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Natural Killer (NK) Cell Alloreactivities against Leukemic Cells: Functions beyond Defense

Suwit Chaisri and Chanvit Leelayuwat

Abstract

Immunotherapy using adoptive transfer of natural killer (NK) cells has progressively been utilized in hematologic malignancies over the past decade. Presently, NK cell immunotherapy has been promising and feasible in acute leukemia, particularly in acute myeloblastic leukemia (AML). Alloreactive NK cells have been exploited under the killer immunoglobulin-like receptor (KIR)-ligand mismatches between donors and recipients in haploidentical hematopoietic stem cell transplantation (haplo-HSCT) after immunosuppressive chemotherapy. Of interest, alloreactive NK cells killed residual leukemic cells, dendritic cells (DCs) and T cells in acute leukemia patients and led to significantly improved clinical outcomes. Consequently, this chapter provides the *KIR* genetics and the mechanisms of alloreactive NK cells that are shown to be crucial in the successful therapy of acute leukemia (myeloid and lymphoid). Altogether, the donor selection algorithm of haplo-HSCT is discussed to emphasize the importance and give priority to increase the chances of therapy success. These will be useful for students and researchers who work in immunogenetics. Furthermore, the knowledge would be applicable to clinical research and medical sciences.

Keywords: NK cell alloreactivity, *KIR* polymorphisms, KIR-ligands mismatch, acute leukemia, haploidentical HSCT

1. Introduction

Natural killer (NK) cells play a critical role in innate immune responses against infected cells and transformed cells. In the past decades, the molecular mechanisms of NK cell killings have been extensively elucidated as well as employed in clinical applications [1, 2]. The effector functions of NK cells are being investigated in several pathological conditions, particularly in cancers [3, 4]. Many researches highlight on the role of NK cells in hematologic malignancies, particularly in acute leukemia. Acute leukemia is a type of cancer in which the bone marrow produces too many immature white blood cells and they cannot carry out normal functions. In addition, leukemic cells crowd out all blood cell productions in the bone marrow, affecting normal blood functions and leading to serious health problems. The treatment options for acute leukemia include chemotherapy, radiotherapy and bone marrow (hematopoietic stem cell) transplantation. Considering HLA matching between donors and patients for hematopoietic stem cell transplantation (HSCT),

the patient's outcomes are related with a closely matched donor, however, not all patients are able to find a suitable donor. To overcome the limitations of donor availability, a partially matched or haploidentical HSCT (haplo-HSCT) has been established as an alternative expedient and being a mode of curative therapy for hematologic malignancies [5], particularly in acute leukemia patients [6]. In addition, a complication of allogeneic HSCT has improved with graft versus host disease (GvHD) prophylaxis to prevent the effects of donor T cells. Evidently, the role of NK cell alloreactivity can significantly improve clinical outcomes in acute leukemia patients [7]. Among NK cell receptors, killer immunoglobulin-like receptor (KIR) has increasingly been exploited in the aspect of immunotherapy for acute leukemia, which mismatches between KIR on donor NK cells and their cognate ligand HLA class I on recipients lead to alloreactivity of NK cells in haplo-HSCT setting. Alloreactive NK cells exert powerful activity in killing residual leukemic cells, leading to preventing disease relapse and improving survival [7, 8]. With these reasons, NK cell alloreactivities mediated by KIR-ligand mismatches has been increasingly utilized in aspect of immunotherapy for clinical applications. Therefore, this chapter provides *KIR* genetics and KIR-mediated NK cell alloreactivities that have been shown to be crucial in the successful therapy of acute leukemia (myeloid and lymphoid). Additionally, donor selection algorithm of haploidentical HSCT mismatch is discussed to emphasize its role in increasing success rate of these therapies.

