination of wet lab and dry lab techniques, has identified Circ-ADARB1 as a predictive biomarker for NKTCL patients [23]. Microarray analysis led to pinpointing of 6137 upregulated circular RNAs in NKTLC patients, with Circ-ADARB1 being the most significant one. Assays in SNK-6 cells (EBV + NK cells) have shown that knockdown of mentioned circular RNA, upregulates miR-214–3p and this miRNA targets STAT3. Therefore, Circ-ADARB1 acts as an oncogenic element in the pathogenesis of NKTCL [23].

XIST (X-inactive specific transcript) is a lncRNA with diverse pivotal roles in cellular stability. One of the most studied functions of this lncRNA is its contribution to X chromosome inactivation in females, which is responsible for dosage compensation [24]. Besides, XIST has been known for its direct and indirect interventions in pathogenesis of different conditions [25]. In a specific type of NKTLC, called Extranodal natural killer/T-cell lymphoma (ENKL), XIST has shown upregulated expression. Similar to other lncRNA-miRNA-mRNA axes, in this study, it was shown that XIST sponges miR-497, and upregulates Bcl-w, which is responsible for restraining proapoptotic factors [26]. XIST has been shown to have oncogenic roles in different types of cancers, however, in case of hematological malignancies, a study conducted on mice showed that XIST could act as a tumor suppressor gene in highly aggressive myeloproliferative neoplasm [27], and this makes the therapeutic approaches for XIST challenging, and identifying the exact role of this lncRNA requires further research.

Table 1 summarizes different studies related to interactions between non-coding RNAs and blood related diseases.

1.2. Non-coding RNA profile for NK cells activity in viral diseases

Viral infections are mostly known for their inflammatory responses, and upon infection, they can activate NK cells through various approaches. Once the cell is infected, stress molecules such as MICA and MICB (MHC class I polypeptide-related sequence A and B), and ULBP1-6 (UL16-binding proteins) are overexpressed on the surface of the cell, and NK cells are capable of recognizing this “stress molecules”. Subsequent to recognition, NK cells secrete granzyme and perforin, leading to cellular death of infected cell. In addition, by releasing cytokines such as interferon gamma, NK cells can trigger other immune cells as well [1].

Dengue Virus (DENV) is single-stranded positive-sense RNA virus that spreads from Aedes species mosquito to human. There are four types of DENV, and typical symptoms of their infection include rashes, pain, and nausea [36]. A study has shown that DENV infection causes downregulation of miR-378 in NK cells, and this downregulation is associated with upregulated levels of granzyme B (GrzB). This study shed light on the interaction between non-coding RNAs and of the most important enzymes, GrzB, which is present in NK cells and $CD8^+$ cells. It seems that the cells have a switch mechanism, and upon infection, maintain GrzB levels by downregulating miR-378 [37] (Fig. 1) (see Fig. 2).

In addition to miRNAs, lncRNAs have also proven to be associated with function of NK cells in viral infections. An interesting study with this regard was centered around MALAT1 role in hepatitis B virus (HBV) infection. Tenofovir disoproxil fumarate (TDF) is an FDA approved drug for antiviral therapy against HBV and HIV infections. Most of time, purpose of TDF administration is to prevent viral transmission from mother to fetus during pregnancy [38]. In order to elucidate the role of MALAT1 in HBV affected pregnancies upon TDF administration, expression level of it was analyzed in NK cells before and after TDF treatment. Interestingly, it was shown and TDF causes reduced levels of MALAT1 in HBV infected pregnant women. Furthermore, it was demonstrated that MALAT1 reduces IFN-γ expression, so TDF actually contributes to elevated levels of IFN-γ in NK cells by reducing MALAT1 [39].

Zika Virus (ZIKV) is another type of virus that is also transmitted by Aedes mosquitoes. Symptoms are usually similar to DENV infection, but the main problem arises in the pregnancies that are affected with ZIKV. Infection with ZIKV in pregnancy could lead to microcephaly and irreversible CNS problems [40]. A study conducted by Li et al. showed that Interferon β (IFNβ) treatment results in linc-EPHA6-1 upregulation in ZIKV infected A549 cells. Upon treatment with IFNβ, exosomal levels of linc-EPHA6-1 are elevated. Additionally, it was shown that this lncRNA sponges miR-4485–5p, and leads to NKp46 upregulation, which is a natural cytotoxicity receptor. This axis shows the important role of exosomes on cytotoxicity, and marks the significance of exosomal studies in NK cells [41].

Table 2 summarizes different studies related to interactions between non-coding RNAs and NK cells in viral infections.

1.3. Non-coding RNA profile for NK cells activity in neurological diseases

It is widely accepted that NK cells play crucial roles in the pathogenesis of different neurological conditions. For instance, a study

Table 1
Non-coding RNA profile for NK cells activity in blood-related diseases.

Diseases	Non-coding RNAs	Human/Animal Study	Cell Lines	CD Cell Markers	Targets & Pathways	Kaplan Meier	Observation	Ref
Natural killer/T Cell Lymphoma (NKTCL)	miR-188–5p (Down)	HTS	Human TR-NK cell (tissue-resident NK cells), NK-92, SNK-1, SNK-6, HANK-1, KHYG-1	–	XRCC5	+	miR-188–5p by targeting XRCC5. Could decrease NKTCL tumorigenesis.	[19]
NKTCL	miR-155 (Up)	HBS, BGI, BLAST, GO, miRNA base database	YTS, SNK-6	–	–	–	miR-155 is higher in the serum of NKTCL patients than in the serum of healthy donors so it could be a biomarker for NKTCL.	[22]
NKTCL	miR-BART2-5p (Up)	HBS	KAI3, SNK-6, SNT-8	–	–	+	miR-BART2-5p could be a new predictive and diagnostic NKTCL factor.	[28]
NKTCL	Circ-KIF4A (Up)	HTS	NK01, NK02, NKTL-7, NKTL-16, NKTL-22, NKTL-29, SNK-1, HANK-1, NK-YS	–	miR-1231	+	CircKIF4A could upregulate BCL11A and PDK1 expression levels by targeting miR-1231 through NKTL tumorigenesis.	[29]
NKTCL	Circ-ADARB1 (Up)	HBS, BALB/c nude mice miRanda, Targetscan, and ENCORI database	YT, HEK293T, SNK-6	–	miR-214, STAT3	–	CircADARB1 could be a predictive and diagnostic biomarker and could enhance the proliferation of NKTCL cells by targeting STAT3 and miR-214.	[30]
NKTCL	ZFAS1, TERC, MIR155HG, SNHG5 (All of them up)	HBS	NK-92, KHYG1	CD56, CD3	–	–	All mentioned lncRNAs are involved in NKTCL pathology.	[31]
Extranodal Natural Killer/T-Cell Lymphoma (ENKL)	XIST (Up)	HTS	NK-92, SNK-6, SNT-8, KHYG-1	–	miR-497	–	XIST could enhance Bcl-w expression level, and therefore ENKL cell proliferation by sponging miR-497.	[26]
NKTCL-Associated Hemophagocytic Syndrome (NKTCL-LAHS)	Cluster of circRNAs	KEGG and GO database	–	–	–	–	These circRNAs could be a therapeutic, diagnostic, and prognostic factor of NKTCL-LAHS.	[32]
B-Cell Precursor Acute Lymphoblastic Leukemia (BCP-ALL)	miR-582 (Down)	HTS, NCG mice, TargetScan database	NK-92, SUP-B15, NALM-6, KOPN-8	CD56, CD107a	PPTC7	–	miR-582 has an apoptotic effect against BCP-ALL via sponging PPTC7 but could decrease NK cells cytotoxicity against them by blocking CD276 mRNA.	[33]
T-Cell Acute Lymphoblastic Leukemia (T-ALL)	miR-29 b (Up)	HBS, C57BL/6 mice	EL4	CD56, CD16	–	–	miR-29 b could suppress NK cell cytotoxicity and then causes immune evasion of blast cell in T-ALL.	[34]
Acute Myeloid Leukemia (AML)	miR-181a (Down)	Healthy HBS, TargetScan database	Human PB-NK cells, KG-1, U-937	CD107a	MAP2K1, MAP3K10, MCL-1, BCL-2	–	NK cell cytotoxicity against blast cells could be increased through down-regulation of tyrosine kinase and BCL-2 family by miR-181a.	[35]

