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Review

MicroRNA regulation of natural killer cell development and function in leukemia

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ABSTRACT

MicroRNAs (miRNAs) are now recognized as important regulators of all cellular processes, including immune function and cancer survival. These evolutionary preserved, single-stranded, non-coding RNA molecules mediate important functional effects primarily through post-transcriptional regulation of protein expression. MiRNAs are known to mediate multiple oncogenic pathways in tumor cells, both tumor promoting and tumor suppressing. In addition to a direct tumor cell effect, miRNAs have also been shown to play a critical role in immune cell development, function and survival. Here we expand on previous reports to evaluate miRNA regulation in natural killer (NK) cells primarily in humans and focus on their influence on NK cell development and function in the setting of hematologic malignancies. In addition, we highlight the most recent miRNA discoveries in hematologic malignancies and discuss areas of future exploration relevant to the translational field of innate immunology and miRNA-based therapeutic intervention.

1. Basic biology, development and function of NK cells

Natural killer (NK) cells are a key population of innate immune cells which constitute roughly 10% of peripheral blood lymphocytes (Caligiuri, 2008). NK cells have the ability to identify, target, and kill cancer cells without prior sensitization, as well as the ability to coordinate both the innate and adaptive immune response against foreign pathogens and transformed cells. Traditionally human NK cells are identified phenotypically as positive for the adhesion molecule CD56 and lacking other "lineage" (CD3, CD14 and CD20) marker expression. While it was originally thought that NK cells developed primarily in the bone marrow, several studies over the past decade support a model of NK cell development in secondary lymphoid tissue (SLT) (Freud et al., 2005, 2006; Yu et al., 2013). Multiple discrete stages of human NK cell development have been identified in SLT characterized by the relative expression of CD34, CD117, CD94, NKp80 and CD16 with development starting in the bone marrow, progressing through SLTs, and resulting in the accumulation of the most terminally differentiated NK cells in the peripheral blood (PB) (Freud and Caligiuri, 2006; Freud et al., 2006; Grzywacz et al., 2006). Stage 1 cells traditionally express CD34 but lack CD117, CD94, NKP80, CD16 and the common IL-2/IL-15 receptor beta chain (Freud and Caligiuri, 2006). Stage 2 cells are more responsive to cytokine stimulation by virtue of the fact that they express the functional IL-2 receptor (CD25) and express CD122 and CD117 (Freud and Caligiuri, 2006). Stage 1 and 2 progenitor cells can differentiate into NK cells, but they also retain the ability to develop into T cells and dendritic cells (DCs). Unlike the more mature NK cell subsets, stage 3 cells lack expression of TBX21 (TBET) and Eomesoderm (EOMES) and are unable to produce interferon-gamma (IFN-γ) (Freud et al., 2006). Still functionally immature, $Lin^-CD34^-CD117^+CD94^-NKp80^-CD16^-$ stage 3 cells also have impaired granules and an inability to perform perforin-dependent cytotoxicity against target cells lacking expression of major histocompatibility complex (MHC) class I (Freud et al., 2006). Recently defined, NKp80, is a marker of maturity, expressed on functionally mature NK cells in SLTs and PB (Freud et al., 2016). Terminal stages of NK cell development in the blood are dependent on the relative expression of CD56 which allows for the distinction between immature $CD56^{bright}$ NK cell subsets ($CD34^-CD117^{+/-}CD94^+NKp80^+CD16^-$) and functionally mature $CD56^{dim}$ ($CD34^-CD117^{lo/-}CD94^{+/-}NKp80^+CD16^+$) (Freud et al., 2016). The $CD56^{bright}$ subset present in both SLT and PB is thought to give rise to the $CD56^{dim}$ stage 5 NK cell subset. Critical differences between $CD56^{bright}$ and $CD56^{dim}$ NK cells include the ability to generate cytokines such as IFN-γ, tumor necrosis factor-alpha (TNF-α), cytolytic

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granules including perforin and granzyme B (GzmB) as well the ability to perform antibody-mediated cellular cytotoxicity (ADCC) through the expression of CD16 (Freud et al., 2014).

Additional populations of terminally differentiated $CD57^+$ "stage 6″ NK cells have also recently been described (Lopez-Verges et al., 2010; Nielsen et al., 2013). Humans who are seropositive for latent human cytomegalovirus (HCMV) or experience acute HCMV infection have an increased percentage of NK cells expressing the activating heterodimeric receptor CD94/NKG2C (Gumá et al., 2004; Lopez-Vergès et al., 2011). These mature NK cells have been shown to have memory-like properties similar to memory T cells with higher expression of IFN-γ, TBET, and interleukin (IL)-15 receptor alpha (IL-15Rα) (Foley et al., 2012). Recent work by Lee et al. (2015) and others has further defined these memory NK cells are antibody-dependent and characterized by the downregulation of FcRy along with multiple transcription factors and signaling molecules, including SYK, EAT-2 and PLZF (Hwang et al., 2012; Lee et al., 2015; Zhang et al., 2013). These changes were associated with promoter hypermethylation, suggesting a role for epigenetic regulation of memory NK cell maintenance and/or generation (Lee et al., 2015).

Expansion of this NK memory subset after CMV reactivation in seropositive recipients receiving a donor CMV negative umbilical cord blood transplantation was associated with enhanced KIR expression, downregulation of the inhibitory CD94/NKG2A receptor complex and a reduced risk of leukemia relapse (Cichocki et al., 2016; Foley et al., 2012). Although $NKG2C^+$ NK cells expand in response to other viral infections (eg. hantavirus, chikungunya, human immunodeficiency virus (HIV) and hepatitis C virus (HCV)), they do not do so without prior CMV exposure (Béziat et al., 2012; Björkström et al., 2011; Gumá et al., 2006; Petitdemange et al., 2011). The pro-inflammatory cytokines IL-12, IL-15, and IL-18 have also been shown to enhance NK cell activation and function inducing a similar memory-like NK cell phenotype although these cell do not express NKG2C (Romee et al., 2016). The potential role of the inflammatory cytokine environment following CMV infection and memory NK cell generation, as well as the relationship between the NKG2C + NK cells and "memory-like" NK cells is an area of ongoing investigation.

Murine NK cells also have predictive maturation profiles. NK cell progenitors in mice traditionally are identified as $Lin^-CD122^+NK1.1^+CD94^+NKp46^+Ly49^-DX5^-$ cells (Vosshenrich et al., 2005). While there is no direct homolog of CD56 in mice, murine NK cell maturation can be identified by the expression of surface antigens CD27 and CD11b post acquisition of NK1.1 in the following order beginning from least mature or stage 1 $CD27^-CD11b^-$, progressing to stage 2 $CD27^+CD11b^-$, then to stage 3 $CD27^+CD11b^+$ and ending at the most mature stage 4 $CD27^-CD11b^+$ NK cells (Colucci et al., 2003; Hayakawa and Smyth, 2006; Vosshenrich et al.). Similar to the human CMV studies, Sun et al. also showed that mice have both expansion and persistence of a Ly49H + memory NK cell population following murine CMV (MCMV) infection in C57BL/6 mice (Sun et al., 2009). This subset is also thought to have important anti-tumor abilities (Nabekura and Lanier, 2016) and requires pro-inflammatory cytokines to develop exhibiting some similarity to humans (Cooper et al., 2009).

NK cell mediated cytotoxicity is strictly controlled by "killer-cell immunoglobulin like receptor" or KIR, which are germline encoded activating or inhibitory receptors critical for HLA class I recognition (Freud et al., 2017). There are approximately 15 recognized KIRs including KIR2DL1, KIR2DL2/L3, KIR2DL4, KIR2DL5A, KIR2DL5B, KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, KIR2DS5, KIR3DL1/S1, KIR3DL2 and KIR3DL3 (Varbanova et al., 2016). NK cells must go through an education process to be fully functional by engaging with "self" MHC class I receptors (Caligiuri, 2008). In an effort to evade T cell recognition, cancer cells may downregulate MHC class I. The downregulation of MHC class I leads to NK cell engagement and activation by lack of inhibitory stimulation through KIR binding, also called the "missing self" hypothesis (Kärre et al., 1986; Ljunggren and Kärre, 1990). The MHC class I interaction has been exploited in the post-transplant setting to activate NK cells against host leukemia termed "graft verse leukemia effect" (GVL). In these studies, alloreactive NK cells have been shown to be protective against acute myeloid leukemia (AML) relapse without inducing acute graft versus host disease (GVHD) (Moretta et al., 2011; Ruggeri et al., 2002). In addition to exploiting the KIR/MHC mismatch and GVL effect through haploidentical allogeneic transplantation, alternative NK cell-based approaches are being utilized in several tumor models including antibody therapy manipulation through CD16 engagement, cytokine supplementation, adoptive NK cell transfer and the use of genetically modified chimeric antigen receptor NK cells (Romee et al., 2016),(X. Chen et al., 2016; Knorr et al., 2014; Vasu and Blum, 2013).

In hematological malignancies, NK cells undergo environmental changes deleterious to the host which enhance malignant cell immune survival and proliferation. We now recognize that AML, for example, benefits from immune cell escape through several unique mechanisms including downregulation of activating receptors including NKp30, NKp44, NKp46 (Costello et al., 2002; Fauriat et al., 2007) and downregulation of NKG2D ligands important for binding to NKG2D, a potent activating receptor expressed on NK cells (Lion et al., 2012). NKG2D activation has been shown to be relevant to anti-tumor immunity as AML patients treated with decitabine (DAC), a hypomethylating agent, exhibited significantly higher ADCC as compared to controls. Patients treated with DAC had higher expression of activating NKG2D ligands and enhanced susceptibility to a fully human anti-CD33 antibody Fc engineered for increased binding to FcγRIIIa (BI 836858) (Vasu et al., 2016). Cany et al recently demonstrated that NK-cell anti-leukemic functions are enhanced by decitabine treatment by both upregulating the expression of DNAM-1 and NKG2D activating ligands on AML blasts as well as increasing NK cell expression of inflammatory cytokines, perforin and TRAIL (Cany et al., 2018; Khaznadar et al., 2015). In addition, NK cell defects in AML patients were recently demonstrated to be associated with an immune-edited transcription program in AML which decreases NK cell activity and impacts relapse risk (Cany et al., 2018; Khaznadar et al., 2015). Further studies have shown that expression of certain KIRs, such as KIR2DL2, on AML blasts has been associated with decreased NK cell IFN-γ secretion (Tajima et al., 1996). AML cells have also been shown to be resistant to apoptosis mediated through TRAIL and Fas ligand mediated cytotoxicity (Min et al., 2004; Schimmer et al., 2003; Tourneur et al., 2004). More broadly, the microenvironment created in part by AML cells, leads to inherent downregulation of perforin and granzyme B expression which inhibits NK cell mediated lysis (Mundy-Bosse et al., 2016a, 2016b).

