Review
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Natural Killer Cell Diversity in Viral Infection: Why and How Much?

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ABSTRACT
Natural killer cells are a diverse group of innate lymphocytes that are specialized to rapidly respond to cancerous or virus-infected cells. NK cell function is controlled by the integration of signals from activating and inhibitory receptors expressed at the cell surface. Variegated expression patterns of these activating and inhibitory receptors at the single cell level leads to a highly diverse NK cell repertoire. Here I review the factors that influence NK cell repertoire diversity and its functional consequences for our ability to fight viruses.

Keywords: NK cell or natural killer cell, virus, diversity, repertoire, lymphocyte, mass cytometry

INTRODUCTION

Natural killer (NK) cells are innate lymphocytes that can rapidly eliminate infected or tumor cells and modulate immune responses through the secretion of cytokines and chemokines. First identified in mice and humans in the 1970s on the basis of their ability to kill tumor cells, they form a critical first line of defense, capable of acting within minutes and without the need for priming [1, 2]. NK cells are now recognized to be part of the larger family of innate lymphoid cells (ILCs) [3],

though this review will focus exclusively on "classical" NK cells in humans. A single NK cell can act as a serial killer—engaging multiple targets in sequence over a rapid time scale [4]. NK cells may help prevent cancer; individuals with high NK cell activity are less likely to develop cancer [5]. The important role of NK cells in cancer recognition, coupled with their remarkable speed and potency, has led to excitement about the development of immunotherapies harnessing NK cells to attack cancer [6-9].

The importance of NK cells for fighting viral infections was revealed by Biron and colleagues' description of severe herpes virus infectious in NK cell-deficient individuals [10]. The association between NK cells and viral susceptibility has held true for additional immunodeficiencies in which NK cell dysfunction is a prominent feature, including X-linked lymphoproliferative syndrome (XLP) and X-linked immunodeficiency with Mg^{2+} defect, EBV infection, and neoplasia (XMEN) [11-16]. These findings, combined with the recent descriptions of NK cells with memory-like capacity [17-22], has raised the possibility that NK cells might be an important component of new antiviral vaccine or immunotherapy strategies. However, for these vaccine or immunotherapy approaches to be a success, we must first understand which NK cells to harness and how to best tune their activity to attack the appropriate pathogen. This requires consideration of the diversity of the human NK cell repertoire, and how, within that diverse repertoire, we can select the NK cell activities we desire.

NK CELLS: A DIFFERENT KIND OF DIVERSITY

Diversity is an intrinsic and critical characteristic of the immune system, aiding in our ability to recognize and eliminate a wide variety of potential pathogens. Diversity is often attributed primarily to T and B cells, lymphocytes that somatically rearrange their antigen-specific receptors to provide billions of potential specificities [23]. During B and T lymphocyte development, there are checks and balances in place to avoid autoreactivity while generating flexibility and a vast array of specificities. Natural killer cells, on the other hand, do not have somatically rearranged antigen-specific receptors. They are therefore tasked with responding to the vast array of potential pathogens through germline-encoded receptors, requiring different pathways to provide a response that is rapid, tunable, and self-tolerant.

To achieve this, NK cells generate diversity through two primary mechanisms: the first based on genetic diversity within killer immunoglobulin-like receptor (KIR) genes, and the second based on the assortment of receptors at the cell surface. In humans, KIR are the second most polymorphic genes after the human leukocyte antigen (HLA) genes, and individuals differ in their KIR gene content [24, 25]. As a result, KIR genes are a major driver of NK cell diversity, which will be summarized only briefly here. KIRs consist of two major types of receptors, the inhibitory KIR (denoted by an "L" in the name for a long cytoplasmic tail), and the activating KIR (denoted by an "S" for a short cytoplasmic tail). Individuals can be sorted into two groups based on their KIR genotypes. The KIR A group has primarily inhibitory KIR and either no or one activating KIR, while group B has additional activating KIR genes [25]. Inhibitory KIRs recognize HLA, sending an "all-clear" signal to prevent the NK cell from lysing the target cell. As a result, KIR are a critical component of NK cell function, and NK cells are educated (also called licensed or armed) through their KIR to be exquisitely sensitive to perturbations in HLA expression [26-28]. As KIR and HLA are inherited independently, KIR-expressing NK cells are educated if the KIR encoun-