2. Natural killer (NK) cells

NK cells are considered a part of lymphocytes that account for approximately 10% of blood lymphocytes. NK cells are characterized by expression of CD56 surface antigen and a lack of CD3 antigen. Based on the density of CD56 expression, human NK cells are phenotypically divided into two groups: CD56^{bright} and CD56^{dim}. Of these NK cell populations, CD56^{dim} NK cells represent up to 90% of NK cells in human peripheral blood mononuclear cells (PBMCs) and are considered the most cytotoxic subset, while CD56^{bright} NK cells comprise approximately 10% of NK cells in PBMCs and are known as the cytokine-producing subset. NK cells play important role of the first line of defense to infected cells and transformed cells without prior sensitization [9, 10]. Several receptors present on NK cells are currently identified, however, they are classified into two groups depended on signal transductions derived from those receptors, namely activating and inhibitory receptors [11] (**Table 1**). Importantly, the dynamic equilibrium of signals obtained by these receptors is important to determine whether NK cells are activated to kill target cells [12, 13]. The missing self-hypothesis has been proposed to explain whether NK cells discriminate target cells from healthy "self" cells by their various receptors [14]. Normally, engagement of inhibitory receptors by self MHC class I molecule leads to transmission of an inhibitory signal to switch off the NK cell functions, while down-regulated MHC molecules on target cells by viral infection or malignant transformation is recognized and attacked by NK cells. Cytotoxicity and cytokine secretion of NK cells depended on the interaction between their receptors and their corresponding ligands. Activated NK cells usually exert cytotoxic activity through three main pathways. Firstly, the perforin/granzymes pathway, activated NK cells release these molecules to intracellular space. The perforin directly forms a transmembrane channel on the target cell, leading to increased permeability of the target cell membrane and causing osmotic lyses of target cells. In addition, granzymes enter the cytoplasm of target cells through transmembrane pores to promote target cells apoptosis [15]. Secondly, the Fas/FasL pathway, when Fas on NK cells binds to FasL on the target cells, Fas delivers a death signal to the target cell

Type of receptors	Ligands
<i>Activating receptors</i>	
CD94-NKG2C/E	HLA-E
NKG2D	MIC-A/-B, ULBP1-6
KIR-S	HLA-C
NKp30	B7H6, BAT3
NKp44	Proteoglycans
NKp46	Heparin
CD16	IgG
<i>Inhibitory receptors</i>	
KIR-L	HLA-A, -B, -C
LAIR-1	Collagen
LILRB1	HLA-A, -B, -C
NKR	LLT-1
KLRG1	Cadherins
SIGLEC3, 7,9	Sialic acid
CD94-NKG2A	HLA-E
<i>Activating or inhibitory receptors</i>	
KIR2DL4	HLA-G?
<i>KIR-S: killer cell immunoglobulin-like receptor with short cytoplasmic tail; KIR-L: killer cell immunoglobulin-like receptor with long cytoplasmic tail; LAIR-1: leukocyte-associated immunoglobulin-like receptor 1; LILRB1: leukocyte immunoglobulin-like receptor B1; KLR: killer cell lectin-like receptor; NKR: NK cell receptor; SIGLEC: sialic acid-binding immunoglobulin-type lectins; HLA: human leukocyte antigen; LLT: lectin-like transcript 1. IgG: immunoglobulin G; BAT3: leukocyte antigen-B-associated transcript 3; MIC: MHC class I-related chain family; ULBP: UL16-binding proteins; HLA-G?: It is controversial whether HLA-G is a ligand of KIR2DL4.</i>	

Table 1.
NK cell receptors and their cognate ligands.

and they undergo apoptosis [16, 17]. Lastly, the cytokine pathway, NK cells secrete various cytokines, such as IFN- γ , TNF- α , GM-CSF and IL-10. These cytokines play an important role in immune responses of NK cells. For example, TNF- α alters the stability of lysosome in target cells, resulting in leakage of various hydrolases, effect on metabolism of cell membrane phospholipid and degradation of genomic DNA by endonuclease [18]. With these mechanisms, applications of NK cells have currently been established in tumor immunotherapy as chimeric antigen receptor-modified NK cells (CAR-NK cells) and adoptive immunotherapy.

