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REVIEW ARTICLE

Interactions between Immunoglobulin like receptors and the Peptidome in the Allogeneic Hematopoietic Stem Cell Transplantation in the Cytomegalovirus context. A mini review.

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ABSTRACT

The Natural Killer cells are innate lymphoid cells that play essential roles in defense against viral and parasitic infections, elimination of tumor cells, regulation of adaptive immunity through cytotoxicity, and cytokine secretion. Fundamental knowledge about the regulation of Natural Killer cells can be applied to study their function in patients undergoing hematopoietic stem cell transplantation, with or without Cytomegalovirus reactivation. The function of Natural Killer cells is governed by a repertoire of receptors responsible for initiating intracellular activating or inhibitory signaling. The balance of this signaling directs the cytotoxic activity of these cells, as well as cell proliferation and cytokine release.Understanding the interaction of receptors expressed on the surface of Natural Killer cells with their ligands expressed on target cells is a topic of discussion in the context of alloreactivity and the graft-versus-leukemia effect in transplant patients. Recent investigations have shown that KIR/HLA interactions go beyond affinity and describe that many of them depend on the peptide being presented by the HLA at that moment. Analysis of the peptidome (HLA class I + bound peptide) has demonstrated that some Natural Killer cell receptors are peptide-dependent. Therefore, understanding these interactions by considering the entire Natural Killer cell receptor + HLA class I + peptide complex is crucial in the reestablishment of immune cells after hematopoietic stem cell transplantation, especially in the context of Cytomegalovirus reactivation, which is very common in these patients. Hence, the aim of this study is to deepen our understanding of the specificity of interactions between human Natural Killer cell KIR receptors and the peptidome in the context of Cytomegalovirus reactivation after allogeneic, related, HLA-compatible hematopoietic stem cell transplantation without T-cell depletion. For the analysis of interactions between Natural Killer cell receptors and peptidomes, specific peptide libraries for HLA class I alleles will be created to evaluate the specificities of interactions between KIR + HLA class I + peptide.

Keywords: Natural Killer cells, peptidome, activating and inhibitory receptors, HLA class I molecules, recognition specificity.

Introduction

The innate lymphoid cells (ILCs) are heterogeneous lymphocytes, considered distinct from B or T cell subsets, and, like these cells, they are involved in immune responses, inflammation, and tissue homeostasis. ILCs can be classified into five main subsets: Natural Killer (NK) cells, lymphoid tissue inducer cells (LTi), ILC type 1 (ILC1s), ILC type 2 (ILC2s), and ILC type 3 (ILC3s). ILC1s express T-Bet and produce interferon-gamma (IFN-γ), ILC2s are dependent on GATA-3 and secrete interleukin (IL)-12 and -5, while ILC3s express RORγt and produce IL-17 and IL-22. (Vivier e col., 2018; Lopes e col., 2022).

Initially, Natural Killer (NK) cells were considered part of the ILC type 1 subset because both share many characteristics such as the expression of T-Bet and the production of IFN-γ. However, several markers have been proposed to discriminate between these cells, such as the integrins α1 (CD49a), CD200R, interleukin-7 receptor (CD127), CD69, and chemokine receptor CXCR6. Additionally, type 1 ILCs reside in tissues, whereas NK cells circulate in peripheral blood. (Gasteiger e col., 2015; Seillet e col., 2020).

Natural Killer cells are characterized as cytotoxic lymphocytes of the innate immune response, constituting approximately 5 to 15% of circulating mononuclear lymphocytes and phenotypically defined as CD3-CD56+NKp46+ (Bryceson et al., 2005). These cells play crucial roles in host defense due to their ability to recognize and eliminate virus-infected cells and transformed tumor cells without the need for prior sensitization. NK cells develop in the bone marrow niche from hematopoietic stem cell progenitors, distributing throughout lymphoid organs and other tissues, undergoing a continuous maturation process that confers tissue-specific functions. For instance, this is evident in NK cells found in the uterus, liver, and tonsils (Bryceson et al., 2005; Bashirova et al., 2006).