2. miRNA biology and regulation of natural killer cell development and function

2.1. miRNA biology

MiRNAs are conserved non-coding single stranded RNA molecules, which play important roles in the post-transcriptional regulation of protein expression and degradation (He and Hannon, 2004). MiRNA genes are located in the nucleus where they are transcribed into primary miRNA transcripts. The transcripts are then exported from the nucleus into the cytoplasm where processing is completed by an enzyme called Dicer to generate the mature miRNAs (Baek et al., 2008). The RNA-induced silencing complex (RISC) functions to hold mature miRNAs that then target the 3′ untranslated region (UTRs) of protein-encoded mRNAs, leading to translational modifications of protein stability. Although small in length (~22 nucleotides), miRNAs appear to be highly conserved between species (Bartel, 2009). This conservation enhances the utility of murine models for assessing the role of miRNA in human cellular processes.

2.2. miRNA in NK cell overview

In both mice and humans, miRNAs have been shown to be critical regulators of NK cell activation, survival and function (Leong et al., 2012; Liu et al., 2012; Sullivan et al., 2013b). Microarray studies have compared the miRNA expression profiles in humans and mice and found over 150 unique miRNAs in primary NK cells showing that 59% of the miRNAs present in murine NK cells were also found in human NK cells (Bezman et al., 2010b). The miRNAs found to have the highest similarity between mice and human NK cells were let-7a, let-7f, let-7 g, miR-15b, miR-16, miR-21, miR-23a, miR-23b, miR-24, miR-26a, miR-29a, miR-103, miR-150 and miR-720. Two additional studies utilized next generation sequencing to identify miRNAs in humans and mice, and both studies identified over > 300 miRNAs detectable in NK cells (Fehniger et al., 2010; Liu et al., 2012). The first examined the miRNA profile in murine splenic NK cells and similarly to humans, they discovered that although > 200 miRNAs were expressed in NK cells in a resting state and following IL-15 activation, the top 50 miRNAs made up 95% of the total miRNA sequence content (Fehniger et al., 2010). In the same year, Bezman et al. was one of the first to show a dependence of NK cells on miRNAs through the use of a murine model with a conditional deletion of Dicer and the DiGeorge syndrome critical region 8 (Dgcr8) which are essential for miRNA transcription (Bezman et al., 2010b). This and subsequent studies, showed that NK cells deficient in miRNAs had decreased overall survival, maturation, and lacked the ability to expand during MCMV infection highlighting the critical role miRNAs play in innate immune function and paving the way for more specific experiments targeting miRNA regulation of NK cells (Sullivan et al., 2013b; Bezman et al., 2010).

2.3. miRNA in NK cell development

Recently multiple murine studies have demonstrated the essential functions miRNAs play in NK cell development. Initial work with global miRNA knock out through the absence of an essential miRNA processor, Dicer1, resulted in impaired NK cell development (Bezman et al., 2010b). Several specific miRNAs have since been found to mediate normal NK cell development directly including miR-15/16, miR-155, miR-181, miR-483-1, and miR-583. Sullivan et al. demonstrated that mice with global deletion of miR-15a/16-1 had defective NK cell maturation with a block in the most mature stage 4 murine NK cells (CD27-CD11b^{+}) cells with an associated buildup of immature stage 2 and 3 cells. This was shown to be regulated by Myb protein expression, and knockdown of Myb restored the block in NK cell maturation (Sullivan et al., 2015). Along with altered development, miR-15a/16-1 also directly represses IFN-γ transcripts in NK cells (Sullivan et al., 2015). Similarly, using a murine transgenic model with miR-155 overexpressed under an *lck* promoter, Trotta et al. demonstrated that increased miR-155 expression led to an increase in splenic NK cell numbers with an excess of immature (CD11b-CD27^{+}) NK cells with high cytokine generation but low cytolytic activity (Trotta et al., 2013). In human NK cells, miR-155 overexpression was strongly associated with enhanced IFN-γ production in the presence of cytokine stimulation with IL-12 and IL-18 or CD16 stimulation (Trotta et al., 2012). The overexpression of miR-155 was also shown to directly down-regulate SHIP1 (SH2-containing Inositol 5′-Phosphatase 1), a growth receptor important for hematopoietic cell development, found to be expressed in CD56^{bright} and CD56^{dim} NK cell subsets (Trotta et al., 2012, 2005). Murine studies have likewise demonstrated that miR-150 is also important for NK cell maturation. A global knockout of miR-150 resulted in a significant deficiency of mature NK cells due to defects in development and survival. Alternatively, mice that overexpress miR-150 had an accumulation of mature hyperfunctional NK cells suggesting that miR-150 plays a significant role in NK cell survival and maturation (Bezman et al., 2011).

Additional studies have recently been conducted that further our understanding of how miRNA regulate human NK cell development. MiR-181 has been demonstrated to modulate human NK cell development through the regulation of notch signaling by targeting nemo-like kinase, an inhibitor of notch (Frank Cichocki et al., 2011). Notch signaling promotes NK cell maturation via CD56 acquisition, and can also bypass the need for stroma or cytokines like IL-15 to drive NK cell maturation (Haraguchi et al., 2009). In humans, ex vivo differentiation assays demonstrated the absence of notch signaling dramatically reduced the development of NK cells from CD34^{+} progenitors (Beck et al., 2009). Cichoki et al. reported that knockdown of either miR-181a or miR-181b led to a ~3-fold decrease in the percentage of mature CD56^{+} NK cells generated in culture. In contrast, over-expression of miR-181a/b via lentiviral constructs transduced separately into primary CD34^{+} progenitor cells resulted in a 2-fold increase in CD56^{+} NK cells at day 28 of an ex vivo culture on the EL08-1D2 murine stromal line when compared to scrambled controls (Cichocki et al., 2011; Cichocki and Miller, 2010). Importantly, the authors found that these results were not due to differences in proliferation between cultures and not dependent on relative CD56 protein expression. A similar defect in NK cell development was seen when analyzing additional markers of differentiated NK cells (such as CD94/NKG2A and CD16) in miR-181a and miR-181b knockdown cultures (Cichocki et al., 2011). Additional groups have evaluated the role of miRNA in modulating the ability of NK cells to develop from CD34^{+} precursors. MiR-483-3p has been shown to block NK cell development via the downregulation of insulin-like growth factor 1 (IGF-1) from human CD34^{+} hematopoietic stem cells. High exogenous IGF-1 has been shown to be associated with increased perforin expression in the NK cell, which is critical for cytolytic NK cell function (Ni et al., 2013). Another negative regulator of NK cell development is miRNA-583, which acts by silencing the IL-2 receptor gamma, known to be critical for NK cell maturation and important for functional regulation of NK cells (Yun et al., 2014).

2.4. miRNA in NK cell function

MiRNAs have been implicated in regulating several essential innate immune functions of NK cells including IFN-γ secretion, cytotoxicity and response to MCMV infected targets. The effect of miRNAs impeding NK cell function has wide ramifications on the effectiveness of immune-based therapies, innate immune surveillance and tumor progression. The true impact of miRNA on NK cell function is still being elucidated. Initial studies with global knockout of mature miRNAs show that NK cells may have decreased survival and absolute numbers as well as decreased overall function in the absence of miRNA. In addition, the activating receptor NKG2D, which binds to MHC class I-like molecules (ie. MICA, MICB, ULBP1) upregulated in virally infected and malignant cells, was diminished on NK cells from miRNA global knockout mice (Bezman et al., 2010b). Intriguingly, when mature miRNA were knocked out in NK cells more specifically using lymphocyte restricted knockout murine models, function was not impaired but rather enhanced. Specifically, studies using a lymphocyte restricted Cre transgenic mouse (hCD2-Cre) model combined with Dicer1 lox-P flanked alleles to generate loss of Dicer1 in the early stages of NK cell development by Fehniger and colleagues found both enhanced IFN-γ production and degranulation capacity to a number of stimuli ex vivo, along with enhanced response to MCMV stimulation via IFN-γ production (Sullivan et al., 2012). Several miRNAs have also been shown to be important regulators of both NK cell development and immune function including miR-15a/16-1, miR-155, and miR-223. Studies examining the role of miR-15a/16-1 deletion in 15a/16-1 KO mice showed that total NK cell IFN-γ was diminished after stimulation with anti-NK1.1 and cytokines (IL-12 + IL-15 or IL-12 + IL-18) as compared to NK cells from control mice (Sullivan et al., 2015). MiR-155, which is found in resting human and murine NK cells, is upregulated after cytokine stimulation with IL-12, IL-15 and IL-18 or MCMV stimulation and is associated with enhanced IFN-y response to stimulation (Trotta

et al., 2012). Interestingly, while a murine miR-155 transgenic overexpression model suggests enhanced cytokine secretion due to an increase in immature NK cells(Trotta et al.), others have reported that knocking out murine miR-155 also leads to increased secretion of IFN-γ following cytokine stimulation. The miR-155 knock out NK cells produced more GzmB and surface CD107a after NK1.1 ligation (Sullivan et al., 2013a). The authors conclude that miR-155$^{-/-}$ NK cells have increased expression of activation proteins such as PI3K and NF-κB which lead to enhanced activation potential (Trotta et al., 2012). These studies highlight the complexity of evaluating miRNA regulation of function and development as miRNA may have differing roles depending on the environment in which they are being evaluated. MiR-223 has been specifically found to target the 3′ untranslated region of murine GzmB in vitro, indicating that this miRNA may contribute to control of GzmB translation in resting NK cells (Ni et al., 2015).

Recently the role of miRNA on NK cell function in solid tumors has also been reported by several groups. In ovarian cancer, MICA/B expression was decreased due to increased levels of miR-20a, which led to the silencing of activating NKG2D ligands in breast cancer via the miR-17-92 cluster and miR-10b downregulation in several cell lines. While these miRNA have yet to be evaluated for their role in immune modulation in the hematologic setting, these studies suggest additional potential targets to be evaluated in this setting (Shen et al., 2017; Tsukerman et al., 2012; Xie et al., 2014).

3. The role of miRNA in the development and/or progression of hematologic malignancies

MiRNA signatures have been linked to both the development and prognosis of several hematological malignancies including acute and chronic leukemias, multiple myeloma, large granulocytic leukemia (LGL) and lymphomas (Calin et al., 2002; Cimmino et al., 2005; Corthals et al., 2011; Costinean et al., 2006; Croce, 2009; Garzon et al., 2008a, b; Mishra et al., 2012). MiRNA have been described as both tumor suppressive and oncogenic, with our understanding of the specificity of these roles in different cell types changing rapidly. Out of the ~100 miRNAs associated with known leukemic genomic alterations (Starczynowski et al., 2011), only a few have been shown to be important for NK cell function, survival and/or development including miR-15/16, miR-29b, miR-150, miR-155 and miR-181 (see Table 1). Here, we will focus on these specific miRNAs dysregulated in leukemia and define their role in NK cell development, maturation and/or function in hematological malignancies which may be future target for therapeutic manipulation.