3. Killer immunoglobulin-like receptor (KIR) polymorphisms mediated-heterogeneity of NK cell responses

Killer immunoglobulin-like receptors (KIRs) are cell surface receptors expressed on NK cells and subpopulation of T cells. Similar to HLA class I, KIR ligands, *KIRs* are highly polymorphic genes, including allelic polymorphisms, genes content and copy number variations [19]. Genetic variations of *KIRs* and *HLA* among individuals generate heterogeneity of immune responses of NK cells [20]. Interestingly, current evidences demonstrate the impact of *KIR* gene variations on disease susceptibility or resistance in several pathological conditions, such as infection, autoimmune/ inflammatory disorder, implantation and particularly in hematopoietic stem cell

transplantation [21]. Here, to better understand the role of NK cell alloreactivities, we thoroughly describe the basis of KIRs as well as its role in the immune system.

3.1 Killer immunoglobulin-like receptors (KIRs, CD158)

Killer immunoglobulin-like receptors are type I transmembrane glycoprotein expressed on the plasma membrane of NK cells, subpopulations of memory T cells and most of CD8⁺ T cells [22, 23]. The KIR family consists of 15 functional genes (*KIR2DL1–4*, *2DL5A*, *2DL5B*, *2DS1–5*, *3DL1–3*, *3DS1*) and 2 pseudogenes (*2DP1* and *3DP1*) encoded within a 150 kb region of the leukocyte receptor complex (LRC) located on chromosome 19 (19q13.4) [24, 25]. The KIR proteins have either two or three extracellular immunoglobulin domains (KIR2D or KIR3D) and cytoplasmic (CYT) tails with long (L) or short (S) tails. Based on structural feature, a long *cytoplasmic tail* (KIR2DL or KIR3DL) contains immunoreceptor tyrosine-based inhibitory motif (ITIM) that functions to inhibit NK cell responses [26]. In contrast, a short *cytoplasmic tail* (KIR2DS or KIR3DS) has a positive charge amino acid residue in the transmembrane region to associate with DAP12 containing an immunoreceptor tyrosine-based activating motif (ITAM) that turns on NK cell functions [27]. Uniquely, KIR2DL4, a long cytoplasmic tail containing ITIM and linking with an adaptor molecule FcεRI, can deliver both activating and inhibitory signals to control NK cell responses [28, 29]. However, the mechanism by which KIR2DL4 delivers activating or inhibitory signals to NK cells is not established. Two pseudogenes, *KIR2DP1* and *KIR3DP1*, are not expressed on NK cells.

3.2 Diversity of KIRs

The extensive variation of *KIR* loci is achieved through allelic polymorphisms, a combination of gene content (absence/presence polymorphisms) and copy number variations. Firstly, allelic polymorphisms of *KIR* have been documented in the Immuno Polymorphism Database (IPD) showing each *KIR* locus contains 16–164 alleles of different genes [30]. Later, a combination of genes content generates distinct *KIR* genotypes, showing 625 different *KIR* genotypes reported in 171 populations worldwide [31]. Lastly, copy number variation (CNV) of *KIR* is currently studied and demonstrated that equal and unequal crossing over generates individual *KIR* gene duplication, deletion and hybridization [32]. Moreover, stochastic and variegated *KIR* expressions on NK cells by epigenetic regulation facilitate a diverse repertoire of NK cell clones within an individual [33] (**Figure 1**). As a consequence, the influence of *KIR* diversity on immune responses has been reported in several diseases [21, 34–36]. On the basis of gene content, *KIRs* are classified into group A and B haplotypes [37]. Both group A and B haplotypes are conserved with four framework genes (*KIR3DL3–3DP1–2DL4–3DL2*). Group A haplotype consists of the four framework genes and *2DL3*, *2DP1*, *2DL1*, *3DL1* or *2DS4*, whereas group B haplotype has variable gene content. Distinctly, group A haplotype shows predominantly inhibitory *KIR* genes except *KIR2DS4*, but group B haplotype contains dominantly activating *KIR* genes. The distributions of *KIR* haplotypes have been studied, showing variations of A and B are found among populations [38–43].