The function of NK cells is governed by a repertoire of receptors responsible for issuing intracellular activating or inhibitory signals. The balance of this signaling directs the cytotoxic activity of these cells, as well as cell proliferation and cytokine release. Typical activating receptors on these cells include the natural cytotoxicity receptors (NCRs) NKp44 (CD336), NKp46 (CD335), and NKp30 (CD337), as well as some of the killer cell immunoglobulin-like receptors (KIRs), which recognize human leukocyte antigen (HLA) class I antigens expressed on the surface of target cells (Hsu et al., 2005). The NCRs receptors recognize a diverse set of ligands, such as heparan sulfate proteoglycans, cell surface proteins, and proteins that reach the surface after their intracellular cleavage. These ligands are not exclusively activating but can also have an inhibitory effect, depending on the splice variant of the receptor (Hsu et al., 2005).

Some of the most well-studied receptors include the transcript associated with B7-H6 and HLA-B 3 (BAT3), which binds to NKp30, and the proliferating cell nuclear antigen (PCNA), which binds to NKp44. The mechanism of positive regulation of NK cell-activating ligands isn't entirely elucidated, although increasing evidence suggests transcriptional and post-translational modifications occur as a result of the cellular response to stressful stimuli and DNA damage (Karvouni et al., 2022).

In NK cells, receptors such as CD224 (2B4), CD226 (DNAM-1), CD94:NKG2C, and NKG2D are also expressed. Several ligands for these receptors, considered activators, are upregulated after cellular stress, infection, or malignant transformation. In tumor formation, positively regulated ligands include MICA and MICB (MHC class I polypeptide-related sequence A and B), UL16 binding proteins (ULBPs), and the adhesion molecules PVR (poliovirus receptor, also known as CD155) and Nectin-2. MICA/B and ULBPs mediate activating signals by binding to NKG2D, while PVR and Nectin-2 bind to DNAM-1 (Bottino et al., 2003).

In addition to activating KIRs, many of the KIR group receptors are known to propagate inhibitory intracellular signaling upon interaction with their ligands. Inhibitory signals are also mediated by the sialic acid-binding Ig-like lectin 7 (siglec-7) and 9 (siglec-9) receptors, which bind to sialic acid-containing carbohydrates (e.g., mucins) expressed aberrantly in tumor cells. Other inhibitory receptors include the CD94-NKG2A complex and the receptors CD161 and KLRG1, which bind to HLA-E, lectin-like transcript 1, and cadherins, respectively (Karvouni et al., 2022).

Many studies seek to explain the interactions between NK cell receptors and their ligands expressed on target cells as either low or high-affinity interactions. According to these findings, it's not merely the binding of an activating/ inhibitory receptor to its ligand that matters, but the affinity at which these interactions occur can dictate the intracellular signaling processes in NK cells, either activating or inhibiting them. Therefore, affinity represents a key factor in directing NK cell responses (Hilton et al., 2015; Pende et al., 2019).

Recent investigations have shown that certain specific interactions like KIR/HLA go beyond mere affinity and describe that many of these interactions depend on the peptide being presented by the HLA at that moment. Analysis of the peptidome (HLA class I + bound peptide) has demonstrated that some NK cell receptors are peptide-dependent. Therefore, the need to understand these interactions by examining the entire complex of NK cell receptor + HLA class I + peptide is fundamental in various human diseases across different immunological contexts (Sim et al., 2023).

Given the above, the objective of this mini-review is to explore the main findings in the literature regarding the interaction between NK cell receptors, HLA, and peptides and to understand the immunological mechanisms involved in these interactions.