3.1. miR-15 and miR-16

MiR-15 and miR-16 are located in a cluster at 13q14, and are commonly down regulated or deleted in chronic lymphocytic leukemia (CLL) promoting anti-apoptosis and subsequent leukemia cell survival (Calin et al., 2002). Specifically, expression of miR-15a and miR-16-1 were found to be inversely correlated with the protein expression of a pro-survival protein, B cell lymphoma 2 (Bcl2), expressed in CLL and other hematological malignancies (Cimmino et al., 2005). Restoration of miR-15-a/16-1 expression was able to induce apoptosis in a cell line derived from acute megakaryocytic leukemia (MEG-01) emphasizing the potential therapeutic role of miR-15-a/16-1 (Cimmino et al., 2005). Not only have these two miRNAs been found to downregulate the oncogene BCL2, but has recently been shown to also downregulate other important oncogenes critical for leukemia survival including MCL1, ETS1, JUN, CCND1, and WNT3a (Calin et al., 2008). Functionally, miR-15a and miR-16-1 may also inhibit proliferation of leukemic cells through down regulation of the WT1 gene (Gao et al., 2011). WT1 is an oncogene that has been found to be overexpressed in AML, acute lymphoblastic leukemia (ALL), blast crisis chronic myeloid leukemia (CML), and myelodysplastic syndrome which is associated with a poor

Table 1
Selected miRNA Alterations in Leukemia.

Altered miRNA	Leukemia	Role in leukemic cells	Role in NK cell Biology	References
MiR-15/MiR-16	CLL, AML	↓ miR-15/16 downregulates WT1 in AML and CLL; associated with poor prognosis	miR15a/16-1 KO leads to block in terminal NK cell maturation and represses IFN-γ transcripts in NK cells	Bergmann et al. (1997); Cimmino et al. (2005); Gao et al. (2011); Sullivan et al. (2015)
MiR-29b	AML, LGL, CLL	↑ miR-29b induces apoptosis in AML; ↓ miR-29b associated with LGL/CLL development and poor prognosis in CLL; Associated with CLL exosomes	↑ miR-29b associated with decreased perforin/granzyme B, block in maturation with loss of intermediate population of NK cells	Calin et al. (2005); Mishra et al. (2012); Mundy-Bosse et al. (2016a, 2016b)
MiR-150	AML, CLL	↑ levels associated with good prognosis; Associated with CLL exosomes	Loss of miR-150 results in reduced absolute numbers and impaired maturation and defective IFN-γ secretion	Bezman et al. (2010b); Yeh et al. (2015)
MiR-155	AML, CML, CLL	↑ miR-155 associated with poor prognosis in AML; Associated with mutations FLT3-ITD, RUNX1, WT1; ↓ miR-155 in CML; Associated with CLL exosomes	miR-155 KO leads to upregulation of SHIP1 with resultant inhibition of cell proliferation and promotion of cell apoptosis, maturation block and enhanced IFN-γ. miR-155 KO NK cells are more easily activated with increased expression of proteins in the PI3K, NF-kB and calcineurin pathways.	Hershkovitz Rokah et al. (2012); Sullivan et al. (2013a); Trotta et al. (2012, 2013); Yeh et al. (2015)
MiR-181	AML	↑ miR-181 associated with increased OS and enhanced NK cell mediated killing	↑miR-181 associated with NK cell maturation and enhanced IFN-γ production via NOTCH signaling	Cichocki et al. (2011); Marcucci et al. (2008)

prognosis (Bergmann et al., 1997; Miwa et al., 1992). The miR-15a/16-1 cluster has also been shown to be important for NK cell maturation and function as previously described above, supporting a role for miR-15a/16-1 in mediating both a direct anti-leukemic effect in tumor cells and decreasing NK cell cytotoxic capacity (Sullivan et al., 2015).

3.2. miR-29b

The miR-29 family includes miR-29a, miR-29b, and miR-29c and has been shown to be important for immune function against pathogens and tumors (Ma et al., 2011). MiR-29b is the most highly expressed of the family and has been found independently to have both tumor suppressor properties when expressed in malignant cells, likely because of its ability to target Mcl-1, SP1, DNMT3a and DNMTb, Tcl-1, and Cdk6 (Garzon et al., 2009; Sampath et al., 2012; Yan et al., 2015), as well as tumor promoting properties when expressed in NK cells (Mundy-Bosse et al., 2016a, 2016b). In addition, it has been reported to be predictive of response to therapy in certain settings (Blum et al., 2010; Mims et al., 2013). In CLL, loss of miR-29b is associated with apoptotic resistance and a poor prognosis (Calin et al., 2005; Sampath et al., 2012). Overexpression of both miR-29a and -29b in two myeloid cell lines (K562 and Kasumi-1) and primary AML patient samples inhibited cell growth and induced apoptosis via a caspase 3 and 7 activation (Garzon et al., 2009). In xenograft models utilizing K562 cells in immunocompromised mice, the authors show that synthetic miR-29b injection into the tumors was associated with decreased tumor growth with compete remissions seen in 2 out of 12 mice suggesting an important tumor suppressor ability of miR-29b when overexpressed in leukemic cells (Garzon et al., 2009). MiR-29b has also been demonstrated to be elevated in LGL leukemia, a disease highly dependent on IL-15 overexpression. IL-15 has been shown to downregulate miR-29b in LGL leukemia through the Myc pathway, leading to DNMT3b overexpression and hypermethylation (Mishra et al., 2012). Mishra et al. show that LGL transformation occurs as a direct cause of miR-29b inhibition, and that the use of bortezomib (a proteasome inhibitor) which enhances miR-29b levels, led to disease free survival in a spontaneous murine model of LGL leukemia. These data support the potential utility of targeting miR-29b in leukemic cells as a therapeutic strategy, however little was known about the impact of miR-29b on immune effectors cells in the leukemic microenvironment. Recently, our group described the role of miR-29b in NK cell function and maturation showing a close inverse correlation between miR-29b expression and the expression of two transcription factors critical for NK cell development TBET and EOMES, as was previously demonstrated in T cells (Steiner et al., 2011). In a spontaneous double mutation knock-in (FLT3-ITD and MLL-PTD) AML mouse model and across all evaluated subtypes of human primary AML, NK cells were found to have high levels of miR-29b correlating with impaired innate immune function and reduced TBET and EOMES. This reduction was associated with a block in an intermediate population of $CD56^{+}/Lin^{-}/CD94^{+}/CD16^{-}$ NK cells previously shown to be associated with high cytokine-secreting potential, critical for the initiation of both adaptive immunity and cell proliferation (Poli et al., 2009). The loss of this NK cell developmental precursor or “bright NK cell” correlated with AML progression over time (Mundy-Bosse et al., 2016a, 2016b). Forced overexpression of TBET and EOMES through a knockout mouse model of miR-29b lead to normalization of NK cell development suggesting the innate immune defect is mediated via a mir-29b dependent mechanism (Blum et al., 2010).

3.3. miR-150

MiR-150 is primarily expressed in mature NK cells and iNKT cells (Bezman et al., 2010a, 2011; Fehniger et al., 2010). Its expression has also been shown to induce myeloid differentiation in acute leukemia (Morris et al., 2013), and is associated with favorable prognosis when expressed in AML cells. A direct target of mir-150 is the transcription factor c-Myb(Xiao et al., 2007), which is needed for NK cell maturation in the liver, spleen and peripheral blood (Monticelli et al., 2005). It has been recently shown that the AML microenvironment may suppress hematopoiesis by releasing exosomes containing miRNAs targeting c-MYB such as miR-150 as a survival strategy against host defense (Hornick et al., 2016). Myb expression inversely correlates with NK cell maturation, so miR-150 overexpression has the potential to drive NK cell maturation and hyperfunctionality, perhaps leading to NK cell exhaustion (Sullivan et al.). In CLL, miR-150 was found to be the most abundant miRNA expressed and a significant regulator of B cell signaling (Mraz et al., 2014). Recently, plasma-derived exosomes in the microenvironment of AML and CLL patients have been shown to be important carriers of miRs including miR-29a-c, miR-150, miR-155 and miR-223 (Hornick et al., 2016; Yeh et al., 2015). Further research has shown that miR-150 and miR-155 containing exosomes may suppress hematopoiesis by targeting c-MYB as a survival strategy against host defense (Hornick et al., 2016).

3.4. miR-155

One of the first miRNAs found to be overexpressed in cancers, miR-155 is an adverse prognostic factor for AML and identifies high risk patients associated with lower complete remission rates, shorter disease-free survival and overall survival(Blum et al.). High miR-155 levels were found to be associated with the presence of FLT3-ITD mutated, RUNX1 mutated, and WT1 mutated AML subtypes, each associated with a poor prognosis (Gaidzik et al., 2016; Hou et al., 2010; Marcucci et al., 2012; Quentmeier et al., 2003). Garzon et al. recently reported the miRNA signature of AML showing that specific miRNA profiles are highly connected to mutation status including a strong correlation between upregulation of miR-155 and FLT3-ITD mutations in AML (Garzon et al., 2008b). Mir-155 acts in AML blasts as an onco-miR through the mir-155/SHIP1/PI3K/AKT signaling pathway important for the pathogenesis of AML (Xue et al., 2014). In AML, SHIP1 levels are reduced and correlate with overexpression of miR-155. In NK cells, regulation of by miR-155 is complex and likely impacted on model system used. In general, the inhibition of miR-155 in NK cells leads to upregulation of SHIP1 with resultant inhibition of cell proliferation and promotion of cell apoptosis. The absence of SHIP1 results in loss of peripheral NK cells with impaired ability to secrete IFN-γ during cytokine receptor-mediated responses (Banh et al., 2012). Therefore, one could speculate that in the setting of AML, reduced SHIP1 and high levels of miR-155 may be associated with innate immune evasion through impaired NK cells response. Overexpression of MiR-155 has been found in NK cell type lymphoma and leukemia, and may contribute to increased survival and proliferation of malignant NK cell tumors as well (Leong et al., 2012).