3.3 KIR and their cognate ligands

Both inhibitory and activating KIRs on NK cells recognize HLA class I molecules of target cells. Most KIR ligands have recently characterized as shown in **Table 2**, whereas some KIR ligands are still unknown [44–47]. The affinity of KIR and HLA interaction affects NK cell responses [48]. Remarkably, activating KIRs

Figure 1.
NK cell repertoires. Individual KIR genotype generates a diverse repertoire of NK cells by stochastic expression. KIR expression on NK cells is influenced by HLA class I and CD94:NKG2A.

KIR	KIR ligand (HLA)	Function
2DL1	HLA-C2 (HLA-C ^{Lys80})	Inhibition
2DL2	HLA-C1 (HLA-C ^{Ans80})	Inhibition
2DL3	HLA-C1, HLA-C2 (weak)	Inhibition
2DL4	HLA-G? [*]	Activation/inhibition?
2DL5	Unknown	Inhibition
2DS1	HLA-C2 (HLA-C ^{Lys80})	Activation
2DS2	HLA-C1 (HLA-C ^{Ans80}), β ₂ -Microglobulin	Activation
2DS3	Unknown	Activation
2DS4	HLA-A11 and some HLA-C alleles	Activation
2DS5	Unknown	Inhibition
3DL1	HLA-Bw4	Inhibition
3DL2	HLA-A3, -A11	Inhibition
3DL3	Unknown	Inhibition
3DS1	HLA-Bw4?	Activation

^{*}The ligand for KIR2DL4 is still controversy [44, 45].

Table 2.
KIR and their ligands (HLA) specificity.

(KIR2DS1/2) and inhibitory KIRs (KIR2DL1/2) can bind the same HLA molecules. However, the affinity of inhibitory KIR-binding HLA is higher than activating KIR-binding HLA [49, 50]. It is believed that the lower affinity of activating KIR and HLA interaction would be evolved to avoid self-aggression.

4. Alloreactive NK cells from transplantation to adoptive immunotherapy

Over the past decade, adoptive transfer allogeneic NK cells have been emerged as promising immunotherapy for hematological malignancies [8, 51, 52]. The role of alloreactive NK cells is considered to be beneficial in achieving better outcomes

after haploidentical HSCT (haplo-HSCT). Presently, haplo-HSCT is an alternative option when completely matched related or unrelated donors are not available. Historically, although haplo-HSCT can lead to graft versus host disease (GvHD) which has undesirable effect in post HSCT, this problem has been currently solved by performing of T cell depletion before graft infusion. After chemotherapy in AML patients, T cell prophylaxis has been used together with high stem cell doses, resulting in fast NK cell alloreactivities and slow T cell reconstitution. Moreover, graft versus leukemic cells mediated by NK cell, alloreactivities have been exploited which they can beneficially lead to reduced relapse, and improve survival [53]. Based on the interactions between NK cell receptors and their ligands, it was believed that allogeneic NK cells do not receive inhibition signals from the recipient HLA, leading NK cells to exert powerful anti-leukemia activity [54]. Regarding KIR-ligand mismatches between donor and recipient under haplo HSCT setting, alloreactive NK cells play crucial roles against leukemic cells, recipients' DCs and T cells [55], resulting in reduced leukemic relapses, GvHD and graft rejection, respectively (**Figure 2**). With these reasons, a number of studies have extensively investigated the role of KIR-ligand mismatches in both pre-clinical and clinical setting to evaluate the success in leukemia therapy. Additionally, four situations in predicting NK cell alloreactivities after haplo-HSCT have been proposed based on the deference in definition of KIR mismatches between the donor NK cells and the recipient's HLA [56] (**Figure 3**).