showed that in mouse models of CNS listeriosis, NK cells are the main source of IFN-γ that fights against bacterial growth [49]. In the case of neurogenerative diseases, such as Alzheimer' disease, Parkinson and multiple sclerosis, NK cell has shown prominent roles [50]. In multiple sclerosis, functional and efficient activity of NK cells are decreased as the disease progresses [51]. So, one should also consider the possible involvement of non-coding RNAs in the regulation of NK cells activity, especially in neurological conditions.

Chronic Fatigue Syndrome (CFS), also known as myalgic encephalomyelitis, is a neurological condition which is usually characterized by extreme fatigue and inability to perform daily tasks. Despite of the extensive advances in the technological aspects of medical genetics, genetic risk factors for CFS are still widely unknown. Studies have been done on the mitochondrial inheritance of disease, since mtDNA is responsible for the production of crucial enzymes involved in ATP synthesis [52].

A microarray analysis on PBMC of CFS/ME patients showed altered levels of 35 miRNAs. Further analysis and validation by qPCR showed that two specific miRNAs, namely miR-99 b and miR-330 are upregulated in NK cells of CFS patients [53]. It was demonstrated that this upregulation leads to altered expression of 37 genes, mainly involved in the cellular activation. This study proved that neurological conditions are capable of altering non-coding RNA profile, and subsequently affecting NK cells activity.

Since non-coding RNAs exert a variety of effects, their dysregulation also varies from one case to another. In ischemic stroke, two distinct studies were performed with regard to miRNA interaction with NK cell activity in the affected individuals. Firstly, it was shown that CXCL8-CXCR2 chemotactic axis recruits granulocytes and NK cells to the site of ischemia. Interestingly, CXCR2 itself is regulated by miR-4437. It was evident that CXCR2 upregulation is a direct result of miR-4437 down-regulation [54]. In another study performed on C57BL/6 mice models, miR-1224 showed significant upregulation [55]. Elevated levels of this miRNA led to inhibition of SP1, which controls cytokine secretion in NK cells. Overall, this study proved the importance of non-coding RNAs in NK cell regulation. Moreover, these transcripts have the potential to be targeted in the future [55]. Same condition also applies for neuroblastoma, which has shown different dysregulations in its NK cell activity,

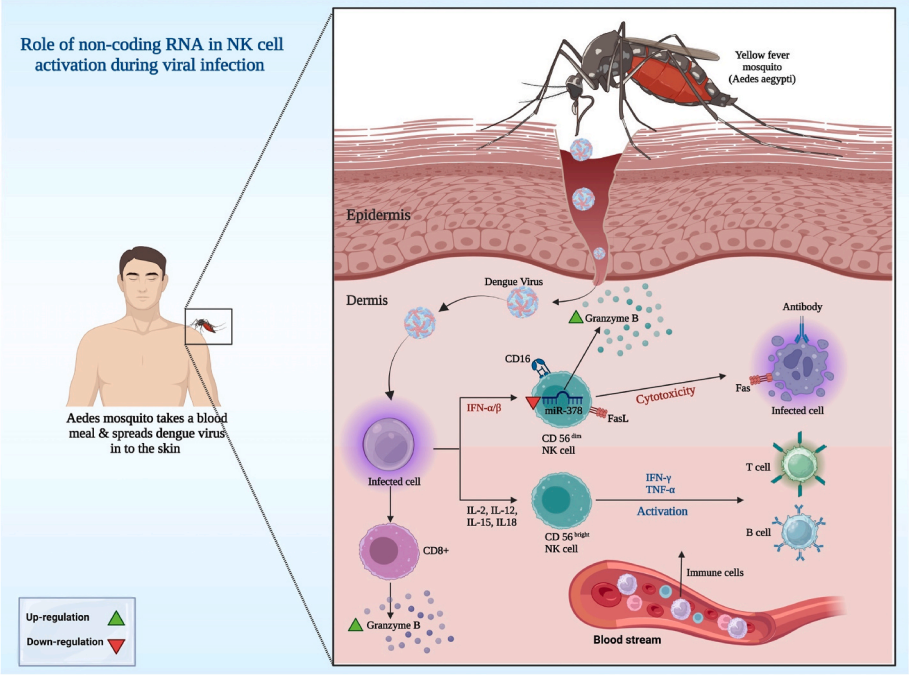

Fig. 1. The illustration shows the activation of NK cells and $CD8^+$ cells during dengue virus infection. MiR-378 in NK cells is downregulated by DENV infection, and this downregulation is accompanied by an increase in granzyme B (GrzB) levels, which is present in NK cells and $CD8^+$ cells.