ters its cognate HLA ligand during development, or uneducated if the HLA ligand for the KIR is absent. The importance of KIR diversity for the NK cell repertoire and its responsiveness has been studied and reviewed extensively [22, 25, 29-31]. In particular, a significant body of work points to the importance of balancing selection in maintaining divergent KIR haplotypes that favor either survival from infectious disease (during times of epidemics) or reproduction (to favor recovery) [24, 32]. The critical balance between reproductive needs and protection from infection is beautifully highlighted in a series of studies demonstrating how different maternal and paternal KIR/HLA combinations influence reproductive outcome [22, 24, 33-38]. These findings, and many others, establish the critical importance of genetics in maintaining NK cell diversity.

Rather than reiterate the importance of the genetic contributions to NK cell diversity, in this review I seek to focus instead on the second major contributor to NK cell diversity: how the assortment of receptors at the cell surface generates NK cell diversity. The phenotypic diversity of NK cells is based upon combinatorial expression patterns of activating and inhibitory natural killer receptors (NKRs), including KIR and many other genes, with each NK cell capable of expressing a different combination of NKRs. Since NK cells integrate signals from this array of activating and inhibitory signals, this phenotypic diversity has significant implications for NK cell function. For instance, a NK cell with a large number of activating NKRs may be more readily triggered. Thus, the phenotype and function of NK cells are tightly linked.

THE MAGNITUDE OF HUMAN NK CELL DIVERSITY

The idea of subsetting NK cells based on phenotypic markers was first proposed by Lanier and colleagues in 1983 [39], and since then the number of populations and recognition that they can perform distinct functions has steadily increased [40-43]. NK cells are traditionally divided based on CD56 and CD16 expression, with $CD56^{bright}CD16^{-}$ NK cells thought to be relatively immature and specialized for cytokine secretion while the more abundant $CD56^{dim}CD16^{+}$ NK cells are fully mature and primed for killing. In fact, there is significant functional overlap between these groups, and intermediate populations of $CD56^{-}CD16^{-}$ NK cells can also arise, particularly in the setting of chronic infection [44].

In light of their critical importance in distinguishing self from "altered self," several studies have elegantly explored the expression patterns of the major inhibitory receptors: inhibitory KIRs, NKG2A, and LILRB1 [45-50]. These studies demonstrated that NK cells express every possible combination of the inhibitory receptors they encode, resulting in NK cell subsets with one or several inhibitory receptors as well as a significant subset of NK cells lacking inhibitory receptors. Further, the education status of these NK cells varies based on the combined KIR and HLA genotypes, conferring a distinct functional capacity to these NK cell subsets [45-50].

More recently, the advent of cytometry by time-of-flight (CyTOF, also called mass cytometry) [51, 52], has allowed us to generate a more complete understanding of the diversity of receptor expression patterns on NK cells that includes the activating receptor profiles [50, 53-55]. CyTOF is a flow cytometry platform that uses metals instead of fluorophores to tag antibodies, with the readout by mass spectrometry, and thus allows the use of ~40 parameters simultaneously without the need for compensation [51, 52]. CyTOF profiling of the healthy human NK cell repertoire revealed between 6,000 and 30,000 unique NK cell subsets, based on combinatorial expression patterns of NKR, per individual [50]. As these subsets were not necessarily shared between indi-

viduals, more than 120,000 NK cell subsets were present in the 22 individuals studied [50]. The magnitude of this diversity was surprising; studies of the receptor profiles in twins revealed both genetic and environmental influences. Inhibitory receptor profiles were genetically determined, but the activating receptor expression patterns appeared to be under environmental influence [50]. The result is a highly diverse and adaptable repertoire that is quite distinct even among adult twins, but maintains self-tolerance through strict regulation of inhibitory receptor expression patterns [50].