4.1 KIR-ligand (HLA) mismatch or missing-self-model

The KIR-ligand mismatch model, also called ligand incompatibility, has been proposed that an expression of HLA class I molecules (KIR ligand) on donor are

Figure 2.
The role of NK cell alloreactivities in acute leukemia. Beneficial effects of NK cell alloreactivities on the outcomes of acute leukemia under haplo-HSCT setting, adoptive transfer NK cells mediated activity against residual leukemic cells, recipient's T cells and dendritic cells, resulting in reduced the risk of relapse, graft rejection and GvHD, respectively.

Figure 3. Situations of NK cell alloreactivity in post-HSCT. (A) The KIR-ligand (HLA) mismatch or missing-self-model; NK cell alloreactivity is mediated by the lack of HLA ligand expression on recipient for inhibitory KIR on donor's NK cell which the presence of KIR expression on donor is assumed. High resolution HLA genotyping is performed in donor and recipient. (B) The receptor-ligand model; NK cell alloreactivity is mediated by the lack of HLA ligand expression on recipient for inhibitory KIR which the presence of KIR expression on donor NK cell is verified by genotyping and flow cytometry. The donor HLA is irrelevant to recipient. (C) The missing-ligand model; NK cell alloreactivity is mediated by the lack of at least one of HLA ligand (HLA-C1, -C2 or -Bw4) expression on recipient for inhibitory KIR and the donor HLA is irrelevant to recipient. (D) The presence of activating KIR model; NK cell alloreactivity is mediated by interaction of activating KIR on donor NK cell and HLA ligand on recipient target cell which KIR B haplotype contains more activating KIR than A/A haplotype. KIR genotyping was investigated in donor and recipient and some studies detected activating KIR on donor cells.

incompatible with recipient's HLA class I molecules [57, 58]. This model has been assumed that donor NK cells have inhibitory KIR that is missing its ligand on recipient. For example, NK cells from a HLA-C1/C2 donor will be alloreactive against a HLA-C2/C2 recipient, where it is assumed that KIR2DL2 is expressed on donor NK cells (Figure 3A).

4.2 Receptor-ligand mismatch model

The receptor-ligand mismatch model states that donor NK cells represent inhibitory KIR in mismatching with HLA class I on the recipient target cells,

leading to NK cell alloreactivities in graft versus host direction [59]. This model is therefore required for KIR genotyping in donor as well as HLA typing in recipient (**Figure 3B**).

4.3 Missing-ligand model

Notably, the HLA is only genotyped in recipients and missing HLA-C1, C2 or Bw4 for inhibitory KIR on donor can lead to NK cell alloreactivities [58]. For example, recipient represents HLA-C2/C2, therefore, it is assumed (not investigated) that donor NK cells expressing KIR2DL2 to be alloreactive due to missing HLA-C1 ligand (**Figure 3C**).

4.4 Presence of activating KIR model

Here, in this model, activating KIR on donor cells is measured to predict NK cell alloreactivities because the interactions between donor activating KIRs and their ligands on recipient can lead to NK cells achieving activation signals [60] (**Figure 3D**).

5. The role of NK cell alloreactivities in post HSCT

Several studies have revealed an influence of alloreactive NK cells in acute leukemia patients, where alloreactive NK cells deliver promising better outcomes in term of anti-leukemia activity. Predominantly, KIR-mediated NK alloreactivity has been demonstrated to be the most clinically significant relevance to AML, while its role in ALL remains unclear.