3.5. miR-181

The miR-181 family consists of two miRNAs, miR-181a and miR-181b, both of which are located on chromosomes 1 and 9 respectively (Weng et al., 2015). MiR-181 acts as a tumor suppressor in the pathogenesis of AML and exhibits a significant impact on the survival of patients with AML (Weng et al., 2015), and increased expression of miR-181 has been associated with increased overall survival in AML patients (Marcucci et al., 2008). Marcucci et al. showed that expression of miR-181a and miR-181b in AML blasts was positively associated with the clinical outcome in molecular high-risk cytogenically normal (CN)-AML (with FLT3-ITD and/or wild-type NPM1) and inversely associated with the risk of an event, such as failure to achieve complete remission (CR), relapse, or death (Marcucci et al., 2008). Elevated expression of miR-181a has also been observed in less aggressive AML subtypes, further supporting an inverse correlation between miR-181a and disease severity (Debernardi et al., 2007; Isken et al., 2008). Nanbakhsh et al. demonstrated a direct impact of miR-181 modulation on tumor

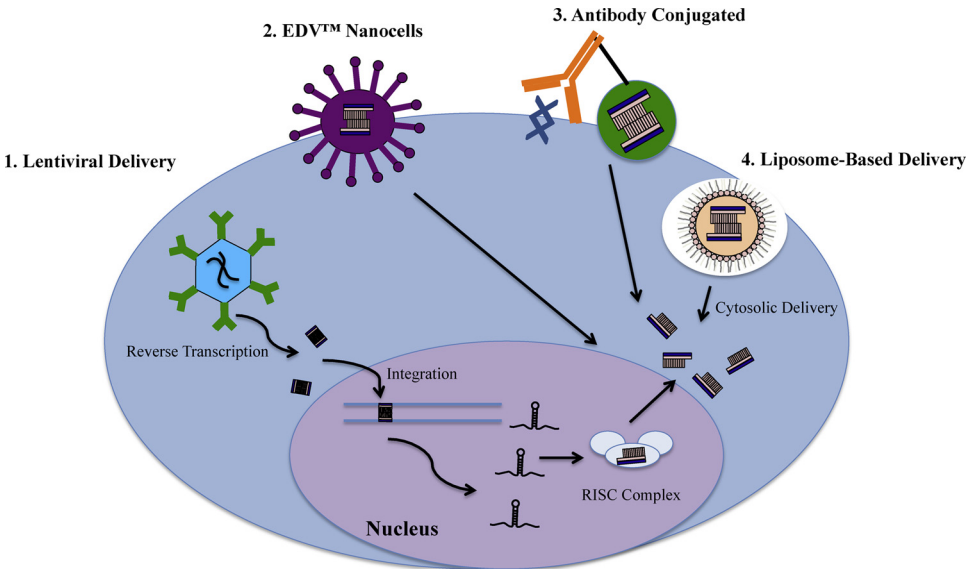

Fig. 1. MiRNA-based therapeutic strategies currently in development for the treatment of hematologic diseases.
Various miRNA therapeutic strategies are in preclinical development, the primary classes of therapeutics being evaluated include: 1) Viruses which deliver transcript encoding specific miRNA antagonists or mimics to the target cells where they are then integrated and processed to form mature products (Chen et al., 2015). Viral delivery is being evaluated clinically for the delivery of miR-15a/16 (Kasar et al., 2012); 2) EDV™ nanocells are bacterially-derived, nonviable minicells containing the miRNA mimic or antagonist of interest. MiR-16 has been evaluated in other malignancies, but has potential implications in multiple leukemias (Reid et al., 2013). EDV™ nanocells are often utilized with antibody conjugation for enhanced tumor targeting; 3) Antibody conjugation of encapsulated miRNA or attached to an RNA-binding protein (Li and Rana); 4) Liposomal-based delivery of miRNA involves the encapsulation of miRNA in liposomal complexes to protect miRNA from degradation and enhance stability in circulation (Chen et al., 2015; Huang et al., 2013; Rupaimoole and Slack, 2017).

immune evasion by knocking down miR-181 in AML cells and evaluating AML resistance to NK cell killing. AML blasts with decreased miR-181 expression were more susceptibility to NK cell mediated killing, likely due to resistance of GzmB-induced apoptosis (Nanbakhsh et al., 2015). Furthermore, silencing of miR-181a target genes (Bcl^{-}2 and MAP3K10 for U-937AML cells and MCL^{-}1 and MAP2K1 for KG-1 AML cells) significantly decreased leukemia cells susceptibility to NK mediated-lysis (Nanbakhsh et al., 2015).

4. Therapeutic targeting of miRNAs

The development of miRNA-based therapeutics for the treatment of cancer is a rapidly evolving field. The ability of a single miRNA to regulate multiple pathways promoting tumor growth simultaneously makes this treatment modality an appealing candidate for development. The majority of initial studies evaluating the role of miRNA in cancer regulation have focused on the functions of miRNA in the tumor cells themselves (Naidu et al., 2015; Rupaimoole and Slack, 2017) where miRNA are frequently downregulated. The basis of most miRNA therapies to date has been the development of synthetic oligonucleotides that mimic the functions of that particular miRNA, along with additional modifications to enhance stability and efficacy. While there are multiple miRNA-based therapies in preclinical development, there are just over 20 clinical trials that have been initiated to evaluate the efficacy of miRNA or siRNA therapies for all diseases, and only 2 of these are focused on the use of miR-based therapeutics for the treatment of cancer (Chakraborty et al., 2017). MRG-106, a synthetic miR antagonist (LNA antimiR®) of miR-155 has been one of the first to be evaluated in a Phase I clinical trial to determine the efficacy of blocking miR-155 in cutaneous T-cell lymphoma (CTCL) patients (Trial Number: NCT02580552) (Foss et al., 2017). MiR-155 has been shown to regulate multiple pro-tumorigenic pathways (including apoptosis, proliferation, and survival), and it is overexpressed in malignant CD4 + T cells in CTCL patients, along with acute myeloid leukemia (Gaidzik et al.; Kopp et al., 2013; Marcucci et al., 2012; Ralfkiaer et al., 2011; van Kester et al., 2011; Xue et al.). This clinical trial avoided several of the major roadblocks miR-based therapies have encountered when translating into the clinic. One of the early issues has been the delivery method. The anti-miR-155 trial delivers the miR-155 antimiR® directly in skin lesions in CTCL patients, circumventing major issues with systemic miR treatment. Due to their small size and natural properties, miRNA are degraded quickly by nucleases and can undergo endosomal escape upon entering the in vivo environment (Rupaimoole and Slack, 2017). This has posed a challenge to effectively deliver sufficiently high doses of the therapy to the site of the tumor. There are multiple approaches to combat these delivery issues, including encapsulating the miRNA in lipid-based nanoparticles, conjugation-based approaches to enhance cellular uptake, miRNA “sponges” for miRNA inhibition, or dendrimer complexes to enhance specific targeting (Ebert and Sharp, 2010; Li and Rana, 2014; Rupaimoole and Slack, 2017). One alternative currently being explored is the use of EDV™ nanocells (EDVs). The EDV technology seeks to exploit the endocytosis process through the introduction of bacterially-derived nonviable minicells containing the miRNA of interest coated with a bispecific antibody targeting the tumor type of interest (MacDiarmid et al., 2007). Each of these methods is focused on both protecting the miRNA therapeutic from degradation and increasing the level of specificity to enhance tumor-targeting. These approaches are currently being evaluated pre-clinically with the goal of rapid translation into the clinic (see Fig. 1).

While the ability of miRNA to target multiple tumor-promoting pathways simultaneously makes them attractive targets for development in cancer, this also elevates their off-target effects, particularly with systemic administration. In addition, emerging studies in non-tumorous cell populations indicate miRNA have the ability to play differing roles in a tissue/cell-specific manor as previously discussed (Baragaño Raneros et al., 2014). MiR-29b for example has been shown to be anti-tumorigenic in the setting of AML (Blum et al., 2010; Garzon et al., 2009; Liu et al., 2010), and pro-tumorigenic when overexpressed in NK cells (Mundy-Bosse et al., 2016a, 2016b). Recent studies suggest a major mechanism of immune evasion may be the shedding of tumor suppressing miRNA into surrounding tissue in extracellular vesicles (Yeh et al., 2015). This would eliminate the negative survival/proliferative effects in the tumor cells, while potentially decreasing the efficacy of immune cells present in the microenvironment (Minciacchi et al., 2015; Zhang et al., 2015). This evasion strategy should be considered when developing miR-based therapeutics, even when the miRNAs are targeted to specific tumor cells.

The tissue specific diversity of miRNA has led to challenges translating miRNA-based therapeutics from limited preclinical testing into successful clinical therapies. Recently, Mirna Therapeutics halted a Phase I clinical trial of MRX34, a liposomal encapsulated miR-34a mimic, being evaluated in patients with advanced solid tumors due to severe immune-related responses, including multiple fatalities (Clinical Trial Number: NCT01829971) (Beg et al., 2017). These early challenges

of miRNA-based therapeutics indicate the continued need for further evaluation into the effects of miRNA not just on the tumor cells, but within the complex microenvironment that exists within patients.

5. Conclusion

NK cells are powerful immune effectors capable of improving therapy-related outcomes. MiRNA regulation of NK cells may be a targetable therapeutic strategy to improve NK cell maturation and function, thus promoting anti-leukemic efficacy. Specific targeting with miRNA therapeutics will be critical for success as miRNA often play opposing roles in tumor and non-tumorous cells. Although the NK cells that are derived from AML patients are impaired, it has also been shown that the impaired NK cell phenotype is reversible, indicating the potential for therapeutic intervention (Fauriat et al., 2007; Lion et al., 2012; Nguyen et al., 2008). Several unanswered questions remain as to the true mechanism of miRNAs as regulators of NK cell development and anti-leukemic function. These include: 1) Does the role of miRNA in NK cell development differ depending on the tissue site? 2) What role do miRNA play in regulating the developmental transitions between functionally competent NK cells ($CD56^{bright}$ and $CD56^{dim}$) 3) How do changes in miRNA profiles impact NK cell development in normal and leukemic environments? 4) Is miRNA modulation a means of evading innate immune evasion in developing leukemias? It is our hope that continued research in this area will help augment NK cell therapy and contribute to improved patient outcomes.

Conflicts of interest

The authors declare that there are no conflicts of interest in relation to this manuscript.