An important consideration in quantifying NK cell diversity is that these calculations are highly dependent on the number of markers and methods used. For instance, the diversity score is diminished if fewer markers are used or if the markers selected are either highly and universally expressed or expressed at a very low frequency. Thus, while these methods are very valuable to compare populations within a given study, comparison between studies requires that identical markers be used. A second consideration is the fact that any single diversity score does not fully capture the repertoire characteristics and distributions. For example, the Inverse Simpson Index is commonly used to quantify both immune repertoire and microbiome diversity because it is adaptable to count data and does not require normally distributed data. However, this index can result in the same value with very different population structures—which may have significant functional implications. A specific example of this is that two healthy adults have nearly identical NK cell diversity scores by the Inverse Simpson Index (123 and 126), but a very different number of NK cell subsets among the same number of total NK cells (2189 and 446), indicating that the distribution of the populations must be quite different (Simpson and Blish, unpublished). Thus, while diversity calculations provide a convenient method to quantify and understand the NK cell population structure, their limitations must be understood as well. With these limitations in mind, it is still important to understand the factors that control the development, maintenance, and function of this diverse NK cell repertoire.

THE IMPACT OF IMMUNE EXPERIENCE ON THE NK CELL REPERTOIRE

Some clues about the factors that control the development and maintenance of NK cell diversity have come from studies of age-related changes in the NK cell repertoire (reviewed in [56]). Aged individuals have decreased expression of NKp30, NKp46 and NKG2D, and NKG2A and increased expression of KIR, LILRB1, and TIGIT [57-61]. Some studies suggest that NK cells maintain their cytolytic function with aging [57, 58], while others suggest that cytotoxicity and cytokine production decrease with aging [62]. The extent to which age-related changes are due to intrinsic aging vs. accumulated environmental exposures, including cytomegalovirus (CMV) infection, are not entirely clear. However, while CMV infection is clearly a driver of many of these changes [63], some of these changes are not driven solely by CMV. Regardless of age and CMV status, "experienced" $CD57^+$ NK cells express more NKRs per cell and significantly increase expression of a distinct pattern of activating and inhibitory NKR [53]. $CD57^+$ NK cells are also skewed towards cytokine production at the cost of cytotoxicity [54]. These data suggest that "immune experience" may be a better metric for NK repertoire perturbations than aging itself. Consistent with this idea, in healthy adults, NK cell diversity significantly correlates with expression of CD57, but not with age, suggesting that immune experience is a major driver of NK cell diversity [54]. The idea that immune experience shapes NK cell repertoire diversity is also supported by the fact that cord blood NK cells have low CD57 expression and significantly lower NK cell diversity than adult NK

cells [54]. Finally, short-term *in vitro* exposure to viruses (HIV-1, West Nile Virus [WNV]) augments NK cell diversity [54], suggesting that serial viral exposures might shape and diversify the NK cell repertoire. Thus, if a wide range of receptor profiles accumulates immune experience, it is interesting to consider whether different NKR, singly or in combination, are particularly important in the response to different viruses.

ROLE OF SPECIFIC RECEPTORS AND COMBINATIONS IN DIFFERENT VIRAL INFECTIONS

One explanation for the generation of NK cell diversity during an acute antiviral response is that the repertoire is adapted to generate a range of specificities in order to find the right "solution" for each virus. Along these lines, it stands to reason that a variety of different NK cell receptors might contribute to the recognition of any given virus, quite possibly with complementary and overlapping functions. Consistent with this idea, many different studies have identified the role of particular NK cell receptors in the response to different viruses. I have summarized these findings in Table 1. They represent a mixture of epidemiologic associations and mechanistic studies. As even this exhaustive list does not comprehensively assess all of the literature, I also refer the reader to excellent reviews on the role of natural cytotoxicity receptors (NCRs) and NKG2D in responding to multiple viruses [64-68] and recent reviews of the role of KIR and their evolution in disease [69, 70].

NK CELL RECEPTORS AND HIV

Perhaps one of the most studied interactions between specific NK cell receptors and a virus is the interaction between KIR3DS1/L1 and HIV. In fact, the influence of KIR3DS1 on disease, particularly HIV, has recently been the topic of an entire review [71] . This association came to light based on the discovery that HIV-infected individuals with both KIR3DS1 and the HLA-B alleles containing the Bw4-80Ile epitope experience slower progression to AIDS [72, 73]. An additional study found that the combination of KIR3DL1 and HLA-Bw4-80I was also associated with slower disease progression [74]. Further confirming the importance of NK cell expression of KIR3DS1/L1/HLA-Bw4-80I, copy number variation in KIR3DS1 and KIR3DL1 are associated with the HIV set point viral load, but only in the presence of the Bw4-80I allele [75]. KIR3DS1/L1 alleles are also associated with lower risk of HIV transmission between partners [76].