5.1 Acute myeloblastic leukemia (AML)

As acute myeloblastic leukemia was more susceptible to NK cell cytotoxicity than solid tumors [61], the role of adoptive transfer NK cells against leukemia was investigated in AML patients [62]. Anti-leukemic effect of allogeneic NK cells has been extensively studied under haplo-HSCT with the mismatches of KIR and cognate ligands between donor and recipient. Interestingly, Ruggeri and coworkers initially reported allogeneic NK cells mediated cytotoxicity against recipients' leukemic cells [53]. Later, the impact of NK cells alloreactivity in preventing AML relapse, GVHD and rejection was confirmed in clinical setting and mouse model [63]. Taken together, this condition has been explored under T cell depleted to avoid graft versus host effect and high doses of infused stem cell transplantation [54, 63, 64]. Remarkably, this approach was investigated in 21 AML children who received haplo-HSCT, showing donor-derived alloreactive NK cells killed leukemic cells in KIR-ligand mismatches, even late after transplantation [7]. Altogether, the doses of infused NK cell and immunosuppression were evaluated in children with AML to consider safety and effectiveness of alloreactive NK cells therapy [65]. Moreover, successfully transferred NK cells immunotherapy were reported in elderly AML who were not candidates for HSCT, demonstrating this approach was feasible and safe in elderly patients [8, 66].

Haplo-HSCT with KIR-ligand mismatches has been a promising strategy in AML for adoptive transfer of NK cells for immunotherapy [67, 68]. The incompatibility of three main inhibitory *KIR* loci (*2DL1*, *2DL2/3* and *3DL1*) with their ligands (*HLA-C2*, *HLA-C1* and *HLA-Bw4*) has been extensively investigated, and

found to be relevant for better clinical outcomes [69, 70]. To explain the potential benefits of alloreactive NK cells against leukemia based on an absence of inhibitory signal delivered by KIR on donor's NK cells, it has been shown that KIR2DL1⁺ NK cells lyse leukemia in HLA-C1/C1 recipients, whereas KIR2DL2/3⁺ NK cells partially lyse leukemia in HLA-C2/C2 recipients due to low-affinity binding, and that KIR3DL1 + NK cells lyse HLA-Bw4⁻ leukemia of recipients, where HLA-Bw4⁻ would be HLA-A or HLA-B as determined by the serotypic specificity. However, for the activating KIR model, KIR2DS1⁺ NK cells have demonstrated a potent reactivity against HLA-C2 expressing allogeneic target cells *in vitro* [60, 71], particularly on T cells and dendritic cells. As mentioned, although NK cell-based immunotherapy has been a promising approach in adult and childhood [8, 65, 66], there are additional issues that need to be considered in achieving a successful therapy. Firstly, the minimum or optimal number of infused NK cells is really required to achieve therapeutic effect that remains inconclusive due to lack of standardized technical procedure for qualifying alloreactive NK cells [67, 68]. Additionally, it became clear that infused NK cells favor IL-2 and IL-15 for expansion and survival [51, 72], however, administration of IL-15 after infusion has been recommended because IL-2 can promote host regulatory T cells to inhibit allogeneic NK cells.

Given the crucial role of alloreactive NK cells in graft versus leukemia (GVL) effect in haplo-HSCT, the predictive algorithm for donor selection is being developed in AML treatment. Several research groups have explored feasibility of NK cell-based immunotherapy, including *in vivo* and *in vitro* studies as well as clinical trials. Predominantly, mismatches of donors' inhibitory KIR expressing NK cells (2DL1, KIR2DL2/3 and KIR3DL1) with HLA class I of the patients have been well-documented that were relevant to therapeutic effect of NK immunotherapy in AML [7, 66, 73]. For activating KIRs, only KIR2DS1 has been reported to associate with NK cell alloreactivities against target cells expressing HLA-C2 [60, 74]. Moreover, *KIR* haplotypes and clinical outcomes have been observed, showing donors with group B *KIR* haplotype have improved relapse-free survival for AML patients under unrelated HSCT [75]. With these reasons, KIR-mediated NK cell functions in haplo-HSCT should be taken in to account for donor selections, since the potential benefit of NK alloreactivity has improved survival and clinical outcomes in AML patients. Moreover, phase I and II clinical trials have been being studied to evaluate the feasibility and safety [76, 77] for further applications. Therefore, haplo-HSCT with T cell depletion, KIR-mediated NK cell alloreactivities should be considered for donor selections using an algorithm in which KIR-ligand mismatches could be predicted. This is available as an online calculator (<https://www.ebi.ac.uk/ipd/kir/ligand.html>).