Interaction of NK cell receptors with the peptidome

In humans, class I HLA molecules are highly polymorphic and are expressed on the surface of all nucleated cells. Variations in the class I HLA molecule enable the display of thousands of distinct peptides on the cell surface. As these molecules become ligands for NK cell receptors, their assembly and expression are subject to intricate cellular quality control mechanisms (Zaitoua et al., 2020).

The assembly pathway of class I HLA molecules begins in the endoplasmic reticulum (ER), migrates to the Golgi apparatus, and follows the secretory pathway to reach the cell surface. Assembly in the ER involves the peptide-loading complex (PLC), a large macromolecular complex comprising subunits such as TAP1, TAP2, tapasin, ERp57, calreticulin, in addition to the heavy chain of

HLA-I and β2m. Alongside the PLC proteins, variants like ERAP1, ERAP2, and TAPBPR are crucial in peptide trimming and also in quality control mechanisms (Raghavan et al., 2015).

Natural Killer (NK) cells and CD8+ T lymphocytes play complementary roles in cellular immune responses. While CD8+ T cells recognize and eliminate cells presenting non-self peptides bound to HLA class I, NK cells kill cells with deficient surface expression of HLA class I. Analyzing these distinct functions, T cells are highly sensitive to changes in the repertoire of bound peptides. On the other hand, Killer Immunoglobulin-like Receptors (KIRs), representing the most polymorphic receptors on NK cells, are less sensitive to changes in the peptide repertoire, capable of recognizing a broader range of peptide-HLA combinations (Garcia and Adams, 2005).

Despite their broader specificity, pioneering studies in this field have suggested that patterns of NK cell-mediated cytotoxicity are influenced by the nature of the peptide bound to HLA class I. Although NK cell receptors are not as peptide-specific as T cell receptors (TCRs), there is considerable evidence that they exhibit sophisticated peptide selectivity (Malnati et al., 1995; Peruzzi et al., 1996; Storkus et al., 1992).

Based on these findings, a growing number of studies have been exploring the potential peptide selectivity of NK cells, its extent, and functional consequences (Zappacosta et al., 1997; Rajagopalan et al., 1997; Boyington et al., 2000; Fan et al., 2001; Stewart et al., 2005; Sim et al., 2017; Hilton et al., 2017; Sim et al., 2023).

Interaction of KIR receptors with the peptidome

Natural Killer cells express, among other receptors, different combinations of inhibitory KIR receptors (KIR2DL1, KIR2DL2, KIR2DL3, KIR2DL4, KIR2DL5, KIR3DL1, KIR3DL2, and KIR3DL3) and activating ones (KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, KIR2DS5, and KIR3DS1). KIR receptors exhibit a high degree of polymorphism, second only to molecules in the major histocompatibility complex, and specifically recognize epitopes present on HLA-A, HLA-B, and HLA-C molecules, divided into serological groups: C1, C2, Bw4, and A3/A11 (Khakoo et al., 2006; Purdy et al., 2009).

Five inhibitory KIRs and three activators recognize specific HLA class I ligands. Inhibitory KIR2DL1 recognizes HLA-C alleles from group 2, characterized by the presence of a lysine residue at position 80 in the peptide-binding groove of the HLA molecule. KIR2DL2 and KIR2DL3 recognize HLA-C alleles from group 1, which are characterized by the presence of an asparagine residue at position 80 in the peptide-binding groove. KIR3DL1 recognizes HLA-Bw4 alleles, and KIR3DL2 recognizes HLA-A3/-A11 alleles (Table 1) (Khakoo et al., 2006; Pende et al., 2009).