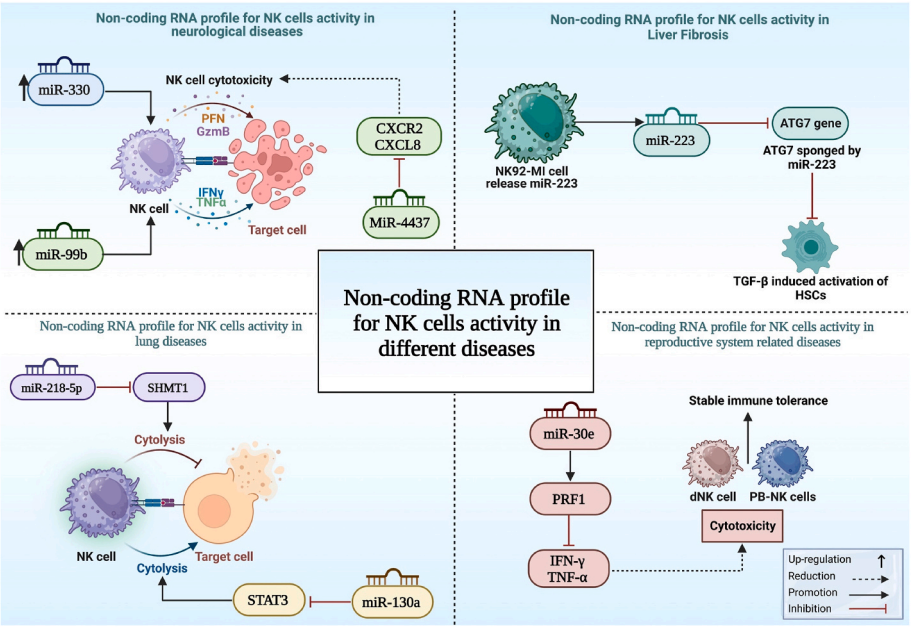

Fig. 2. Specialized non-coding RNA profiles increase awareness of NK cell activity in different disease pathologies.

mainly due to dysregulated microRNAs (Table 3).

1.4. Non-coding RNA profile for NK cells activity in gastrointestinal diseases

Liver fibrosis is a condition in which the scar tissue and extracellular matrix (ECM) accumulate in different parts of liver and ultimately results in liver failure, usually reversed by liver transplantation [59]. An interesting study conducted in 2020 showed that exosomal miR-223 have antifibrotic properties, and could be a potential target for future studies [60]. Mechanistically, it was shown that miR-223 released from NK92-MI cells, targets ATG7, which is a key autophagy gene. Upon targeting, this miRNA inhibits TGF-β induced activation of hepatic stellate cells (HSCs). HSCs are shown to have detrimental effects on liver fibrosis and they contribute to its progression [61]. Hence, miRNAs have shown to be regulated by NK cells, and they are not the regulators in this specific study.

Hepatocellular carcinoma (HCC) is amongst the cancers with high mortality rate, and different risk factors include alcohol consumption, viral infection like hepatitis B/C and genetic predispositions. In the category of gastrointestinal diseases, interaction of NK cells and non-coding RNAs, especially miRNAs, has been studied to a greater extent

Table 2
Non-coding RNA profile for NK cells activity in viral diseases.

Diseases	Non-coding RNAs	Human/Animal Study	Cell Lines	CD Cell Markers	Targets & Pathways	Kaplan Meier Analysis	Observation	Ref
Dengue Virus (DENV)	miR-378 (Down)	HBS	–	CD3, CD56, CD107	GrzB	–	During DENV infection GrzB expression is induced by miR-378 in human NK cells and $CD8^+$ T cells.	[37]
HHV-6A/6 B	The cluster of miRNAs (Up)	–	NK-92	–	–	–	HHV-6A/6 B induces expression of these miRs that decrease NK cell activity.	[42]
Hepatitis C Virus (HCV)	miR-29a (Up)	HBS	Human PB-NK cells, Huh7	–	PU.1, miR-155, NKGD2, Prf-1	–	HCV infection could decrease NK cytolysis activation by targeting the NKG2D receptor, PU.1, and Prf-1.	[43]
HCV	miR-155 (Down)	HBS	Human PB-NK cells, NK-92, Huh-7	CD3, CD56, CD16	Tim-3	–	miR-155 could increase *IFN-γ* production in NK cells by inhibiting the Tim-3/T-bet/STAT-5 signaling pathway.	[44]
HCV	miR-182 (Down)	HBS, VITA, VBRC, mic rorna.org, Target Scan, mirDIP, and Segal lab database	Human PB-NK cells, Huh7	–	ULBP2, NKGA/D	–	miR-182 could decrease NKG2A/D and NK cell activity by sponging ULBP2 mRNA and could increase HCV genotypes 2 and 4 proliferation.	[45]
HCV	miR-122 (Up)	HBS	Human PB-NK cells	CD56, CD16	–	–	*Anti*-miR-122 could attenuate HCV RNA expression and NK cell activation.	[46]
Chronic Hepatitis B (CHB)	miR-155 (Down)	HBS	Human PB-NK cell, HepG2.2.15	CD3, CD56, CD16, CD69, CD107a	SOCS1	–	Dysregulation of miR-155 could attenuate NK cell activation by sponging SOCS1.	[47]
hepatitis B virus (HBV)	MALAT1 (Up)	HBS	Human PB-NK cell, NK-92	CD3, CD14, CD19, CD16,	miR-155–5p	–	Treatment with tenofovir disoproxil fumarate (TDF) in pregnant women with HBV infection could decrease lncRNA MALAT1 expression and increase the immune recovery of NK cells.	[39]
Human Cytomegalovirus (HCMV)	HCMV-miR-UL112 (Up)	Healthy HBS	Human PB-NK cells	CD56, CD3, CD107a	IFN-α/β	–	HCMV-miR-UL112 by dysregulating IFN-α/β could decrease NK cell function.	[48]
Zika Virus (ZIKV)	linc-EPHA6-1 (Down)	Healthy HBS	Human PB-NK cells, NK-92, A549, HEK293T	–	miR-4485–5p	–	linc-EPHA6-1 could suppress NK cell cytotoxicity against ZIKV by targeting miR-4485–5p that sponges NKp46.	[41]

Table 3
Non-coding RNA profile for NK cells activity in neurological diseases.