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References

Baek, D., Villén, J., Shin, C., Camargo, F.D., Gygi, S.P., Bartel, D.P., 2008. The impact of microRNAs on protein output. Nature 455, 64.
Banh, C., Miah, S.M.S., Kerr, W.G., Brossay, L., 2012. Mouse natural killer cell development and maturation are differentially regulated by SHIP-1. Blood 120, 4583–4590.
Baragaño Raneros, A., Martín-Palanco, V., Fernandez, A.F., Rodriguez, R.M., Fraga, M.F., Lopez-Larrea, C., Suarez-Alvarez, B., 2014. Methylation of NKG2D ligands contributes to immune system evasion in acute myeloid leukemia. Genes Immun. 16, 71.
Bartel, D.P., 2009. MicroRNAs: target recognition and regulatory functions. Cell 136, 215–233.
Beck, R.C., Padival, M., Yeh, D., Ralston, J., Cooke, K.R., Lowe, J.B., 2009. The notch ligands jagged2, delta1, and delta4 induce differentiation and expansion of functional human NK cells from CD34+ cord blood hematopoietic progenitor cells. Biol. Blood Marrow Transplant. 15, 1026–1037.
Beg, M.S., Brenner, A.J., Sachdev, J., Borad, M., Kang, Y.K., Stoudemire, J., Smith, S., Bader, A.G., Kim, S., Hong, D.S., 2017. Phase I study of MRX34, a liposomal miR-34a mimic, administered twice weekly in patients with advanced solid tumors. Invest. New Drugs 35, 180–188.
Bergmann, L., Miething, C., Maurer, U., Brieger, J., Karakas, T., Weidmann, E., Hoelzer, D., 1997. High levels of wilms' tumor gene (wt1) mRNA in acute myeloid leukemias are associated with a worse long-term outcome. Blood 90, 1217–1225.
Béziat, V., Dalgard, O., Asselah, T., Halfon, P., Bedossa, P., Boudifa, A., Hervier, B., Theodorou, I., Martinot, M., Debré, P., Björkström, N.K., Malmberg, K.-J., Marcellin, P., Vieillard, V., 2012. CMV drives clonal expansion of NKG2C+ NK cells expressing self-specific KIRs in chronic hepatitis patients. Eur. J. Immunol. 42, 447–457.
Bezman, N.A., Cedars, E., Steiner, D.F., Blelloch, R., Hesslein, D.G.T., Lanier, L.L., 2010. Distinct requirements of microRNAs in NK cell activation, survival, and function. J. Immunol. 185, 3835–3846.
Bezman, N.A., Chakraborty, T., Bender, T., Lanier, L.L., 2011. miR-150 regulates the development of NK and iNKT cells. J. Exp. Med. 208, 2717–2731.
Björkström, N.K., Lindgren, T., Stoltz, M., Fauriat, C., Braun, M., Evander, M., Michaëlsson, J., Malmberg, K.-J., Klingström, J., Ahlm, C., Ljunggren, H.-G., 2011. Rapid expansion and long-term persistence of elevated NK cell numbers in humans infected with hantavirus. J. Exp. Med. 208, 13–21.
Blum, W., Garzon, R., Klisovic, R.B., Schwind, S., Walker, A., Geyer, S., Liu, S., Havelange, V., Becker, H., Schaaf, L., Mickle, J., Devine, H., Kefauver, C., Devine, S.M., Chan, K.K., Heerema, N.A., Bloomfield, C.D., Grever, M.R., Byrd, J.C., Villalona-Calero, M., Croce, C.M., Marcucci, G., 2010. Clinical response and miR-29b predictive significance in older AML patients treated with a 10-day schedule of decitabine. Proc. Natl. Acad. Sci. U. S. A. 107, 7473–7478.
Caligiuri, M.A., 2008. Human natural killer cells. Blood 112, 461–469.
Calin, G.A., Dumitru, C.D., Shimizu, M., Bichi, R., Zupo, S., Noch, E., Aldler, H., Rattan, S., Keating, M., Rai, K., Rassenti, L., Kipps, T., Negrini, M., Bullrich, F., Croce, C.M., 2002. Frequent deletions and down-regulation of micro- RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. Proc. Natl. Acad. Sci. U. S. A. 99, 15524–15529.
Calin, G.A., Ferracin, M., Cimmino, A., Di Leva, G., Shimizu, M., Wojcik, S.E., Iorio, M.V., Visone, R., Sever, N.I., Fabbri, M., Iuliano, R., Palumbo, T., Pichiorri, F., Roldo, C., Garzon, R., Sevignani, C., Rassenti, L., Alder, H., Volinia, S., Liu, C.-g., Kipps, T.J., Negrini, M., Croce, C.M., 2005. A microRNA signature associated with prognosis and progression in chronic lymphocytic leukemia. N. Engl. J. Med. 353, 1793–1801.
Calin, G.A., Cimmino, A., Fabbri, M., Ferracin, M., Wojcik, S.E., Shimizu, M., Taccioli, C., Zanesi, N., Garzon, R., Aqeilan, R.I., Alder, H., Volinia, S., Rassenti, L., Liu, X., Liu, C.G., Kipps, T.J., Negrini, M., Croce, C.M., 2008. MiR-15a and miR-16-1 cluster functions in human leukemia. Proc. Natl. Acad. Sci. U. S. A. 105.
Cany, J., Roeven, M.W.H., Hoogstad-van Evert, J.S., Hobo, W., Maas, F., Franco Fernandez, R., Blijlevens, N.M.A., van der Velden, W.J., Huls, G., Jansen, J.H., Schaap, N.P.M., Dolstra, H., 2018. Decitabine enhances targeting of AML cells by $CD34^{+}$ progenitor-derived NK cells in NOD/SCID/$IL2Rg^{null}$ mice. Blood 131, 202–214.
Chakraborty, C., Sharma, A.R., Sharma, G., Doss, C.G.P., Lee, S.S., 2017. Therapeutic miRNA and siRNA: moving from bench to clinic as next generation medicine. Mol. Ther. Nucleic Acids 8, 132–143.
Chen, Y., Gao, D.Y., Huang, L., 2015. In vivo delivery of miRNAs for cancer therapy: challenges and strategies. Adv. Drug Deliv. Rev. 81, 128–141.
Chen, X., Han, J., Chu, J., Zhang, L., Zhang, J., Chen, C., Chen, L., Wang, Y., Wang, H., Yi, L., Elder, J.B., Wang, Q.-E., He, X., Kaur, B., Chiocca, E.A., Yu, J., 2016. A combinational therapy of EGFR-CAR NK cells and oncolytic herpes simplex virus 1 for breast cancer brain metastases. Oncotarget 7, 27764–27777.
Cichocki, F., Miller, J.S., 2010. In vitro development of human killer-immunoglobulin receptor-positive NK cells. Methods Mol. Biol. 612, 15–26.
Cichocki, F., Felices, M., McCullar, V., Presnell, S.R., Al-Attar, A., Lutz, C.T., Miller, J.S., 2011. Cutting edge: microRNA-181 promotes human NK cell development by regulating notch signaling. J. Immunol. 187, 6171–6175.
Cichocki, F., Cooley, S., Davis, Z., DeFor, T.E., Schlums, H., Zhang, B., Brunstein, C.G., Blazar, B.R., Wagner, J., Diamond, D.J., Verneris, M.R., Bryceson, Y.T., Weisdorf, D.J., Miller, J.S., 2016. CD56(dim)CD57(+)NKG2C(+) NK cell expansion is associated with reduced leukemia relapse after reduced intensity HCT. Leukemia 30, 456–463.
Cimmino, A., Calin, G.A., Fabbri, M., Iorio, M.V., Ferracin, M., Shimizu, M., Wojcik, S.E., Aqeilan, R.I., Zupo, S., Dono, M., Rassenti, L., Alder, H., Volinia, S., Liu, C.G., Kipps, T.J., Negrini, M., Croce, C.M., 2005. miR-15 and miR-16 induce apoptosis by targeting BCL2. Proc. Natl. Acad. Sci. U. S. A. 102.
Colucci, F., Caligiuri, M.A., Di Santo, J.P., 2003. What does it take to make a natural killer? Nat. Rev. Immunol. 3, 413.
Cooper, M.A., Elliott, J.M., Keyel, P.A., Yang, L., Carrero, J.A., Yokoyama, W.M., 2009. Cytokine-induced memory-like natural killer cells. Proc. Natl. Acad. Sci. U. S. A. 106, 1915–1919.
Corthals, S.L., Sun, S.M., Kuiper, R., de Knegt, Y., Broyl, A., van der Holt, B., Beverloo, H.B., Peeters, J.K., el Jarari, L., Lokhorst, H.M., Zweegman, S., Jongen-Lavrencic, M., Sonneveld, P., 2011. MicroRNA signatures characterize multiple myeloma patients. Leukemia 25, 1784.
Costello, R.T., Sivori, S., Marcenaro, E., Lafage-Pochitaloff, M., Mozziconacci, M.-J., Reviron, D., Gastaut, J.-A., Pende, D., Olive, D., Moretta, A., 2002. Defective expression and function of natural killer cell–triggering receptors in patients with acute myeloid leukemia. Blood 99, 3661–3667.
Costinean, S., Zanesi, N., Pekarsky, Y., Tili, E., Volinia, S., Heerema, N., Croce, C.M., 2006. Pre-B cell proliferation and lymphoblastic leukemia/high-grade lymphoma in Eμ-miR155 transgenic mice. Proc. Natl. Acad. Sci. 103, 7024–7029.
Croce, C.M., 2009. Causes and consequences of microRNA dysregulation in cancer. Nat. Rev. Genet. 10.
Debernardi, S., Skoulakis, S., Molloy, G., Chaplin, T., Dixon-McIver, A., Young, B.D., 2007. MicroRNA miR-181a correlates with morphological sub-class of acute myeloid leukaemia and the expression of its target genes in global genome-wide analysis. Leukemia 21, 912.
Ebert, M.S., Sharp, P.A., 2010. MicroRNA sponges: progress and possibilities. RNA 16, 2043–2050.
Fauriat, C., Just-Landi, S., Mallet, F., Arnoulet, C., Sainty, D., Olive, D., Costello, R.T., 2007. Deficient expression of NCR in NK cells from acute myeloid leukemia: evolution during leukemia treatment and impact of leukemia cells in NCR^{dull} phenotype induction. Blood 109, 323–330.
Fehniger, T.A., Wylie, T., Germino, E., Leong, J.W., Magrini, V.J., Koul, S., Keppel, C.R., Schneider, S.E., Koboldt, D.C., Sullivan, R.P., Heinz, M.E., Crosby, S.D., Nagarajan, R., Ramsingh, G., Link, D.C., Ley, T.J., Mardis, E.R., 2010. Next-generation sequencing identifies the natural killer cell microRNA transcriptome. Genome Res. 20, 1590–1604.
Foley, B., Cooley, S., Verneris, M.R., Pitt, M., Curtsinger, J., Luo, X., Lopez-Vergès, S., Lanier, L.L., Weisdorf, D., Miller, J.S., 2012. Cytomegalovirus reactivation after allogeneic transplantation promotes a lasting increase in educated $NKG2C^{+}$ natural killer cells with potent function. Blood 119, 2665–2674.
Foss, F., Querfeld, C., Porcu, P., Kim, Y., Pacheco, T., Halwani, A., DeSimone, J., William, B., Seto, A., Ruckman, J., Landry, M., Jackson, A., Pestano, L., Dickinson, B., Sanseverino, M., Rodman, D., Rubin, P., Gordon, G., Marshall, W., 2017. Phase 1 trial evaluating MRG-106, a synthetic inhibitor of microRNA-155, in patients with cutaneous t-cell lymphoma (CTCL). Abstract #7564. J. Clin. Oncol. 35.
Freud, A.G., Caligiuri, M.A., 2006. Human natural killer cell development. Immunol. Rev.