Table 1. Classical NK cell receptors and their ligands

Inhibitory receptors	Ligands	Activating receptors	Ligands	Coreceptors	Ligands
KIR2DL1	HLA-C2	KIR2DS1	HLA-C2	2B4	CD48
KIR2DL2	HLA-C1	KIR2DS2	HLA-C1	NTB-A	NTB-AL
KIR2DL3	HLA-C1	KIR2DS3	Unknown	CS1	CS1L
KIR2DL4	HLA-G	KIR2DS4	HLA-A11	NKp80	AICL
KIR2DL5	Unknown	KIR2DS5	Unknown	TLR	TLRL
KIR3DL1	HLA-Bw4	KIR3DS1	HLA-F	DNAM-1 (CD226)	VR, Nectin-2
KIR3DL2	HLA-A3/A11	NKG2C	HLA-E	CD96	PVR
KIR3DL3	Unknown	NKG2D	MICA, MICB, ULBP-4		
NKG2A	HLA-E	NKp30	B7-H6, BAT3, CMV pp65		
LIR-1	HLA class I	NKp44	Hemaglutinines viral		
		NKp46	Hemaglutinines viral		
		CD16	IgG-1, 3, 4		

Recent studies indicate that the classical recognition between KIR receptors and HLA molecules might have exceptions and alternative forms of interaction. In multiplex binding assays using KIR2DL1-Fc and class I HLA, it has been demonstrated that KIR2DL1 specifically and with high affinity binds to all HLA-C group 2 molecules but not to HLA-C group 1 or any HLA-A or HLA-B alleles. However, there is an exception represented by KIR2DL1*022, a receptor that carries Lysine at position 44 instead of Methionine 44, making this receptor specific to the HLA-C*08:02 allele (HLA-C1), which in turn presents a restricted number of peptides (Hilton et al., 2015).

KIR2DL2 and KIR2DL3 are characterized by a higher selectivity for peptides than KIR2DL1, and this capacity seems particularly relevant for the recognition of low-affinity HLA-C2 allotypes. Growing evidence suggests that both KIR2DL2/3 and KIR2DL1, apart from their ability to discriminate between C1 and C2 epitopes, bind to numerous combinations of peptide/HLA-C, maintaining a variable degree of peptide selectivity. We know that KIR2DL2/3 binds to HLA-C1 with high affinity; however, these receptors can also bind to HLA-B*46:01 and HLA-B*73:01 with high affinity, as well as to HLA-C2 with low affinity. These findings suggest that NK cells are capable of detecting not only the negative regulation of HLA class I but also alterations in the peptidome presented by HLA, which can occur during viral infections or malignant transformations (Pende et al., 2019).

Sim and colleagues recently evaluated over 3,500 specific interactions to determine the specificity of five types of KIR receptors for peptides presented by four HLA-C ligands, groups 1 and 2. Among their findings, the inhibitory KIR2DL1 was largely non-specific regarding peptide sequences and could bind to roughly 60% of the hundreds of tested HLA-peptide complexes. The inhibitory KIR2DL2, KIR2DL3, and activating KIR2DS1 and KIR2DS4 only bound to 10% and 1% of the tested HLA-peptide complexes, respectively. The binding of KIR2DS1 with HLA-C2, previously described as having low affinity, showed high-affinity binding to HLA-C, with high specificity for peptide sequence. Hence, NK cell responses can be shaped by peptidomes (HLA class I + bound peptide) in healthy cells as well as in infectious, inflammatory, and tumor processes. However, due to the high degree of polymorphism in HLA class I molecules and the vast range of peptides they can present, coupled with the high polymorphism of KIR receptors, many questions regarding these interactions and their influences on various human diseases are still not fully elucidated (Sim et al., 2023).

Few studies have been published evaluating human diseases and the peptidomes associated with NK cell receptors. The vast majority of these studies assess these interactions in the context of HIV infection. However, there are limited reports explaining these specificities with other diseases, whether infectious, inflammatory, and even fewer within the tumor microenvironment (Alter et al., 2011; van Teijlingen et al., 2014; Holzemer et al., 2015).

Influence of the interaction between KIR receptors and HLA ligands in allogeneic hematopoietic stem cell transplantation (HSCT).