Consistent with these epidemiologic associations, NK cells expressing both KIR3DS1 and KIR3DL1 expand during HIV infection, but only in the presence of the HLA Bw4-80I allele [77]. The ability to suppress viral replication *in vitro* was associated with KIR3DS1 or KIR3DL1 and HLA-Bw04 expression [77, 78]. In addition, individuals with protective KIR3DL1/S1 genotypes inhibited HIV replication more potently than those lacking such alleles through secretion of CC-chemokines [79]. The antiviral efficacy of KIR3DS1 may relate to its association with the ITAM-bearing receptor DAP12 [80]. In all of these studies, it is important to note that many of the effects of KIR3DS1 vs. KIR3DL1 are difficult to dissect, as most KIR3DS1$^+$ individuals also express KIR2DL1. In addition, KIR3DL1 is the most diverse of all the KIR, and different allotypes have dramatically different effects on HLA binding [81]. Taken together, both epidemiologic and experimental data suggest that both KIR3DS1 and KIR3DL1 play a role in the response to HIV, yet it is not apparent how both an activating and inhibitory receptor, that are nearly identical in

their extracellular domain, might both enhance responses to the same pathogen.

Recent data may provide some insight into this potential conundrum. The first issue is whether KIR3DS1 and KIR3DL1, given their similar extracellular domains, truly bind to the same ligand (in which case it would be hard to reconcile their similar effects in light of their opposing roles on NK cell activation). The inhibitory receptor KIR3DL1 binds to HLA-B molecules containing the Bw4-80Ile epitope [82]; however, several studies have failed to demonstrate similar binding for the activating KIR3DS1 receptor to Bw4-80I [80, 83, 84]. One potential limitation of these negative data, however, is that the researchers did not study HIV-infected cells, and it is possible that HIV peptides might alter the ability of KIR to bind HLA. Consistent with this idea, O'Connor et al. recently demonstrated that two different HIV peptides allow binding of KIR3DS1 to Bw4 alleles [85]. Furthermore, a recent study demonstrated that KIR3DS1 binds to open conformers of HLA-F [86], indicating that even if it binds Bw4, it has additional ligands. Synthesizing these studies, it appears likely that there are multiple pathways by which KIR3DL1 and KIR3DS1 can contribute to HIV responses. The first, which explains the effects of KIR3DS1, is that NK cells bearing KIR3DS1 become activated through direct recognition of either HLA-F open confomers or of HLA-Bw4 alleles with specific HIV peptides. The second pathway, explaining the contributions of KIR3DL1, involves the effects of KIR3DL1/HLA-Bw4 on educating NK cells—leading to a generalized high activation status. As individuals with KIR3DL1 and the Bw40-80I epitope have highly educated NK cells, they are better able to suppress HIV replication, consistent with recent findings that KIR3DL1 and HLA-Bw4 density significantly influence HIV replication [87]. Thus, two entirely different pathways—one activating and associated with direct recognition, and the other inhibitory but associated with better "arming" NK cells through education/licensing—might contribute to HIV responses. This finding also stresses the importance of diversity within the NK cell response—in this case two different solutions, generated by distinct and overlapping subsets of NK cells—are available to respond to HIV-infected cells.