214, 56–72.
Freud, A.G., Becknell, B., Roychowdhury, S., Mao, H.C., Ferketich, A.K., Nuovo, G.J., Hughes, T.L., Marburger, T.B., Sung, J., Baiocchi, R.A., Guimond, M., Caligiuri, M.A., 2005. A human CD34(+) subset resides in lymph nodes and differentiates into CD56^{bright} natural killer cells. Immunity 22, 295–304.
Freud, A.G., Yokohama, A., Becknell, B., Lee, M.T., Mao, H.C., Ferketich, A.K., Caligiuri, M.A., 2006. Evidence for discrete stages of human natural killer cell differentiation in vivo. J. Exp. Med. 203, 1033–1043.
Freud, A.G., Yu, J., Caligiuri, M.A., 2014. Human natural killer cell development in secondary lymphoid tissues. Semin. Immunol. 26, 132–137.
Freud, A.G., Keller, K.A., Scoville, S.D., Mundy-Bosse, B.L., Cheng, S., Youssef, Y., Hughes, T., Zhang, X., Mo, X., Porcu, P., Baiocchi, R.A., Yu, J., Carson, W.E., Caligiuri, M.A., 2016. NKp80 defines a critical step during human natural killer cell development. Cell Rep. 16, 379–391.
Freud, A.G., Mundy-Bosse, B.L., Yu, J., Caligiuri, M.A., 2017. The Broad spectrum of human natural killer cell diversity. Immunity 47, 820–833.
Gaidzik, V.I., Teleanu, V., Papaemmanuil, E., Weber, D., Paschka, P., Hahn, J., Wallrabenstein, T., Kolbinger, B., Köhne, C.H., Horst, H.A., Brossart, P., Held, G., Kündgen, A., Ringhoffer, M., Götze, K., Rummel, M., Gerstung, M., Campbell, P., Kraus, J.M., Kestler, H.A., Thol, F., Heuser, M., Schlegelberger, B., Ganser, A., Bullinger, L., Schlenk, R.F., Döhner, K., Döhner, H., 2016. RUNX1 mutations in acute myeloid leukemia are associated with distinct clinico-pathologic and genetic features. Leukemia 30, 2160.
Gao, S.-m., Xing, C.-y., Chen, C.-q., Lin, S.-s., Dong, P.-h., Yu, F.-j., 2011. miR-15a and miR-16-1 inhibit the proliferation of leukemic cells by down-regulating WT1 protein level. J. Exp. Clin. Cancer Res. 30, 110.
Garzon, R., Garofalo, M., Martelli, M.P., Briesewitz, R., Wang, L., Fernandez-Cymering, C., Volinia, S., Liu, C.-G., Schnittger, S., Haferlach, T., Liso, A., Diverio, D., Mancini, M., Meloni, G., Foa, R., Martelli, M.F., Mecucci, C., Croce, C.M., Falini, B., 2008a. Distinctive microRNA signature of acute myeloid leukemia bearing cytoplasmic mutated nucleophosmin. Proc. Natl. Acad. Sci. U. S. A. 105, 3945–3950.
Garzon, R., Volinia, S., Liu, C.-G., Fernandez-Cymering, C., Palumbo, T., Pichiorri, F., Fabbri, M., Coombes, K., Alder, H., Nakamura, T., Flomenberg, N., Marcucci, G., Calin, G.A., Kornblau, S.M., Kantarjian, H., Bloomfield, C.D., Andreeff, M., Croce, C.M., 2008b. MicroRNA signatures associated with cytogenetics and prognosis in acute myeloid leukemia. Blood 111, 3183–3189.
Garzon, R., Heaphy, C.E.A., Havelange, V., Fabbri, M., Volinia, S., Tsao, T., Zanesi, N., Kornblau, S.M., Marcucci, G., Calin, G.A., Andreeff, M., Croce, C.M., 2009. MicroRNA 29b functions in acute myeloid leukemia. Blood 114, 5331–5341.
Grzywacz, B., Kataria, N., Sikora, M., Oostendorp, R.A., Dzierzak, E.A., Blazar, B.R., Miller, J.S., Verneris, M.R., 2006. Coordinated acquisition of inhibitory and activating receptors and functional properties by developing human natural killer cells. Blood 108, 3824–3833.
Gumá, M., Angulo, A., Vilches, C., Gómez-Lozano, N., Malats, N., López-Botet, M., 2004. Imprint of human cytomegalovirus infection on the NK cell receptor repertoire. Blood 104, 3664–3671.
Gumá, M., Cabrera, C., Erkizia, I., Bofill, M., Clotet, B., Ruiz, L., López-Botet, M., 2006. Human cytomegalovirus infection Is associated with increased proportions of NK cells that express the CD94/NKG2C receptor in aviremic HIV-1–positive patients. J. Infect. Dis. 194, 38–41.
Haraguchi, K., Suzuki, T., Koyama, N., Kumano, K., Nakahara, F., Matsumoto, A., Yokoyama, Y., Sakata-Yanagimoto, M., Masuda, S., Takahashi, T., Kamijo, A., Takahashi, K., Takanashi, M., Okuyama, Y., Yasutomo, K., Sakano, S., Yagita, H., Kurokawa, M., Ogawa, S., Chiba, S., 2009. Notch activation induces the generation of functional NK cells from human cord blood CD34-positive cells devoid of IL-15. J. Immunol. 182, 6168–6178.
Hayakawa, Y., Smyth, M.J., 2006. CD27 dissects mature NK cells into two subsets with distinct responsiveness and migratory capacity. J. Immunol. 176, 1517–1524.
He, L., Hannon, G.J., 2004. MicroRNAs: small RNAs with a big role in gene regulation. Nat. Rev. Genet. 5, 522–531.
Hershkovitz Rokah, O., Granot, G., Ovcharenko, A., Modai, S., Pasmanik-Chor, M., Toren, A., Shomron, N., Shpilberg, O., 2012. Downregulation of Mir-31, Mir-155, and Mir-564 in chronic myeloid leukemia cells. PLoS One 7, e35501.
Hornick, N.I., Doron, B., Abdelhamed, S., Huan, J., Harrington, C.A., Shen, R., Cambronne, X.A., Chakkaramakkil Verghese, S., Kurre, P., 2016. AML suppresses hematopoiesis by releasing exosomes that contain microRNAs targeting c-MYB. Sci. Signal. 9 ra88-ra88.
Hou, H.-A., Huang, T.-C., Lin, L.-I., Liu, C.-Y., Chen, C.-Y., Chou, W.-C., Tang, J.-L., Tseng, M.-H., Huang, C.-F., Chiang, Y.-C., Lee, F.-Y., Liu, M.-C., Yao, M., Huang, S.-Y., Ko, B.-S., Hsu, S.-C., Wu, S.-J., Tsay, W., Chen, Y.-C., Tien, H.-F., 2010. WT1 mutation in 470 adult patients with acute myeloid leukemia: stability during disease evolution and implication of its incorporation into a survival scoring system. Blood 115, 5222–5231.
Huang, X., Schwind, S., Yu, B., Santhanam, R., Wang, H., Hoellerbauer, P., Mims, A., Klisovic, R., Walker, A.R., Chan, K.K., Blum, W., Perrotti, D., Byrd, J.C., Bloomfield, C.D., Caligiuri, M.A., Lee, R.J., Garzon, R., Muthusamy, N., Lee, L.J., Marcucci, G., 2013. Targeted delivery of microRNA-29b by transferrin-conjugated anionic lipopolyplex nanoparticles: a novel therapeutic strategy in acute myeloid leukemia. Clin. Cancer Res. 19, 2355–2367.
Hwang, I., Zhang, T., Scott, J.M., Kim, A.R., Lee, T., Kakarla, T., Kim, A., Sunwoo, J.B., Kim, S., 2012. Identification of human NK cells that are deficient for signaling adaptor FcRγ and specialized for antibody-dependent immune functions. Int. Immunol. 24, 793–802.
Isken, F., Steffen, B., Merk, S., Dugas, M., Markus, B., Tidow, N., Zühlsdorf, M., Illmer, T., Thiede, C., Berdel, W.E., Serve, H., Müller-Tidow, C., 2008. Identification of acute myeloid leukaemia associated microRNA expression patterns. Br. J. Haematol. 140, 153–161.
Kärre, K., Ljunggren, H.G., Piontek, G., Kiessling, R., 1986. Selective rejection of H–2-deficient lymphoma variants suggests alternative immune defence strategy. Nature 319, 675.
Kasar, S., Salerno, E., Yuan, Y., Underbayev, C., Vollenweider, D., Laurindo, M.F., Fernandes, H., Bonci, D., Addario, A., Mazzella, F., Raveche, E., 2012. Systemic in vivo lentiviral delivery of miR-15a/16 reduces malignancy in the NZB de novo mouse model of chronic lymphocytic leukemia. Genes Immun. 13, 109–119.