Understanding the interactions between NK cell receptors and their ligands requires identifying characteristics that differentiate one interaction from another. This is crucial since these interactions dictate the recognition and the type of response NK cells will mount against the target cell. For instance, certain KIR/HLA associations are linked to spontaneous resolution against Hepatitis C virus; however, other combinations between fetal HLA ligands and maternal NK cell KIR receptor increase the risk of pre-eclampsia. Some NK cell receptors are strongly associated with individuals resistant to malaria infection, and numerous studies demonstrate associations of receptor/ligand pairs with either favorable or poor prognoses in the development of solid tumors and onco-hematologic conditions (Khakoo et al., 2004; Hiby et al., 2004; Ruggeri et al., 2002; Nelson et al., 2004; Pende et al., 2009; Venstrom et al., 2012; Cardozo et al., 2016).

A class I HLA molecule is expressed by all nucleated cells in an individual, playing a crucial role in allowing the immune system to recognize the body's cells as self. Under normal conditions, when engaged with "self" class I HLA, inhibitory KIR receptors dominantly signal over activation receptors, preventing the cytolytic action of NK cells (Diefenbach, 2001; Bryceson et al., 2006; Caligiuri et al., 2008). Thus, NK cells spare autologous cells expressing normal levels of class I HLA while eliminating altered cells such as tumor cells and virus-infected cells, which often lose or have reduced class I HLA

expression (Ljunggren et al., 1990; Garcia-Lora et al., 2003; Schanoski et al., 2004).

In the context of hematopoietic stem cell transplantation (HSCT), the beneficial effect of NK cells relies on the development of alloreactive NK cells from the graft and their functional integrity during the patient's immune system reconstitution. NK cells represent the first subset of lymphocytes to reconstitute following a transplant and thus play a crucial role in controlling early relapses and preventing infections. Additionally, they possess the unique ability to eliminate both recipient T cells and antigen-presenting cells (APCs), which is essential in preventing graft rejection and Graft-versus-Host Disease (GVHD) (Gao et al., 2020). Due to their location on different chromosomes (19q13.4 for KIR genes and 6p-21.3 for HLA genes), there can be KIR/HLA incompatibility between donor and recipient. Typically, NK cells acquire self-tolerance and functional competence through an educational process, wherein inhibitory KIRs can be inhibited by self-HLA ligands and activated in a non-self HLA environment. Additionally, the reduced activation response capacity of KIRs in the presence of their cognate ligands also helps prevent autoimmunity (Leung et al., 2011).

A alloreactivity of NK cells is intriguing in the context of HSCT, as alloreactive NK cells have the capability to eliminate residual leukemic cells, reducing the relapse rates of the underlying disease and preventing graft-versus-host response (GVHD). There are three proposed models to enhance donor selection for HSCT based on KIR receptors, aiming for improved post-transplant outcomes. The first model considers that donor NK cells may be alloreactive against recipient cells if the HLA ligand for the inhibitory KIR receptor is present in the donor's cells but absent in the recipient's cells. Therefore, this model is focused on donor/recipient HLA incompatibility (Ruggerie et al., 2002).

The second model posits that donor NK cells may become alloreactive if the HLA ligand in the patient's cells is incompatible with the inhibitory KIR on the donor's NK cells (receptor-ligand or missing ligand model). This model was initially proposed by Leung and colleagues based on the compatibilities between the recipient's HLA and the donor's inhibitory KIR. The results of this study suggested that the receptor-ligand model better predicted the risk of disease relapse, especially for lymphoid malignancies (Leung et al., 2004).

Recently, our group demonstrated that the absence of the HLA ligand in the patient's cells for the donor NK cell's inhibitory KIR receptor, in HLA-matched related allogeneic hematopoietic stem cell transplantation (allo-HSCT) without T-cell depletion, may result in improved overall survival and event-free survival rates in patients with Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS) (Cardozo et al., 2016).