Diseases	miRNA	Human/ Animal Study	Cell Lines	CD Cell Markers	Targets & Pathways	Kaplan Meier Analysis	Observation	Ref
Chronic Fatigue Syndrome (CFS)/Myalgic Encephalomyelitis (ME)	miR-99 b and miR-330 (Both of them up)	HBS	Human PB-NK cells	CD3, CD56	–	–	Overexpression of miR-99 b and miR-330 could increase NK cell cytotoxicity in CFS/ME patients.	[53]
Ischemic Stroke	miR-4437 (Down)	HBS, TargetScan and GEO database	Human PB-NK cells	CD56	CXCR2	–	MiR-4437 b y sponging the CXCR2-CXCL8 pathway could decrease NK cell cytotoxicity.	[54]
Ischemic Stroke	miR-1224 (Up)	C57BL/6 mice KEGG and GO database	Mice TR-NK cells	CD69, CD3	Sp1	–	After ischemic stroke miR-1224 could decrease NK cell cytotoxicity by targeting Sp1.	[55]
Neuroblastoma (NB)	miR-15a-5p, miR-15 b-5p, (Down)	HTS, GEO database	Human PB-NK cells, NB-19, SK-N-BE [2], SK-N-AS, K562, NB975, $CD8^+$T	CD56, CD16, CD3, CD107a	PD-L1	+	MiR-15a/b via sponging PD-L1 could increase NK cells' cytolysis activation and lead to an immune response as an anti-tumor.	[56]
NB	miR-186 (Down)	Healthy HBS	Human PB-NK cells, CHLA-136, LAN-5	CD56, CD16, CD3	TGFBR1, TGFBR2, MYCN, AURKA	+	MiR-186 derived from NK cells could be a novel therapeutic biomarker for NB.	[57]
NB	miR-27a-5p (Up)	HBS	Human PB-NK cells, HEK293T	–	CX3CR1	–	Overexpression of TGF-β1 could decrease NK cell cytotoxicity by targeting miR-27a-5p that sponges CX3CR1.	[58]

in HCC. As mentioned earlier, one of the main roles of NK cells is fighting against cancerous cells, and this role is regulatable by non-coding RNAs. Recent studies have shown that HLA-G upregulation occurs in different cancers, especially HCC [62]. A recent study conducted by Want et al. showed that miR-152 is downregulated in HCC patients, and that this miRNA directly targets HLA-G. Conveniently, forced expression of miR-152 diminished HLA-G levels, and contributed to better recognition of cancerous cells by NK cells [63].

Expression analysis in primary NK cells from HCC patients and healthy controls showed downregulated and upregulated levels of miR-506 and STAT3, respectively, suggesting that STAT3 have a target site for miR-506 [64]. Interestingly, similar to miR-152, forced expression of miR-506 increases NK cells cytotoxicity by inhibiting STAT3. These types of studies demonstrate the significance of miRNAs in NK cell activity regulation. Moreover, a potential panel of inhibitors/activators of these miRNAs could be beneficial for NK cell functions in cancer patients.

MiRNAs are not the only type of dysregulated non-coding RNAs in

Table 4
Non-coding RNA profile for NK cells activity in gastrointestinal diseases.

Diseases	Non-coding RNA	Human/Animal Study	Cell Lines	CD Cell Markers	Targets & Pathways	Kaplan Meier	Observation	Ref
Liver Fibrosis	miR-223 (Down)	–	NK92-MI, LX-2	–	ATG7	–	miR-223 derived from NK cells could protect the hepatic cell against fibrosis by suppressing the activation of the hepatic stellate cell through sponging ATG7.	[60]
CHB & Hepatocellular Carcinoma (HCC)	miR-146a (Up)	HBS	NK-92, HepG2	CD107a	STAT1	–	miR-146a by sponging STAT1 could improve NK cell cytotoxicity against the liver cells.	[68]
HCC	miR-182 (Up)	HTS	Human PB-NK cells, Huh-7	–	NKG2D, NKG2A	–	miR-182 b y direct targeting NKG2A/D could increase NK-cell lysis activation against HCC cells.	[69]
HCC	miR-152 (Up)	–	Human PB-NK cells, HepG2.2.15, HepG2	–	HLA-G	–	miR-152 overexpression could improve NK cytotoxicity against HCC cells by direct targeting HLA-G.	[63]
HCC	miR-615–5p (Down)	HBS	Human PB-NK cells, HuH-7	CD56, CD16	IGF-1R	–	miR-615–5p by sponging IGF-1R could suppress NK cell function in HCC.	[70]
HCC	miR-544 (Up)	HBS, BALB/c nude mice	NK-92, HepG2	–	RUNX3	–	miR-544 could decrease NK cell cytotoxicity by downregulating NCR1 by sponging RUNX3.	[71]
HCC	miR-506 (Down)	HBS	Human PB-NK cells, NK-92, 293 T, HepG2, SMMC7721	–	STAT3	–	miR-506 b y sponging STAT3 could improve NK cell activity against HCC cells.	[64]
HCC	miR-889 (Up)	HTS	NK-92, SMMC7721, HepG2	–	MICB	–	Overexpression of miR-889 could decrease NK cell- cytotoxicity against HCC cells by sponging MICB.	[72]
HCC	miR-30c (Down)	Healthy HBS	Human PB-NK cells, SMMC-7721	CD107a	HMBOX1	–	microRNA-30c by increasing the level of NKG2D enhances NK cell cytolysis activity.	[73]
HCC	miR-561–5p (Up)	HTS, healthy HBS, BALB/c nu/nu mice, miRDB, and TargetScan database	Human PB-NK cells, HCCLM3, MHCC97 H/L, HepG2, Huh7, SMCC-7721, PLC/PRF/5	CD56	CX3CL1	+	miR-561–5p could enhance metastasis and tumor growth and decrease NK cell activity through the CX3CL1/CX3CR1/STAT3 signaling pathway.	[74]
HCC	circ_0048,674 (Up)	human HCC tissue samples, HBS, BALB/c nude mice	Human PB-NK cells, HCCLM3, HUV, THLE-2	–	miR-223–3p	–	Downregulation of circ_0048,674 could enhance NK cells' cytotoxicity against HCC by targeting the miR-223–3p/PD-L1 pathway.	[75]
HCC	circARSP91 (Down)	nude mice	NK-92MI, SK-Hep1, MHCC-97 h	–	ULBP1	–	NK cell activity could be enhanced against HCC cells by CircARSP91.	[65]
HCC	circ_0007456 (Down)	HTS, healthy HBS	Human PB-NK cells, Huh-7, HepG2, Hep3B, SMMC-7721, QGY-7703, L-02	–	miR-6852–3p	–	The miR6852–3p/ICAM-1 pathway signaling could be targeted by circ_0007456 and enhance the NK cytolysis activity against HCC.	[30]
Colorectal Cancer (CRC)	miR-20a (Up)	HTS	Human PB-NK cells, HCT116, HEK293T, SW480	CD107a, CD3, CD56	MICA	–	miR-20a could attenuate CRC sensitization to NK cells by sponging MICA.	[76]
CRC	miR-24 (Up)	HBS	Human PB-NK cells, NK92, LNK, SW620	–	Paxillin	–	Overexpression of miR-24 b y direct targeting Paxillin could attenuate NK cell's cytotoxicity against CRC cells.	[77]
CRC	SNHG10 (Up)	HTS, TCGA, GO, and KEGG database	NK92-MI, SW480	–	INHBC	–	LncRNA SNHG10 by direct targeting INHBC could attenuate the NK cell's cytotoxicity.	[67]
Pancreatic Cancer (PAC)	miR-3607–3p (Down)	HTS	Human PB-NK cells, Mia PaCa-2, PANC-1	–	IL-26	+	miR-3607–3p derived from NK cells could decrease metastatic behavior and proliferation of PAC cells by sponging IL-26.	[78]
PAC	circ_0000977 (Up)	HBS, HTS	Human PB-NK cells, Panc-1, 293 T	–	miR-153	–	Downregulation of circ_0000977 under hypoxia could attenuate the NK cell's cytotoxicity against PAC cells via targeting miR-153.	[79]
Gastric Cancer (GC)	GAS5 (Down)	HBS	Human PB-NK cells, MGC-803, NK-92	–	miR-18a	–	GAS5 by sponging miR-18a could promote NK cell's cytolysis activity against GC cells.	[80]