5.2 Acute lymphoblastic leukemia (ALL)

Since the role of alloreactive NK cells in AML were reported, the influence of KIR on the outcome of ALL patients in haplo-HSCT setting has been investigated. Like AML, the approach based upon KIR-ligand mismatches and the presence of donor's KIR2DS1⁺ NK cells with HLA-C2 expressing target cells mediated NK cell alloreactivities against leukemic blasts has been tested [7]. In addition, ALL children transplanted from a *KIR* haplotype B donor showed significantly reduced risk of relapse, particularly in donors with high B content score [78]. However, the beneficial effect of NK cell alloreactivity has not been obviously noticeable in ALL patients in particular mechanisms of NK cells against ALL tumor cells [63, 79, 80]. The clinical studies of beneficial effect of NK cell alloreactivities in acute leukemia are summarized in **Table 3**.

Study	Disease	Model	Beneficial effect	Ref.
Ruggeri et al. (1999)	AML, ALL, CML	KIR-ligand mismatch	Antileukemic effect	[53]
Ruggeri et al. (2002)	AML, ALL	KIR-ligand mismatch	Reduced relapse, Reduces graft rejection, protected GvHD	[63]
Miller et al. (2007)	AML, MDS, CML	Missing-ligand	Reduced relapse	[81]
Pende et al. (2008)	AML, ALL	KIR-ligand mismatch	Antileukemic effect	[7]
Rubnitz et al. (2009)	AML	Receptor-ligand mismatch	No GvHD	[65]
Willemze et al. (2009)	AML, ALL	KIR-ligand mismatch	Reduced relapse	[82]
Cooley et al. (2009)	AML	KIR haplotype, KIR-ligand mismatch	Improved survival rate	[75]
Cooley et al. (2010)	AML, ALL	KIR haplotype	Reduced relapse	[83]
Venstrom et al. (2010)	AML, MDS, CML, ALL	KIR haplotype	Decreased acute GvHD	[84]
Curti et al. (2011)	AML	KIR-ligand mismatch	Antileukemic effect	[8]
Venstrom et al. (2012)	AML	Missing-ligand, receptor-ligand mismatch, presence of activating <i>KIR</i>	KIR2DS1 associated with lower relapse, KIR3DS1 associated with lower mortality	[74]
Cooley et al. (2014)	AML	Missing-ligand, KIR haplotype	Reduced relapse	[85]
Curti et al. (2016)	AML	KIR-ligand mismatch	Reduced relapse	[66]

AML: acute myeloid leukemia; ALL, acute lymphoid leukemia; CML: chronic myeloid leukemia; MDS: myelodysplastic syndromes; GvHD: graft versus host disease.

Table 3.
Clinical studies of beneficial effects of NK cell alloreactivities in acute leukemia.

6. Conclusion

This chapter sheds light on adoptive transfer NK cell immunotherapy in haplo-HSCT setting after immunosuppressive chemotherapy. KIR-ligand mismatches, activating KIR with cognate ligand as well as *KIR* B haplotype, could contribute to the potential benefit of allogeneic NK cells against acute leukemia in improving relapse-free and survival in AML patients. Additionally, the donor selection algorithm based on KIR-ligand mismatches is provided and available. Conflicts resulted from studies could be explained by the different definitions of KIR ligand mismatches, failure of infused NK cells to expand and persist, extensive genetic polymorphisms as well as the stochastic surface expressions of specific KIRs on individual NK cells. However, some limitations still need to be elucidated in further studies to overcome obstacles and achieve successful NK cell immunotherapy and clinical impact. For example, the ligands for KIR2DL5 and KIR2DS3 are still

unknown. In addition, the molecular mechanisms of KIR and NK cells need to be well-established. Eventually, this chapter provides a promising approach of NK cell-based immunotherapy that has revolutionized hematologic malignancy treatment, particularly AML, however, the feasibility has been challenged by complexity and understanding of NK cell biology as well as KIRs.

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Conflict of interest

The authors declare no conflict of interest.

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