The third model proposed by Cooley and colleagues is focused on the presence of HLA ligands in the patient for donor's activating KIRs (KIR-B haplotype model). This study demonstrated that unrelated donors with KIR-B haplotypes (presence of up to 5 activating KIRs) conferred a significant benefit in relapse-free survival in patients with Acute Myeloid Leukemia undergoing non-T-cell-depleted hematopoietic stem cell transplantation (Cooley et al., 2009).

However, the results of the studies are still quite controversial, and several important questions remain regarding the biology of NK cells post-HSCT. For instance: what are the exact effects of NK cell alloreactivity in patients after HSCT? Why does NK cell alloreactivity work better for some onco-hematologic diseases than for others? Could the presentation of specific peptides by HLA molecules in the patient modulate the responses of NK cells?

Understanding how the peptidome might influence the recognition of donor NK cells through KIR receptors is of paramount importance in elucidating issues that are still unclear regarding NK cell alloreactivity post-allogeneic transplantation. Furthermore, comprehending the specificity of KIR receptors for specific HLA peptide-bound alleles could enhance the donor selection process and predict post-transplant response.

Influence of the peptidome on cytomegalovirus reactivation post-allogeneic hematopoietic stem cell transplantation (HSCT).

Infections pose a significant challenge for patients post-HSCT due to the immune disturbance resulting from various factors such as intensive conditioning regimens, use of immunosuppressive agents, and potential complications, including graft-versus-host disease (GVHD). Specifically, the reactivation of Cytomegalovirus (CMV) stands as the primary viral infectious complication following allogeneic HSCT and is associated with an increased risk of non-relapse mortality (Green et al., 2016)"

NK cells, as mentioned earlier, are the first immune cells to reconstitute post-HSCT, reaching normal numbers within weeks and contributing to the graft-versus-leukemia effect alongside T cells. However, the cytotoxic and cytokine-producing functions of NK cells decrease from 3 to 6 months after transplant, reaching normal levels of reactivity within the first year. CMV reactivation is a common post-transplant complication, often accompanied by the maturation of graft NK cell reconstitution, resulting in the expansion of adaptive NK cells, which are associated with improved disease-free survival (Cichocki et al., 2019; Rashidi et al., 2019; Apiwattanakul et al., 2020).

NK cells have several mechanisms to recognize and control CMV infection in humans. Activation receptors and co-receptors that are non-specific for HLA class I, such as NCRs, NKG2D, DNAM-1, and 2B4, recognize infected cells through cellular ligands. Another way NK cells kill infected cells is through antibody-dependent cellular cytotoxicity (ADCC) via CD16 engaged by the Fc fragment of antiviral immunoglobulins. The activating receptor NKG2C interacts with the CMV-derived UL-40 peptide presented by non-classical HLA-E molecules. Moreover, NK cells express various toll-like receptors (TLRs) to recognize several pathogen-associated molecular patterns (PAMPs) derived from CMV (Rashidi et al., 2019).

Rashidi and colleagues showed that compared to seronegative individuals, CMV-seropositive individuals exhibit increased NK cells expressing the activating receptor NKG2C, along with high expression of CD57 and KIRs specific to self-MHC class I molecules (sKIRs) (Rashidi et al., 2019). In CMV infection, KIR+ / NKG2C+ / CD57+ / CD49a+ / CD56dim / CD16- cells were identified in the lungs, suggesting that this subset of NK cells may be involved in CMV control (Dogra et al., 2020).

Therefore, NKG2C+ NK cells possess memory-like characteristics and require active or latent (subclinical) CMV antigen expression for clonal expansion of NK cells previously exposed to CMV in the donor. However, the causal relationship between the expansion of adaptive NK cells and CMV control remains unclear (Dogra et al., 2020).