HCC. Dysregulated level of circular RNAs is also seen in NK cells of HCC patients. For instance, CircARSP91 (hsa_circ_0085,154) was upregulated in NK-92MI cell. In order to define its effect on HCC tumors, levels of this circular RNA were positively associated with NK cell cytotoxicity. It was reported that CircARSP91 upregulates ULBP1 in HCC cell lines, and sensitizes them to NK cell cytotoxicity [65]. However, another study showed that elevated levels of ULBP1 is associated with reduced survival rate of HCC patients, suggesting a dual effect of this gene in tumorigenesis of hepatic cells [66].

We had mentioned an exosomal miRNA, secreted from NK cells, with exertion of a particular function. LncRNAs are also eligible for exosomal packaging and secretion in order to regulate NK cell activity. For example, lncRNA SNHG10, which is expressed in a variety of tissues, has been reported to be an exosomal secreted lncRNA that has inhibitory effects on NK cells [67]. In this study, SW480 cells were cultured with TGF-β presented in media, in order to produce an EMT model. It was reported that colorectal cancer (CRC) cells are capable of inhibiting NK92-MI cells, mainly through exosomal SNHG10. This lncRNA upregulates INHBC, and disrupts different functions on NK cells. NK cell inhibition contributes to increased tumor growth, and therefore is associated with poor prognosis in CRC [67].

Table 4 summarizes studies related to interactions between NK cells and ncRNAs in gastrointestinal diseases.

1.5. Non-coding RNA profile for NK cells activity in lung diseases

Interactions between non-coding RNAs and NK cells activity in lung diseases is poorly understood, and a trivial number of studies have been conducted with this regard. One study is related to Tuberculosis (TB), caused by mycobacterium tuberculosis. In this bacterial infection, assessment of miR-155 in the serum of TB patients (n = 90) and healthy controls (n = 31), revealed a downregulated level of this miRNA in the serum of patients. Interestingly, it was shown that miR-155 levels are negatively associated with NK cells cytotoxicity. This study showed that by assessing the expression of a certain non-coding RNA, overall status of NK cells is predictable in TB patients, which paves the way for similar studies [81].

Two other studies are related to malignant conditions of lung, Non-Small Cell Lung Cancer (NSCLC) and Lung Adenocarcinoma (LA). In NSCLC patients, a similar condition like miR-506 sponging STAT3 in HCC [64] exists. The only difference in NSCLC patients is the type of miRNA. In this study, downregulated levels of miR-130a and upregulated STAT3 were seen in the primary NK cells isolated from NSCLC patients. Functional *in vitro* studies led to this conclusion that if overexpressed, miR-130a is capable of increasing NK cells lysis activity against A549 cells through STAT3 inhibition. This marks the importance of STAT3 in exerting adverse effects on NK cells, since a similar condition was also reported in HCC [64].

A study conducted by Yang et al. showed that miR-218–5p levels are upregulated in NK cells of LA patients. This upregulation was negatively associated with SHMT1 levels and functionality of NK cells. Conveniently, activation of NK cells by IL-2, reversed the mentioned ratio, and subsequent increase in NK cells activity occurred [82].

Conclusively, it is understood that miRNAs could act as a potential regulator of NK cell activity in lung diseases. Table 5 summarizes the mentioned studies.

1.6. Non-coding RNA profile for NK cells activity in reproductive system related diseases

Recurrent spontaneous abortion (RSA) refers to two or more than two recurrent pregnancy losses before 28 weeks of gestation with similar partner. There are different factors contributing to this condition, from chromosomal abnormalities to alcohol consumption and obesity [84]. It is interesting to know that NK cell-non-coding RNA interactions are also involved in RSA, since three different studies approved this concept [85–87]. Decidual natural killer (dNK) cells are a distinct type of NK cell that are mainly found in the lining of uterus during pregnancy. These types of cells assist with blood vessel remolding and maintenance of a stable immune system, as well as induction of immune tolerance and secretion of cytokines and growth factors for the development of placenta [88].

A study conducted in 2018 showed that miR-30e levels are downregulated in decidual tissues of women with RSA compared to normal pregnant women. This observation led to further researches to pinpoint the exact role of miR-30e in RSA occurrence. Interestingly, isolated PB-NK cells (peripheral blood natural killer cells) and dNK cells (decidual natural killer) from RSA women showed reduced levels of miR-30a, whereas PRF1 levels where upregulated in these cells. This observation suggested a negative correlation between miR-30a and PRF1, and the possible involvement of this axis in RSA occurrence. Further investigations showed that miR-30a inhibits expression of IFN-γ and TNF-α via suppressing PRF1, and this phenomenon leads to reduced level of cytotoxicity in dNK cells, leading to a stable immune tolerance [85]. Two other studies also confirmed the involvement of miRNA-NK cell interaction in RSA, which are discussed in Table 6.

In the category of malignant conditions of reproductive system, cervical cancer is the 4th common cancer in women, and prostate cancer is the 2nd prevalent cancer in men, according to WHO. As it is evident, NK cells are amongst the resident cells in tumor microenvironment (TME), and if they are fortified and reactivated in an immunosuppressed TME, they yield a better outcome for cervical cancer patients [89]. Therefore, any kind of NK cell regulatory element, especially non-coding RNAs, worth the attention and extensive research. Yu Zhu and colleagues demonstrated a controlling axis between miR-20a and NK cells in cervical cancer patients [90]. It was reported that NK cells derived from cervical cancer patients showed upregulated levels of miR-20a. This elevation was associated with reduced abundance of RUNX1 (which is mainly responsible for hematopoiesis [91]) and cytotoxicity of NK cells against cervical cancer cells. As anticipated, stimulation with IL-2 reversed the mentioned abundances, and led to elevated cytotoxicity of NK cells [90]. Compellingly, the same molecular mechanism was

Table 5
Non-coding RNA profile for NK cells activity in lung diseases.