Of course, recognition of HIV-infected cells is not just associated with KIR3DL1/S1 and HLA-Bw4. Multiple interactions between KIR and HIV have been documented [88], as shown in Table 1. $NKG2A^+$ NK cells respond more frequently to HIV-infected cells than do $NKG2A^-$ NK cells [89]. The recent study by Davis et al., provides a potential mechanistic explanation for why this inhibitory receptor might contribute to HIV recognition [90]. The authors demonstrate that a highly conserved HIV peptide presented by HLA-E renders the cells susceptible to NKG2A-mediated killing (presumably by abolishing the recognition and preventing inhibitory signaling) [90]. Thus, NKG2A-expressing NK cells, which relatively infrequently co-express KIR, are not inhibited by the HLA-E on the surface of HIV-infected cells, whereas the more highly educated KIR-expressing NK cells will be inhibited through recognition of HLA-C that remains highly expressed during HIV infection. Consistent with this idea, another recent study demonstrated that $KIR2DL3^+NKG2A^+$ NK cells potently responded to HIV-infected cells though secretion of CC chemokines. But this effect was primarily seen in $KIR2DL3^+$ individuals lacking HLA-C2 [91]. The "educated" KIR3DL2-expressing cells in HLA-C1 homozygotes might be inhibited by the HLA-C that is retained on the surface of HIV-infected cells. Finally, a variety of activating receptors, including natural cytotoxicity receptors, NKG2D, KIR2DS4, FcRγ, NTB-A, and an additional inhibitory receptor, LILRB1, are all associated with HIV responses (Table 1). These data provide further support for the idea that NK cells have evolved diverse mechanisms to recognize and respond to HIV infected cells, making diversity in receptor expression an intrinsic characteristic of

NK cells responding to viruses.

DIVERSE NK CELL RECEPTORS ARE INVOLVED IN THE RESPONSE TO OTHER VIRUSES

Specific KIR have also been associated with influenza infection. Expression of KIR2DL3 and KIR3DL1 was associated with more robust IFN-γ and cytolytic responses *in vitro* [92]. A more complex picture was observed in a clinical study in which either KIR3DL1/S1- or KIR2DL1-expressing individuals lacking the ligand or KIR2DL2/L3 and its cognate ligand were enriched among ICU patients during the 2009 influenza pandemic [93]. In addition to these KIR associations, there are well documented examples of natural cytotoxicity receptors, NKG2D, 2B4, and NTB-A playing a role in the recognition of influenza-infected cells [94-98], which are summarized in Table 1.

Along similar lines, NK cells expressing KIR2DL3/L3 have increased degranulation to hepatitis C (HCV) [99]. In addition, the compound genotype KIR2DL3 homozygosity and HLA-C1 is associated with HCV responses [100]. This observation may be explained by the fact that HLA-E expression was significantly unregulated in HCV-infected patients, but that KIR2DL3^{+}NKG2A^{-} NK cells were not susceptible to HLA-E mediated inhibition and therefore preserved their function [101]. Many additional associations with antiviral responses are noted and summarized in Table 1. In particular, NKG2D is a recurring mediator of recognition for multiple tumor and infected cells. The fact that viruses have evolved a variety of means to downregulate NKG2D ligands provides evidence for its importance in mediating NK cell responses to a variety of pathogens [68, 102]. It is also important to note that NKG2D is the focus of much research in large part because its ligands are known. However, for many other NK cell activating receptors, the ligands remain unknown. As a result, there might well be other escape mechanisms that we do not fully understand or appreciate.

THE DRAMATIC INFLUENCE OF CMV ON THE REPERTOIRE

While I have touched briefly above on the specific NKRs involved in the recognition of CMV-infected cells, the impact of CMV infection on the NK cell repertoire is so dramatic that it has been the subject of several prior excellent reviews that do the subject far more justice than I can here [63, 103-105]. The most obvious impact of CMV infection is the expansion of a NKG2C^{+} NK cell subpopulation in a subset of CMV-seropositive individuals [106-112]. This NK cell subpopulation is additionally characterized by high expression of CD57, low expression of NKp30, CD161, NKG2A, and Siglec-9 and often expression of self-specific KIR, suggesting that the expansion of these cells is restricted to an educated subset of NK cells [107, 113, 114]. Exposure to CMV-infected fibroblasts drives the generation of this subset *in vitro*, supporting the idea that NK cells expressing NKG2C are preferentially responsive to CMV, likely a result of recognition of a viral antigen in the context of HLA-E, the ligand for NKG2C [109]. There is significant evidence that these NKG2C^{+}CD57^{+} NK cells represent a memory-like subset of NK cells (reviewed in [103, 104]). Supporting the idea that these cells are memory-like, NKG2C^{+}CD57^{+} NK cells dramatically expand post-transplant in the setting of CMV reactivation, and the subsequent reduction in numbers upon control of viremia—kinetics consistent with a recall response [112, 115-117]. The recent demonstration that these memory-like NK cells have epigenetic changes that are associated with their altered functional capacity provides a critical and important mechanistic explanation

for how these memory-like responses might be generated [118-120].