Recently,Hammer and colleagues described that NKG2C+ NK cells differentially recognized distinct strains of CMV that encode variable UL-40 peptides which, in combination with pro-inflammatory signals, controlled the population expansion and differentiation of NKG2C+ cells. Thus, this study suggests that polymorphic CMV peptides contribute to shaping the heterogeneity of adaptive NKG2C+ NK cell populations among CMV-seropositive immunocompetent individuals (Hammer et al., 2018).

Cytomegalovirus (CMV)-responsive NK cells have been reliably detected in peripheral blood, bone marrow, spleen, and lungs of CMV-seropositive donors, but not significantly in seronegative ones. The presence of CD57+NKG2C+ NK cells has also been associated with certain HLA types, strongly linked to HLA-Bw4 and HLA-C1/C2 antigens (Faridi & Agrawal, 2011).

There are reports of KIRs recognizing specific peptide motifs presented by HLA class I molecules. Stewart and colleagues demonstrated that amino acids at positions 7 and 8 of the peptide play a role in KIR2DS1 binding. KIR2DS1 exhibits peptide selectivity similar to KIR2DL1. Peptides with specific motifs have strong inhibitory, weak inhibitory, or antagonistic effects on KIR2DL2 and -2DL3+ NK cells. These findings suggest that NK cells are capable of detecting changes in target cells through selective peptide recognition (Stewart et al., 2005; Fadda et al., 2010).

Several studies have demonstrated that KIR haplotype B genes (with higher expression of activating KIR receptors) protect patients post-HSCT against infections, most notably in non-depleted T-cell-replete (TCR) transplants. Cook et al. first observed that donors with KIR B haplotype exhibited a significant reduction in CMV reactivation rates in related allogeneic HSCT. Wu et al. and Zaia et al. showed that donors expressing higher numbers of activating KIRs were associated with lower rates of CMV reactivation (Chen et al., 2006; Cook et al., 2006; Zaia et al., 2009; Wu et al., 2009; Tomblyn et al., 2010; Gallez-Hawkins et al., 2011).

Moreover, transplants from donors with KIR2DS1 were correlated with better infectious control. Mancusi et al. further demonstrated that the binding of KIR2DS1 to HLA-C2 triggered the production of pro-inflammatory cytokines by alloreactive NK cells (Mancusi et al., 2015).

The presentation of polymorphic peptides derived from CMV by the HLA-E molecule for CD94-NKG2C+ cells is currently better understood, particularly in explaining the differences in the reconstitution of adaptive NK cell subsets after HSCT in patients who do and do not reactivate CMV. Furthermore, some studies demonstrate how peptides presented by HLA class I molecules can shape NK cell responses through activating and inhibitory KIR receptors in patients with CMV infection (Mancusi et al., 2015; Hammer et al., 2018).

However, understanding how peptides may influence the direction of NK cell responses through KIR receptors in patients undergoing HSCT in the context of a CMV infection is still a significant challenge. This is especially true considering the numerous variables that need evaluation in such studies, such as transplant type, KIR compatibility, HLA compatibility, cell source, age, gender, ethnicity, high polymorphism of HLA molecules and KIR receptors, reconstitution of different NK cell subsets, T-cell depletion or non-depletion, conditioning regimen, underlying disease, and donor/recipient CMV serology.

Moreover, within the context of cellular therapy, recent and highly promising results with chimeric antigens expressed in NK cells, such as CAR-NK, have shown encouraging prospects for using these cells in the treatment of onco-hematological diseases, solid tumors, and infectious diseases (Wrona et al., 2021; Sabbah et al., 2022).

Therefore, understanding the complexity of interaction between NK cell receptors and the peptidome could enhance the effectiveness of these cells in recognizing altered and infected cells, thus improving therapy efficacy and reducing adverse events.

In conclusion, many questions regarding the interaction between KIR receptors and the peptidome need to be elucidated, and new investigations will undoubtedly contribute to a better understanding of NK cell response post-transplant, particularly in the context of cytomegalovirus reactivation.

Conflicts of Interest:

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