Diseases	miRNA	Human/ Animal Study	Cell Lines	CD Cell Markers	Targets & Pathways	Kaplan Meier	Observation	Ref
Tuberculosis (TB)	miR-155 (Down)	HBS	Human PB-NK cells, MRC-5	CD56, CD16	–	–	miR-155 is dysregulated in the serum of TB patients and could suppress NK cell cytotoxicity against tuberculosis.	[81]
Non-Small Cell Lung Cancer (NSCLC)	miR-130a (Down)	HBS	Human PB-NK cells, HEK 293 T, NK-92, A549	–	STAT3	–	miR-130a by sponging STAT3 could increase NK cell's cytolysis activation against NSCLC cells.	[83]
Lung Adenocarcinoma (LA)	miR-218–5p (Up)	HBS	NK-92, LNK, A549, 293 T	–	SHMT1	–	miR-218–5p by sponging SHMT1 decreases NK cells' cytolysis activity against LA cells.	[82]

Table 6
Non-coding RNA profile for NK cells activity in reproductive system related diseases.

Diseases	Non-coding RNA	Human/Animal Study	Cell Lines	CD Cell Markers	Targets & Pathways	Kaplan Meier	Observation	Ref
Recurrent spontaneous abortion (RSA)	miR-30e (Down)	HBS	Human PB-NK cells (peripheral blood natural killer cells), dNK cells (decidual natural killer)	CD56, CD3, CD16	PRF1, KIR2DL1	–	Overexpression of miR-30e via the PRF1 could decrease the dNK and PB-NK cells' cytotoxicity.	[85]
RSA	miR-133a (Down)	HBS, HTS	Human dNK cells, Human PB-NK cells, HTR-8/SVneo	CD56, CD94, CD16, CD3	HLA-G	–	miR-133a via sponging HLA-G mRNA could suppress the cytotoxicity of dNK cells.	[86]
RSA	miR-24, miR-141–3p/5p, miR-34a-3p/5p (All of them up)	HTS, TargetScan database	–	CD56, CD3	PI3K-Akt, Wnt, MAPK, TGF-β	–	Overexpression of miR-24, miR-141–3p/5p, and miR-34a-3p/5p in dNK cells could be a predictive, diagnostic, and therapeutic factor in RSA.	[87]
Missed Abortion (MA)	A cluster of lncRNAs (32 of them up and 35 of them down)	HTS, KEGG, UniProt, GO, and STRING database	–	CD56, CD3	–	–	These clusters of lncRNAs and their interaction with mRNAs could involve in MA progression.	[94]
Ovarian Cancer (OC)	miR-140–3p (Up)	HBS, Athymic BALB/c mice	Human PB-NK cells, NK-92, OVCAR-3	–	MAPK1	–	miR-140–3p by sponging MAPK1 could suppress the cytotoxicity of NK cells.	[95]
Cervical Cancer (CC)	miR-20a (Up)	HBS	Human PB-NK cells, NK-92, 293 T	–	RUNX1	–	miR-20a by sponging RUNX1 could decrease the NK cell's cytotoxicity against CC cells.	[90]
Prostate Cancer (PC)	miR-224 (down)	Human PC tissues samples, human normal prostate tissues	NK-92	CD107	HIF-1α, NCR1, NKp46	–	Upregulating miR-224 b y HIF-1α could inhibit NCR1/NKp46 pathway, and increase NK cell's cytotoxicity.	[92]
Castration-Resistant Prostate Cancer (CRPC)	Circ-FKBP5 (Up)	–	NK-92MI, C4-2, 293 T	–	miR-513a-5p, PD-L1	–	The sensitivity of CRPC cells against the NK cell killing effect could be suppressed by a high level of DHT regimen via AR/circFKBP5/miR-513a-5p/PD-L1 pathway.	[96]

also seen in colorectal cancer, but the target gene was MICA in that case (Table 4) [76].

Prostate cancer is another type of cancer in which the regulatory effect of a specific miRNA on NK cells, namely miR-224, was reported [92]. Hypoxia-inducible factor 1-alpha (HIF-1α), is a known tumor promoter in various cancers, mainly due to its hypoxia inducement [93]. In this study, it was shown that HIF-1α plays a different role in carcinogenesis, by upregulating miR-224 in NK cells of prostate cancer patients. This elevation led to inhibition of NCR1/NKp46 pathway, and subsequent immune escape and metastasis.

Table 6 summarizes interactions between NK cells and non-coding RNAs in reproductive system related diseases.

1.7. Non-coding RNA profile for NK cells activity in other diseases

As we discussed in previous sections, non-coding RNAs can exert a variety of effects on NK cells, in a broad range of diseases. However, it should be noted that this interaction is not limited to disorders, and normal development and differentiation of NK cell is also affected by non-coding RNAs, regardless of the pathogenicity. For instance, it is widely accepted that as the humans age, their immune system weakens and this is caused by a variety of factors, such as reduced proliferation of adaptive immune cells, and a downsized thymus gland [97]. Interestingly, miRNA-NK cell axis is also affected by ageing. A study related to this matter was conducted by Lu et al. They investigated the association between ageing and functionality of NK cells in young and aged mice. Compellingly, it was shown that a variety of miRNAs demonstrated significant changes between young and aged NK cells. MiR-181a-5p was one of this miRNAs, which was downregulated in NK cells of aged mice, and since it is a conserved miRNA, its downregulation was also reported in elderly people. In order to fully elucidate the role of this miRNA in NK cell activity, functional *in vitro* studies were performed, and it was determined that miR-181a-5p targets two key genes, namely NLK and BCL2. By targeting these two, miR-181a-5p leads to optimized performance of NK cells, and as we age, this issue is conversed [98].

Systemic Lupus Erythematosus (SLE) is an autoimmune disease that affects a variety of organs in the body, and it is mostly seen in women. Similar to other autoimmune conditions, the exact mechanism of pathogenesis is unknown, but SLE requires a genetic predisposition alongside with environmental factors. Symptoms of SLE include joint paint, rashes, fatigue and swollen lymph nodes [99]. Since SLE is an autoimmune condition, there is no surprise that NK cells are also involved in the pathogenesis of disease. As a matter of fact, a 1980's study showed that SLE patients show reduced activity of NK cells compared to healthy controls [100]. A recent study showed that overexpression of miR-27a in NK cells isolated from SLE patients, leads to elevated expression of NKG2D, which is an activating receptor presented by NK cells [101]. This study suggests that more focus is required in relation to the involvement of NK cells in SLE, and that altering the expression of some non-coding RNAs might be helpful in the treatment of this condition.

Table 7 summarizes other interactions between non-coding RNAs and NK cells.

1.8. Correlation between non-coding RNA profile and disease progression

A number of NK cell-related non-coding RNAs have been found to be correlated with progression of different disorders (Table 8). This correlation is best investigated in the contexts of malignant disorders.