If the existence of NKG2C$^+$CD57$^+$ NK cells represents a "clonal" expansion of CMV-specific NK cells, then it stands to reason that this clonal expansion would diminish the diversity of the NK cell repertoire and restrict downstream responses. This possibility is raised in the commentary by Achour *et al*., who speculate that CMV infection might decrease NK cell diversity and favor the development of certain tumors [103]. Supporting this idea, NKG2C$^+$ NK cells differ in the profile of cytokines produced when compared to immature NK cells from CMV$^-$ patients, and in patterns that typically favor tumorigenesis [121-123].

At the surface, the idea that CMV infection narrows NK cell diversity through clonal expansion appears to be in conflict with the data that viral infection and maturity are both associated with increased NK cell repertoire diversity [53, 54, 124]. Yet, delving more deeply into the data, this apparent conflict does not exist. Indeed, the expansion of NKG2C$^+$CD57$^+$ NK cells can dominate the NK cell repertoire. However, these NK cells still express a vast array of additional activating and inhibitory receptors, and if diversity measures take into account these additional receptors, there is no reduction in NK cell diversity in CMV$^+$ individuals [50, 53, 54, 113, 125]. In fact, individuals who were CMV$^+$ were not significantly different in their NK cell repertoire diversity than CMV$^-$ individuals [50, 54]. Furthermore, we compared the NK diversity between NKG2C$^+$ and NKG2C$^-$ cells within CMV-seropositive individuals, and found a trend for increased diversity among NKG2C$^+$ NK cells (Strauss-Albee and Blish, unpublished). Thus, even with the fixing of expression levels of several receptors due to a clonal-like expansion, the assortment of other activating and inhibitory receptors is sufficient to drive diversification of even these "clonal" cells. While CMV clearly imprints the NK cell repertoire and changes its function, these findings remain consistent with the idea that viral exposure drives NK cell diversification.

DOES NK CELL DIVERSITY DECREASE THE FLEXIBILITY OF THE NK CELL REPERTOIRE?

Perhaps the most surprising finding about NK cell diversity in the last several years is the fact that higher pre-infection NK cell diversity is associated with increased risk of HIV acquisition in a small cohort (n = 37) of Kenyan women [54]. At the surface, this is a counterintuitive finding—as immunologists, we always perceive diversity to be a good thing—so why would diversity be associated with increased risk of acquiring HIV? Simply put, the answer is not entirely clear, but there are several possibilities. First, given the difficulty of finding viably preserved peripheral blood mononuclear cells from prior to HIV infection, this was a small study, and may not hold following analysis of additional cohorts. Second, even if true, this is an association, not a causal finding. NK cell diversity might correlate with some other, unmeasured factors that actually are driving the enhanced risk. Despite these caveats, there are some clues as to potential mechanisms that might drive this exposure. Because viral exposure drives NK cell diversity and alters responsiveness [54], the women who acquired HIV infection may have had more HIV exposures, which result in increased NK cell diversity and increased risk. Another intriguing possibility, which needs to be evaluated in future studies, is that serial viral infections may modulate the NK cell repertoire and its responsiveness (Figure 1). According to this proposed model, the NK cell repertoire begins in a relatively homogenous, but very flexible and tunable state. Each viral exposure diversifies and specializes the repertoire, enhancing recall responses for NK memory, but potentially diminishing the response to *de novo* pathogens. Notably, this model of commitment is consistent with data from murine NK cell memory in which memory NK cells, once committed

to one pathway, have diminished responses to the other [126]. I propose this model not as proven, but as a framework for future studies and for consideration of the impact of vaccination on NK cell responses. It is critical that we understand the mechanisms by which repeated exposures affect NK cell responses to both on-target and off-target antigens.