Khaznadar, Z., Boissel, N., Agaugué, S., Henry, G., Cheok, M., Vignon, M., Geromin, D., Cayuela, J.-M., Castaigne, S., Pautas, C., Raffoux, E., Lachuer, J., Sigaux, F., Preudhomme, C., Dombret, H., Dulphy, N., Toubert, A., 2015. Defective NK cells in acute myeloid leukemia patients at diagnosis are associated with blast transcriptional signatures of immune evasion. J. Immunol. 195, 2580–2590.
Knorr, D., Bachanova, V., Verneris, M.R., Miller, J.S., 2014. Clinical utility of natural killer cells in cancer therapy and transplantation. Semin. Immunol. 26, 161–172.
Kopp, K.L., Ralfkiaer, U., Nielsen, B.S., Gniadecki, R., Woetmann, A., Ødum, N., Ralfkiaer, E., 2013. Expression of miR-155 and miR-126 in situ in cutaneous T-cell lymphoma. APMIS 121, 1020–1024.
Lee, J., Zhang, T., Hwang, I., Kim, A., Nitschke, L., Kim, M., Scott, J.M., Kamimura, Y., Lanier, L.L., Kim, S., 2015. Epigenetic modification and antibody-dependent expansion of memory-like NK cells in human cytomegalovirus-infected individuals. Immunity 42, 431–442.
Leong, J.W., Sullivan, R.P., Fehniger, T.A., 2012. Natural killer cell regulation by microRNAs in health and disease. J. Biomed. Biotechnol. 2012, 632329.
Li, Z., Rana, T.M., 2014. Therapeutic targeting of microRNAs: current status and future challenges. Nat Rev Drug Discov 13, 622–638.
Lion, E., Willemen, Y., Berneman, Z.N., Van Tendeloo, V.F.I., Smits, E.L.J., 2012. Natural killer cell immune escape in acute myeloid leukemia. Leukemia 26, 2019.
Liu, S., Wu, L.C., Pang, J., Santhanam, R., Schwind, S., Wu, Y.Z., Hickey, C.J., Yu, J., Becker, H., Maharry, K., Radmacher, M.D., Li, C., Whitman, S.P., Mishra, A., Stauffer, N., Eiring, A.M., Briesewitz, R., Baiocchi, R.A., Chan, K.K., Paschka, P., Caligiuri, M.A., Byrd, J.C., Croce, C.M., Bloomfield, C.D., Perrotti, D., Garzon, R., Marcucci, G., 2010. Sp1/NFkappaB/HDAC/miR-29b regulatory network in KIT-driven myeloid leukemia. Cancer Cell 17, 333–347.
Liu, X., Wang, Y., Sun, Q., Yan, J., Huang, J., Zhu, S., Yu, J., 2012. Identification of microRNA transcriptome involved in human natural killer cell activation. Immunol. Lett. 143, 208–217.
Ljunggren, H.-G., Kärre, K., 1990. In search of the 'missing self': MHC molecules and NK cell recognition. Immunol. Today 11, 237–244.
Lopez-Verges, S., Milush, J.M., Pandey, S., York, V.A., Arakawa-Hoyt, J., Pircher, H., Norris, P.J., Nixon, D.F., Lanier, L.L., 2010. CD57 defines a functionally distinct population of mature NK cells in the human CD56dimCD16+ NK-cell subset. Blood 116, 3865–3874.
Lopez-Vergès, S., Milush, J.M., Schwartz, B.S., Pando, M.J., Jarjoura, J., York, V.A., Houchins, J.P., Miller, S., Kang, S.-M., Norris, P.J., Nixon, D.F., Lanier, L.L., 2011. Expansion of a unique CD57(+)NKG2C(hi) natural killer cell subset during acute human cytomegalovirus infection. Proc. Natl. Acad. Sci. U. S. A. 108, 14725–14732.
Ma, F., Xu, S., Liu, X., Zhang, Q., Xu, X., Liu, M., Hua, M., Li, N., Yao, H., Cao, X., 2011. The microRNA miR-29 controls innate and adaptive immune responses to intracellular bacterial infection by targeting interferon-[gamma]. Nat Immunol 12, 861–869.
MacDiarmid, J.A., Mugridge, N.B., Weiss, J.C., Phillips, L., Burn, A.L., Paulin, R.P., Haasdyk, J.E., Dickson, K.A., Brahmbhatt, V.N., Pattison, S.T., James, A.C., Al Bakri, G., Straw, R.C., Stillman, B., Graham, R.M., Brahmbhatt, H., 2007. Bacterially derived 400 nm particles for encapsulation and cancer cell targeting of chemotherapeutics. Cancer Cell 11, 431–445.
Marcucci, G., Radmacher, M.D., Maharry, K., Mrózek, K., Ruppert, A.S., Paschka, P., Vukosavljevic, T., Whitman, S.P., Baldus, C.D., Langer, C., Liu, C.-G., Carroll, A.J., Powell, B.L., Garzon, R., Croce, C.M., Kolitz, J.E., Caligiuri, M.A., Larson, R.A., Bloomfield, C.D., 2008. MicroRNA expression in cytogenetically normal acute myeloid leukemia. N. Engl. J. Med. 358, 1919–1928.
Marcucci, G., Maharry, K., Metzeler, K.H., Volinia, S., Wu, Y.-Z., Mrózek, K., Nicolet, D., Kohlschimdt, J., Whitman, S., Mendler, J.H., Schwind, S., Becker, H., Eisfeld, A.-K., Carroll, A.J., Powell, B.L., Kolitz, J.E., Garzon, R., Caligiuri, M.A., Stone, R.M., Bloomfield, C.D., 2012. The clinical role of micrornas (miRs) in cytogenetically normal (CN) acute myeloid leukemia (AML): miR-155 upregulation independently identifies high-risk patients (pts). Blood 120, 1387.
Mims, A., Walker, A.R., Huang, X., Sun, J., Wang, H., Santhanam, R., Dorrance, A.M., Walker, C., Hoellerbauer, P., Tarighat, S.S., Chan, K.K., Klisovic, R.B., Perrotti, D., Caligiuri, M.A., Byrd, J.C., Chen, C.-S., Lee, L.J., Jacob, S., Mrózek, K., Bloomfield, C.D., Blum, W., Garzon, R., Schwind, S., Marcucci, G., 2013. Increased anti-leukemic activity of decitabine via AR-42-induced upregulation of miR-29b: a novel epigenetic-targeting approach in acute myeloid leukemia. Leukemia 27, 871–878.
Min, Y.J., Lee, J.-H., Choi, S.-J., Chi, H.-S., Lee, J.-S., Kim, W.-K., Lee, K.-H., 2004. Prognostic significance of Fas (CD95) and TRAIL receptors (DR4/DR5) expression in acute myelogenous leukemia. Leuk. Res. 28, 359–365.
Minciacchi, V.R., Freeman, M.R., Di Vizio, D., 2015. Extracellular vesicles in cancer: exosomes, microvesicles and the emerging role of large oncosomes. Semin. Cell Dev. Biol. 40, 41–51.
Mishra, A., Liu, S., Sams, Gregory H., Curphey, Douglas P., Santhanam, R., Rush, Laura J., Schaefer, D., Falkenberg, Lauren G., Sullivan, L., Jaroncyk, L., Yang, X., Fisk, H., Wu, L.-C., Hickey, C., Chandler, Jason C., Wu, Y.-Z., Heerema, Nyla A., Chan, Kenneth K., Perrotti, D., Zhang, J., Porcu, P., Racke, Frederick K., Garzon, R., Lee Robert, J., Marcucci, G., Caligiuri, Michael A., 2012. Aberrant overexpression of IL-15 initiates large granular lymphocyte leukemia through chromosomal instability and DNA hypermethylation. Cancer Cell 22, 645–655.
Miwa, H., Beran, M., Saunders, G.F., 1992. Expression of the wilms' tumor gene (WT1) in human leukemias. Leukemia 6, 405–409.
Monticelli, S., Ansel, K.M., Xiao, C., Socci, N.D., Krichevsky, A.M., Thai, T.-H., Rajewsky, N., Marks, D.S., Sander, C., Rajewsky, K., Rao, A., Kosik, K.S., 2005. MicroRNA profiling of the murine hematopoietic system. Genome Biol. 6 R71-R71.
Moretta, L., Locatelli, F., Pende, D., Marcenaro, E., Mingari, M.C., Moretta, A., 2011. Killer Ig–like receptor-mediated control of natural killer cell alloreactivity in haploidentical hematopoietic stem cell transplantation. Blood 117, 764–771.