2. Discussion

NK cells are important immune cells that facilitate the immune responses through secretion of different cytokines. These cells have crucial roles in innate immune system. Recent studies have found that non-

Table 7
Non-coding RNA profile for NK cells activity in other diseases.

Diseases	Non-coding RNA	Human/Animal Study	Cell Lines	CD Cell Markers	Targets & Pathways	Kaplan Meier	Observation	Ref
Systemic Lupus Erythematosus (SLE)	miR-27a (Up)	HBS	Human PB-NK cells	CD56	NKG2D	–	Overexpression of miR-27a could activate and increases the cytotoxicity of NK cell in SLE patients by increasing NKG2D mRNA.	[101]
Type 2 Diabetes (T2D)	miR-1249–3p (Down)	C57 B/6 mice GO and KEGG database	Mice TR-NK cells, 3T3-L1, AML12	CD3, CD49b	SKOR1	–	Exosomal miR-1249–3p derived from NK cells could improve insulin sensitization and decrease inflammation in T2D patients.	[102]
Chronic Mild Stress (CMS)	miR-155 (Up)	Sprague-Dawley (SD) rats	Rat PB-NK cells	–	ERK1/2	–	Downregulation of miR-155 b y regulation of the ERK1/2 pathway could be a new therapeutic biomarker for depression.	[103]
Aging	miR-181a-5p (Up)	C57BL/6 mice	Human PB-NK cells, K562, 293 T, Mouse hematopoietic stem cells (HSCs)	CD27	BCL2, NLK	–	Downregulation of miR-181a-5p could attenuate the NK cell activity with aging.	[98]
Renal Cell Carcinoma (RCC)	miR-183 (Up)	HBS	Human PB-NK cells, primary RCC cells	CD56, CD16	–	+	miR-183 could be used as a helpful way for the prediction of the outcome of NK cell-based immunotherapy.	[104]
RCC	Circ-FOXO3 (Down)	HTS	Human PB-NK cells, ACHN, A498, 786-O, 769-P, Caki-1, HK-2	–	miR-29a-3p, miR-122–5p	–	circFOXO3 via targeting miR-122–5p and miR-29a-3p could improve NK cell killing capacity.	[105]
Breast Cancer (BRC)	miR-519a-3p (Up)	Healthy HBS, GEO database	Human PB-NK cells, MDA-MB-468, MCF10A, MCF-7, MCF-7, T47D, MDA-MB-231	CD107a, CD3, CD56	Caspase-8, TRAIL-R2, MICA	+	miR-519a-3p could inhibit BRC cell proliferation by sponging caspase-8 and TRAIL-R2 and could decrease NK cell activity by targeting MICA	[106]
BRC	miR-20a (Up)	C57BL/6 mice, TCGA database	Mice PB-NK cells, MDA-MB-231, MB-468, BCap37, MCF-7, BR-3, SK-HBL-100, MDA-BT-474	–	MICA/B	–	miR-20a could attenuate NK cell activation by downregulating NKG2D and ULBP2 via sponging MICA/B.	[107]
Bladder Cancer (BLC)	Circ-RHOT1	–	NK-92, HT-1376, 5637, UMUC3, SV-HUC-1, 253 J, BT-B, T24, HTB9	–	miR-3666	–	Overexpression of ZNF652 could enhance NK cell cytotoxicity against BLC cells via expressing circRHOT1 that targets the miR-3666/SMAD5 pathway.	[108]
–	Cluster of miRs	Healthy HBS, healthy HTS, IPA database	Human PB-NK cells, human dNK cells	CD3, CD14, CD45, CD56	TP53, AGO2	–	Some miRs have different expression levels in dNK and PB-NK cells so these different expression levels may have a function in early pregnancy and some other reproductive diseases.	[109]
–	miR-146a	HBS	Human PB-NK cells, NK-92	CD3, CD56	IRAK1, TRAF6	–	Provoke IL-18 and IL-12 could increase miR-146a and decrease NK cell cytotoxicity.	[110]
–	miR-146a-5p	Healthy HBS, miRanda, ElMMo, PITA, Pictar, doRiNA, TargetScan, KEGG, and mirDB database	Human PB-NK cells	CD56, CD16	KIR2DL1/2	–	miR-146a-5p could be a new therapeutic biomarker for treating cancer.	[111]
–	Cluster of miRNAs	HTS, healthy HBS, AmiGO 2 database	Human PB-NK cells, human dNK cell	CD56, CD94, CD127, CD117	–	–	These miRs could differentiate PB-NK and dNK cells from decidual group 3 innate lymphoid cells (dILC3) and they could cause inflammation and cell proliferation at the beginning of pregnancy.	[112]
–	miR-362–5p	HBS	Human PB-NK cells, dNK cell, NK-92, YT, NKG, K562	CD3, CD56, CD69, CD107a	CYLD	–	Through sponging CYLD miR-362–5p could enhance NK-cell cytotoxicity.	[113]
–	miR-143–3p, miR-145–5p, miR-340–5p, miR-340–3p	Healthy HBS, MiRTarBase and GO database	–	CD3, CD56, CD94	NKG2D, KLRD1	–	miR-143–3p/miR-145–5p could enhance $CIK_{IL\text{-}2}$ (cytokine-induced killer) proliferation capacity but miR-340–5p/miR-340–3p decrease $CIK_{IL\text{-}2}$ proliferation.	[114]

(*continued on next page*)

Table 7 (*continued*)

Diseases	Non-coding RNA	Human/Animal Study	Cell Lines	CD Cell Markers	Targets & Pathways	Kaplan Meier	Observation	Ref
–	miR-17∼92	C57BL/6 mice, GO and TargetScan database	–	–	TGF-β	–	miR-17∼92 family could regulate iNKT cell (Invariant NK cell) development by sponging Tgfbr2 mRNA.	[115]
–	miR-155	C57BL/6 mice	–	CD69, CD122, CD44	–	–	miR-155 could inhibit enhancing of iNKT cell number in the thymus.	[116]
–	miR-512–3p	Healthy HBS, IPA, miRNA.org, and miRBase database	Human PB-NK cells	–	–	–	C19MC (chromosome 19 mRNA cluster) miRs of the placenta shift to parental PB-NK cells at the time of pregnancy,	[117]
–	Lnc-CD56	Healthy HBS, SBC, CPC, UCSC Genome Browser, and STRING database	Human PB-NK cells, HEK239T		–		Lnc-CD56 could distinguish NK cells from $CD34^{+}$ hematopoietic stem cells (HSCs).	[118]

Table 8
Correlation between non-coding RNA profile and disease progression.