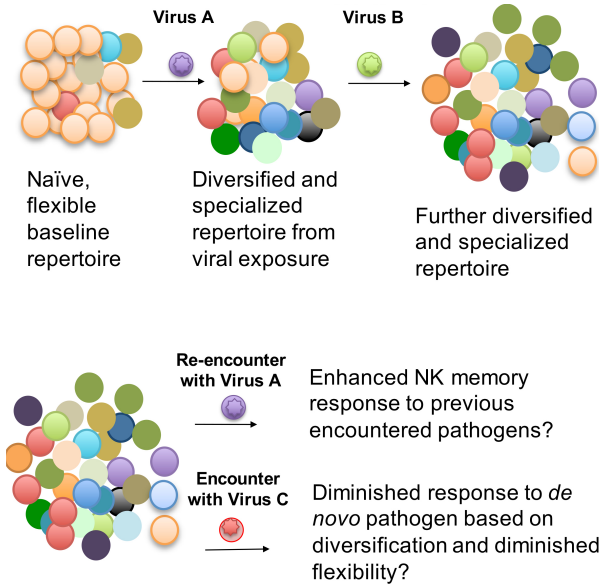

Figure 1. Proposed model of the relationship between NK cell diversity and viral exposure. Based on the association between age, immune experience, and NK cell diversity, I propose that the NK cell repertoire begins as a naïve, flexible repertoire that is relatively homogenous from a phenotypic perspective, though it has extensive diversity in KIR expression patterns based on genetics. Upon encounter with different viruses, the NK cell repertoire diversifies, in part by increasing expression levels of activating receptors, as it seeks to adapt to the viral encounter. Each subsequent encounter further diversifies and specializes the repertoire. This specialization might contribute to memory/recall responses, but may also have the surprising effect of diminishing the ability to respond to de novo pathogens. Vaccine and viral challenge studies in human and animal models will be needed to validate or invalidate this model.

CONCLUSIONS

The advent of new technologies has put us at the cusp of unraveling the answers to many important questions about human NK cells, yet much uncertainty remains. How is NK cell diversity maintained at a stable level, for at least 6 months, when the half-life of NK cells is approximately 2 weeks? Does NK cell diversity truly reflect differentiated NK cells that lack the flexibility to respond to a *de novo* pathogen? Can we identify unique subsets of NK cells that are primed to respond to different viruses or cancers? How does vaccination alter the NK cell repertoire and its responsiveness? In addition to these important questions, it is equally important to consider the limitations of the data presented. The extent to which the phenotype correlates with transcriptional pathways is poorly characterized [63, 127], but might influence future studies, particularly those employing single cell RNA-seq. Finally, I have focused here only on blood NK cells, which are not necessarily representative of the NK cell subsets found in tissues [128-131]. It is an exciting time, and I'm certain that future studies will shed significant light on the dynamics of the NK cell repertoire and its functional responses, and impact on viral susceptibility.

Table 1. NK cell receptor virus interactions

Virus	NK Cell Receptor	Brief Description	Reference
CMV	NKG2C	NGK2C$^+$ cells expand during CMV infection	[106-112, 119, 120, 132, 133]
CMV	LIL-11, LIR-1	UL18 inhibits LIR-11;activates LIR-1	[134]
CMV	NKp30	NKp30 inhibited by pp65	[135]
CMV	NKG2D	Several viral proteins bind NKG2D to limit recognition	[68]
Influenza	2B4 and NTB-A	2B4 and NTB-A receptors bind the influenza viral hemagglutinin and co-stimulate NK cell cytotoxicity.	[98]
Influenza	KIR2DL3 KIR2DL1 KIR3DL1/S1	KIR2DL3 and KIR3DL1 and HLA-C1 homozygosity leads to have enhanced IFN-γ secretion and degranulation to influenza A infection in vitro. Individuals with KIR3DL1/S1 or KIR2DL1 but lacking the ligand enriched among ICU patients during the 2009 flu pandemic, as were individuals with KIR2DL2/L3 and its cognate ligand.	[92, 93]
Influenza	NKp46	NKp46 interaction with HA leads to infected-cell lysis, with potential for escape of this pathway by NA-mediated removal of sialic acid residues from NKp46 to decrease recognition	[94-96] [97]
Influenza	NKG2D	NKG2D (and NKp46) mediated recognition of influenza-infected dendritic cells	[95]
HIV	CD94/HLA-E	CD94/HLA-E interaction may contribute to NK cell dysfunction in HIV infection	[136]
HIV	FcRγ	FcRγ$^-$NKp30$^-$NKp46$^-$ NK cells are expanded in HIV and have enhanced ADCC activity	[137]
HIV	KIR2DS4	Full-length KIR2DS4 associated with disease progression	[138]
HIV	KIR3DS1/KIR3DL1	Combinations of KIR3DS1 and/or KIR3DL1 and HLA-Bw4-80I are associated with delayed HIV progression. KIR3DL1 and HLA-B density and binding alter education and HIV responsiveness; KIR3DS1$^+$ NK cells expand and can kill HIV-infected cells	[72, 73, 75-77, 79, 87, 139-141]
HIV	KIR2DL1-3$^+$	KIR2DL1-imprinting on HIV strains; KIR2DL1-3$^+$ NK cells more responsive	[142, 143]
HIV	KIR2DL3	NKG2A$^+$KIR2DL3$^+$ cells potently secrete CC-chemokines, particularly in HLA-C2 individuals and KIR2DL3 is associated with resistance to HIV acquisition in HIV-exposed babies; selection of p24 sequence associated with KIR2DL3 escape	[91, 144-146]
HIV	LILRB1	LILRB1$^+$ NK cells control HIV-1 replication in DCs	[147]
HIV	NCRs	NCRs are decreased in chronic HIV infection	[148]
HIV	KIR	Nef induces endocytosis of HLA-I molecules, helping virus escape from NK cells	[149]
HIV	NKG2D	Nef downregulated NKG2D ligand in infected cells causing decreased cytotoxicity	[150]