Morris, V.A., Zhang, A., Yang, T., Stirewalt, D.L., Ramamurthy, R., Meshinchi, S., Oehler, V.G., 2013. MicroRNA-150 expression induces myeloid differentiation of human acute leukemia cells and normal hematopoietic progenitors. PLoS One 8, e75815.
Mraz, M., Chen, L., Rassenti, L.Z., Ghia, E.M., Li, H., Jepsen, K., Smith, E.N., Messer, K., Frazer, K.A., Kipps, T.J., 2014. miR-150 influences B-cell receptor signaling in chronic lymphocytic leukemia by regulating expression of GAB1 and FOXP1. Blood 124, 84–95.
Mundy-Bosse, B.L., Scoville, S.D., Chen, L., McConnell, K., Mao, H.C., Ahmed, E.H., Zorko, N., Harvey, S., Cole, J., Zhang, X., Costinean, S., Croce, C.M., Larkin, K., Byrd, J.C., Vasu, S., Blum, W., Yu, J., Freud, A.G., Caligiuri, M.A., 2016a. MicroRNA-29b mediates altered innate immune development in acute leukemia. J. Clin. Invest. 126, 4404–4416.
Mundy-Bosse, B.L., Scoville, S.D., Chen, L., McConnell, K., Mao, H.C., Ahmed, E.H., Zorko, N., Harvey, S., Cole, J., Zhang, X., Costinean, S., Croce, C.M., Larkin, K., Byrd, J.C., Vasu, S., Blum, W., Yu, J., Freud, A.G., Caligiuri, M.A., 2016b. MicroRNA-29b mediates altered innate immune development in acute leukemia. J. Clin. Invest. 126, 4404–4416.
Nabekura, T., Lanier, L.L., 2016. Tracking the fate of antigen-specific versus cytokine-activated natural killer cells after cytomegalovirus infection. J. Exp. Med. 213, 2745–2758.
Naidu, S., Magee, P., Garofalo, M., 2015. MiRNA-based therapeutic intervention of cancer. J. Hematol. Oncol. 8, 68.
Nanbakhsh, A., Visentin, G., Olive, D., Janji, B., Mussard, E., Dessen, P., Meurice, G., Zhang, Y., Louache, F., Bourhis, J.-H., Chouaib, S., 2015. miR-181a modulates acute myeloid leukemia susceptibility to natural killer cells. Oncoimmunology 4, e996475.
Nguyen, S., Beziat, V., Dhedin, N., Kuentz, M., Vernant, J.P., Debre, P., Vieillard, V., 2008. HLA-E upregulation on IFN-γ-activated AML blasts impairs CD94/NKG2A-dependent NK cytolysis after haplo-mismatched hematopoietic SCT. Bone Marrow Transplant. 43, 693.
Ni, F., Sun, R., Fu, B., Wang, F., Guo, C., Tian, Z., Wei, H., 2013. IGF-1 promotes the development and cytotoxic activity of human NK cells. Nat. Commun. 4, 1479.
Ni, F., Guo, C., Sun, R., Fu, B., Yang, Y., Wu, L., Ren, S., Tian, Z., Wei, H., 2015. MicroRNA transcriptomes of distinct human NK cell populations identify miR-362-5p as an essential regulator of NK cell function. Sci. Rep. 5, 9993.
Nielsen, C.M., White, M.J., Goodier, M.R., Riley, E.M., 2013. Functional significance of CD57 expression on human NK cells and relevance to disease. Front Immunol 4, 422.
Petitdemange, C., Becquart, P., Wauquier, N., Béziat, V., Debré, P., Leroy, E.M., Vieillard, V., 2011. Unconventional repertoire profile Is imprinted during acute chikungunya infection for natural killer cells polarization toward cytotoxicity. PLoS Pathog. 7, e1002268.
Poli, A., Michel, T., Thérésine, M., Andrès, E., Hentges, F., Zimmer, J., 2009. CD56bright natural killer (NK) cells: an important NK cell subset. Immunology 126, 458–465.
Quentmeier, H., Reinhardt, J., Zaborski, M., Drexler, H.G., 2003. FLT3 mutations in acute myeloid leukemia cell lines. Leukemia 17, 120.
Ralfkiaer, U., Hagedorn, P.H., Bangsgaard, N., Lovendorf, M.B., Ahler, C.B., Svensson, L., Kopp, K.L., Vennegaard, M.T., Lauenborg, B., Zibert, J.R., Krejsgaard, T., Bonefeld, C.M., Sokilde, R., Gjerdrum, L.M., Labuda, T., Mathiesen, A.M., Gronbaek, K., Wasik, M.A., Sokolowska-Wojdylo, M., Queille-Roussel, C., Gniadecki, R., Ralfkiaer, E., Geisler, C., Litman, T., Woetmann, A., Glue, C., Ropke, M.A., Skov, L., Odum, N., 2011. Diagnostic microRNA profiling in cutaneous T-cell lymphoma (CTCL). Blood 118, 5891–5900.
Reid, G., Pel, M.E., Kirschner, M.B., Cheng, Y.Y., Mugridge, N., Weiss, J., Williams, M., Wright, C., Edelman, J.J., Vallely, M.P., McCaughan, B.C., Klebe, S., Brahmbhatt, H., MacDiarmid, J.A., van Zandwijk, N., 2013. Restoring expression of miR-16: a novel approach to therapy for malignant pleural mesothelioma. Ann. Oncol. 24, 3128–3135.
Romee, R., Rosario, M., Berrien-Elliott, M.M., Wagner, J.A., Jewell, B.A., Schappe, T., Leong, J.W., Abdel-Latif, S., Schneider, S.E., Willey, S., Neal, C.C., Yu, L., Oh, S.T., Lee, Y.-S., Mulder, A., Claas, F., Cooper, M.A., Fehniger, T.A., 2016. Cytokine-induced memory-like natural killer cells exhibit enhanced responses against myeloid leukemia. Sci. Transl. Med. 8 357ra123-357ra123.
Ruggeri, L., Capanni, M., Urbani, E., Perruccio, K., Shlomchik, W.D., Tosti, A., Posati, S., Rogaia, D., Frassoni, F., Aversa, F., Martelli, M.F., Velardi, A., 2002. Effectiveness of donor natural killer cell alloreactivity in mismatched hematopoietic transplants. Science 295, 2097–2100.
Rupaimoole, R., Slack, F.J., 2017. MicroRNA therapeutics: towards a new era for the management of cancer and other diseases. Nat. Rev. Drug Discov. 16, 203–222.
Sampath, D., Liu, C., Vasan, K., Sulda, M., Puduvalli, V.K., Wierda, W.G., Keating, M.J., 2012. Histone deacetylases mediate the silencing of miR-15a, miR-16, and miR-29b in chronic lymphocytic leukemia. Blood 119, 1162–1172.
Schimmer, A.D., Pedersen, I.M., Kitada, S., Eksioglu-Demiralp, E., Minden, M.D., Pinto, R., Mah, K., Andreeff, M., Kim, Y., Suh, W.S., Reed, J.C., 2003. Functional blocks in caspase activation pathways are common in leukemia and predict patient response to induction chemotherapy. Cancer Res. 63, 1242–1248.
Shen, J., Pan, J., Du, C., Si, W., Yao, M., Xu, L., Zheng, H., Xu, M., Chen, D., Wang, S., Fu, P., Fan, W., 2017. Silencing NKG2D ligand-targeting miRNAs enhances natural killer cell-mediated cytotoxicity in breast cancer. Cell Death Dis. 8, e2740.
Starczynowski, D.T., Morin, R., McPherson, A., Lam, J., Chari, R., Wegrzyn, J., Kuchenbauer, F., Hirst, M., Tohyama, K., Humphries, R.K., Lam, W.L., Marra, M., Karsan, A., 2011. Genome-wide identification of human microRNAs located in leukemia-associated genomic alterations. Blood 117, 595–607.
Steiner, David F., Thomas, Molly F., Hu, Joyce K., Yang, Z., Babiarz, Joshua E., Allen, Christopher D.C., Matloubian, M., Blelloch, R., Ansel, K.M., 2011. MicroRNA-29 regulates T-box transcription factors and interferon-γ production in helper T cells. Immunity 35, 169–181.
Sullivan, R.P., Leong, J.W., Schneider, S.E., Keppel, C.R., Germino, E., French, A.R., Fehniger, T.A., 2012. MicroRNA-deficient NK cells exhibit decreased survival but enhanced function. J. Immunol. 188, 3019–3030.
Sullivan, R.P., Fogel, L.A., Leong, J.W., Schneider, S.E., Wong, R., Romee, R., Thai, T.-H., Sexl, V., Matkovich, S.J., Dorn, G.W., French, A.R., Fehniger, T.A., 2013a. MicroRNA-155 tunes both the threshold and extent of NK cell activation via targeting of multiple signaling pathways. J. Immunol. 191, 5904–5913.
Sullivan, R.P., Leong, J.W., Fehniger, T.A., 2013b. MicroRNA regulation of natural killer cells. Front. Immunol. 4, 44.
Sullivan, R.P., Leong, J.W., Schneider, S.E., Ireland, A.R., Berrien-Elliott, M.M., Singh, A., Schappe, T., Jewell, B.A., Sexl, V., Fehniger, T.A., 2015. MicroRNA-15/16 antagonizes myb to control NK cell maturation. J. Immunol. 195, 2806–2817.
Sun, J.C., Beilke, J.N., Lanier, L.L., 2009. Adaptive immune features of natural killer cells. Nature 457, 557.
Tajima, F., Kawatani, T., Endo, A., Kawasaki, H., 1996. Natural killer cell activity and cytokine production as prognostic factors in adult acute leukemia. Leukemia 10, 478–482.
Tourneur, L., Delluc, S., Lévy, V., Valensi, F., Radford-Weiss, I., Legrand, O., Vargaftig, J., Boix, C., Macintyre, E.A., Varet, B., Chiocchia, G., Buzyn, A., 2004. Absence or low expression of fas-associated protein with death domain in acute myeloid leukemia cells predicts resistance to chemotherapy and poor outcome. Cancer Res. 64, 8101–8108.
Trotta, R., Parihar, R., Yu, J., Becknell, B., Allard, J., Wen, J., Ding, W., Mao, H., Tridandapani, S., Carson, W.E., Caligiuri, M.A., 2005. Differential expression of SHIP1 in CD56^{bright} and CD56^{dim} NK cells provides a molecular basis for distinct functional responses to monokine costimulation. Blood 105, 3011–3018.
Trotta, R., Chen, L., Ciarlariello, D., Josyula, S., Mao, C., Costinean, S., Yu, L., Butchar, J.P., Tridandapani, S., Croce, C.M., Caligiuri, M.A., 2012. miR-155 regulates IFN-γ production in natural killer cells. Blood 119, 3478–3485.
Trotta, R., Chen, L., Costinean, S., Josyula, S., Mundy-Bosse, B.L., Ciarlariello, D., Mao, C., Briercheck, E.L., McConnell, K.K., Mishra, A., Yu, L., Croce, C.M., Caligiuri, M.A., 2013. Overexpression of miR-155 causes expansion, arrest in terminal differentiation and functional activation of mouse natural killer cells. Blood 121, 3126–3134.
Tsukerman, P., Stern-Ginossar, N., Gur, C., Glasner, A., Nachmani, D., Bauman, Y., Yamin, R., Vitenshtein, A., Stanietsky, N., Bar-Mag, T., Lankry, D., Mandelboim, O., 2012. MiR-10b downregulates the stress-induced cell surface molecule MICB, a critical ligand for cancer cell recognition by natural killer cells. Cancer Res. 72, 5463–5472.
van Kester, M.S., Ballabio, E., Benner, M.F., Chen, X.H., Saunders, N.J., van der Fits, L., van Doorn, R., Vermeer, M.H., Willemze, R., Tensen, C.P., Lawrie, C.H., 2011. miRNA expression profiling of mycosis fungoides. Mol. Oncol. 5, 273–280.
Varbanova, V., Naumova, E., Mihaylova, A., 2016. Killer-cell immunoglobulin-like receptor genes and ligands and their role in hematologic malignancies. Cancer Immunol. Immunother. 65, 427–440.
Vasu, S., Blum, W., 2013. Emerging immunotherapies in older adults with acute myeloid leukemia. Curr. Opin. Hematol. 20, 107–114.
Vasu, S., He, S., Cheney, C., Gopalakrishnan, B., Mani, R., Lozanski, G., Mo, X., Groh, V., Whitman, S.P., Konopitzky, R., Kössl, C., Bucci, D., Lucas, D.M., Yu, J., Caligiuri, M.A., Blum, W., Adam, P.J., Borges, E., Rueter, B., Heider, K.-H., Marcucci, G., Muthusamy, N., 2016. Decitabine enhances anti-CD33 monoclonal antibody BI 836858–mediated natural killer ADCC against AML blasts. Blood 127, 2879–2889.
Vosshenrich, C.A.J., Samson-Villéger, S.I., Di Santo, J.P., 2005. Distinguishing features of developing natural killer cells. Curr. Opin. Immunol. 17, 151–158.
Weng, H., Lal, K., Yang, F.F., Chen, J., 2015. The pathological role and prognostic impact of miR-181 in acute myeloid leukemia. Cancer Genet. 208, 225–229.
Xiao, C., Calado, D.P., Galler, G., Thai, T.-H., Patterson, H.C., Wang, J., Rajewsky, N., Bender, T.P., Rajewsky, K., 2007. MiR-150 controls B cell differentiation by targeting the transcription factor c-myb. Cell 131, 146–159.
Xie, J., Liu, M., Li, Y., Nie, Y., Mi, Q., Zhao, S., 2014. Ovarian tumor-associated microRNA-20a decreases natural killer cell cytotoxicity by downregulating MICA/B expression. Cell. Mol. Immunol. 11, 495–502.
Xue, H., Hua, L.M., Guo, M., Luo, J.M., 2014. SHIP1 is targeted by miR-155 in acute myeloid leukemia. Oncol. Rep. 32, 2253–2259.
Yan, B., Guo, Q., Fu, F.-j., Wang, Z., Yin, Z., Wei, Y.-b., Yang, J.-r., 2015. The role of miR-29b in cancer: regulation, function, and signaling. Onco. Ther. 8, 539–548.
Yeh, Y.-Y., Ozer, H.G., Lehman, A.M., Maddocks, K., Yu, L., Johnson, A.J., Byrd, J.C., 2015. Characterization of CLL exosomes reveals a distinct microRNA signature and enhanced secretion by activation of BCR signaling. Blood 125, 3297–3305.
Yu, J., Freud, A.G., Caligiuri, M.A., 2013. Location and cellular stages of natural killer cell development. Trends Immunol. 34, 573–582.
Yun, S., Lee, S.U., Kim, J.M., Lee, H.-J., Song, H.Y., Kim, Y.K., Jung, H., Park, Y.-J., Yoon, S.R., Oh, S.-R., Kim, T.-D., Choi, I., 2014. Integrated mRNA-microRNA profiling of human NK cell differentiation identifies MiR-583 as a negative regulator of IL2Rγ expression. PLoS One 9, e108913.
Zhang, T., Scott, J.M., Hwang, I., Kim, S., 2013. Cutting edge: antibody-dependent memory-like NK cells distinguished by FcRγ deficiency. J. Immunol. 190, 1402–1406.
Zhang, J., Li, S., Li, L., Li, M., Guo, C., Yao, J., Mi, S., 2015. Exosome and exosomal microRNA: trafficking, sorting, and function. Genom. Proteom. Bioinf. 13, 17–24.