Study points	Ref
The serum level of miR-183 had a positive correlation with the grading of RCC.	[104]
Higher PD-L1 expression showed lower overall survival in NB patients.	[56]
The high expression level of miR-188–5p is associated with a good prognosis in NKTCL patients.	[19]
NB patients with a higher level of miR-186 have a higher survival rate and good prognosis.	[57]
High levels of miR-519a-3p and low levels of caspase 7/8 and TRAIL-R2 are associated with poor prognosis and lower survival rates in BRC patients.	[106]
Low level of miR-3607–3p in PAC patients associated with lower metastasis-free survival rate.	[78]
There is an association between a high level of miR-561–5p and poor prognosis in HCC patients.	[74]
There is a significant correlation between a high level of miR-BART2-5p and a lower survival rate in NKTCL patients.	[28]
High expression level of circKIF4A is associated with a poor prognosis of NKTCL disease.	[29]

coding RNAs play important roles in the development and function of NK cells. Several novel non-coding RNAs have been identified through advanced sequencing techniques in recent years, many of them being involved in these processes. Notably, miRNAs are the mostly investigated non-coding RNAs in the field of NK cell biology. These small-sized transcripts also mediate the effects of lncRNAs and circular RNAs on function of NK cells, since they are sponged by lncRNAs and circular RNAs. LncRNA/miRNA and circular RNA/miRNA axes that contribute to the modulation of function of NK cells are putative targets for further research in this field to understand the biology of NK cells. MiRNAs can regulate expression of cytokines, immune checkpoints, ligands for NK cell receptors, apoptotic genes and other molecules that affect immune-related signaling pathways. The sponging effects of lncRNAs and circular RNAs on miRNAs have an important effect on modulation of impact of miRNAs on these molecules and signaling pathways. PI3K-Akt, Wnt, MAPK and TGF-β are the main pathways affected by these transcripts in this field. LncRNAs can also directly regulate expression of immune-related genes through changing the stability of transcripts, modulating DNA configuration and other epigenetic mechanisms.

Based on the importance of NK cells in the pathogenesis of human disorders and the availability of novel therapeutic agents that modulate their functions, identification of the regulatory effects of non-coding RNAs on NK cells would pave the way for enhancement of the efficacy of mentioned drugs in the clinical settings.

A research field that needs better investigation is the importance of non-coding RNAs in immunotherapeutic options that affect activity of NK cells. For instance, miR-155 can suppress expression of PD-L1 in lymphatic endothelial cells and fibroblasts. Thus, it can influence the effectiveness of immunotherapeutic approaches that rely on this molecule [119]. Moreover, miRNAs that suppress expression of MHC class I chain-related protein A/B (MICA/B) as a kind of NK cells receptor ligands are possible targets for regulation of NK cells cytotoxicity [120]. Better recognition of the role of these transcripts in this field would affect the survival of patients with different types of cancer.

Finally, several non-coding RNAs that affect the activity of NK cells have been found to influence survival time of patients with malignancies. This observation further highlights the importance of these transcripts in the pathogenesis of cancer and potentiates them as probable predictive factors for these disorders. Since they can be traced in body fluids, they can also be served as non-invasive biomarkers.

A limitation of mentioned studies in the field of non-coding RNAs and NK cell activity is lack of clinical evidence. Many of these studies have assessed function of these transcripts only in cell liens or animal models. The exact effect of up-regulation or down-regulation of them on disease progression is less studied. Moreover, no clinical trial has assessed the effects of NK cell-modulating non-coding RNAs on disease course.

Taken together, modulation of activity and function of NK cells by non-coding RNAs represents a novel field of research that would be benefitted from additional functional analyses. This field would pave the way for design of personalized routes of treatment, particularly for cancers.

Ethics approval and consent to participant

Not applicable.

Consent of publication

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Authors' contributions

SGF wrote the draft and revised it. MT and HP designed and supervised the study. AA, HS and AZ collected the data and designed the figures and tables. All the authors read the submitted version and approved it.

Declaration of competing interest

The authors declare they have no conflict of interest.

Data availability

Data will be made available on request.

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Abbreviation list

AGO2	Argonaute RISC catalytic component 2
ATG7	Autophagy-related 7
AURKA	*Aurora kinase A*
BCL2	B-cell leukemia/lymphoma 2
CX3CL1	*C*-X3-C motif chemokine ligand 1
CX3CR1	CX3C motif chemokine receptor 1
CXCR2	*C*-X-C motif chemokine receptor 2
CYLD	*CYLD lysine 63 deubiquitinase*
ERK1/2	Extracellular signal-regulated protein kinases 1 and 2
GrzB	*Granzyme B*
HIF-1α	Hypoxia-inducible factor-1α
HLA-G	Human leukocyte antigen-G
HMBOX1	Homeobox containing 1
IFN	Interferon
IGF-1	Insulin like growth factor1
IGF-1R	Insulin like growth factor1 receptor
IL-26	Interleukin 26
INHBC	Inhibin subunit beta C
INS	*Insulin*
IRAK1	Interleukin-1 receptor associated kinase 1
KIR2DL1	Killer cell immunoglobulin like receptor, two Ig domains and long cytoplasmic tail 1
KIR2DL2	Killer cell immunoglobulin like receptor, two Ig domains and long cytoplasmic tail 2
KLRD1	killer cell lectin-like receptor subfamily D, member 1
MAP2K1	Mitogen-activated protein kinase 1
MAP3K10	Mitogen-activated protein kinase kinase 10
MAPK	Mitogen-activated protein kinase
Mcl-1	Myeloid cell leukemia 1
MICA	Major histocompatibility complex class I polypeptide-related sequence A
MICB	Major histocompatibility complex class I polypeptide-related sequence B
NCR1	Natural cytotoxicity triggering receptor 1
NKG2A	*Natural killer group 2A*
NKG2D	*Natural killer group 2D*
NLK	*Nemo like kinase*
PD-L1	Programmed death-ligand 1
PPTC7	Protein phosphatase targeting COQ7
PRF1	Perforin 1
RUNX1	Runt-related transcription factor 1
RUNX3	Runt-related transcription factor 3
SHMT1	Serine hydroxylmethyltransferase 1
SKOR1	*SKI family transcriptional corepressor 1*
SOCS1	*Suppressor of cytokine signaling 1*
Sp1	Specificity protein 1
STAT1	Signal transducer and activator of transcription 1
STAT3	Signal transducer and activator of transcription 3
TGFBR1	Transforming growth factor beta receptor 1
TGFBR2	Transforming growth factor beta receptor 2
TGF-β	Transforming growth factor-β
Tim-3	T cell immunoglobulin domain and mucin domain
TP53	Tumor protein P53
TRAF6	Tumor necrosis factor receptor associated factor 6
TRAIL-R2	Tumor necrosis factor (*TNF)-related* apoptosis-inducing ligand-receptor 2
ULBP1	UL16 binding protein 1
ULBP2	UL16 binding protein 1
XRCC5	X-ray repair cross-complementing 5

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