HIV	NTB-A, UL-16BP	vpu/nef downregulate NK cell ligands: NTB-A, UL16-BP	[151]
HIV	NKG2A	NKG2A$^+$ NK cells respond more frequently than NKG2A- to HIV$^+$ T cells; based on a conserved HIV-1-dervired peptide presented by HLA-E that renders cells susceptible to NKG2A	[89, 90]
HIV	NKG2D	NKG2D acts as a co-receptor for natural killer cell-mediated anti-HIV-1 antibody-dependent cellular cytotoxicity.	[152]
HIV	NKG2D/NKp46	Lysis of HIV-1-infected autologous CD4$^+$ primary T cells by interferon-alpha-activated NK cells requires NKp46 and NKG2D.	[153]
HIV	NKp46 NKp30	NKp30 and NKp46 expression correlates with AIDS-status of successfully treated patients	[154]
HIV	NTB-A	Vpu downregulates NTB-A in infected T-cells, causing decreased degranulation by NK cells	[155]
HIV	Siglec-7	Siglec-7 is decreased in NK cells of viremic patients	[156]
HIV and other pathogens	DNAM-1 and NKG2D	Review on NK-T crosstalk mediated by DNAM-1 and NKG2D and their ligands, in the context of infections	[67]
HIV/HCV and other pathogens	NCRs	Reviews on NCRs and pathogen interactions	[65, 66]
HCV	KIR2DL2/L3	KIR2DL3/L3 increases function; KIR2DL3/HLA1C1 is associated with response.	[99-101]
HSV-2	NKG2C, KIR, CD57	HSV-2 infection drives NKG2A$^-$NKG2C$^+$KIR$^+$CD57$^+$ NK cells	[157]
HSV, VSV	NKG2D	HSV decreases MICA, ULBP1, ULBP2, ULBP3	[158]
KSHV	LFA, others	K3 and K5 viral proteins downregulate MHC class I molecules, ICAM-1 ad B7-2, ligands for NK cell-mediated cytotoxicity receptors	[159]
Hantavirus	NKG2C	NK cells expressing NKG2C expand (though most subjects also CMV$^+$)	[160]
Multiple viruses	NKG2D and NCR	Review summarizing data from multiple viruses mwith methods to decrease NKG2D and possible NCR ligands	[64]
CHIKV	NKG2C and CD57	Mature cells more responsive	[161]
Dengue	Inhibitory KIRS	NK cells with inhibitor KIRs respond preferentially to DENV	[161, 162]
WNV and Dengue	NKp44	NKp44 directly binds to purified DV and WNV envelope proteins. Interaction of NK cells with infective and inactivated WNV results in NKp44-mediated NK degranulation	[163]

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POTENTIAL CONFLICTS OF INTEREST

No conflicts to report.

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