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Review Article

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Human CD8⁺ T-Cell Populations That Express Natural Killer Receptors

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Conflict of Interest
The authors declare no potential conflicts of interest.

ABSTRACT

CD8⁺ T cells are activated by TCRs that recognize specific cognate Ags, while NK-cell activation is regulated by a balance between signals from germline-encoded activating and inhibitory NK receptors. Through these different processes of Ag recognition, CD8⁺ T cells and NK cells play distinct roles as adaptive and innate immune cells, respectively. However, some human CD8⁺ T cells have been found to express activating or inhibitory NK receptors. CD8⁺ T-cell populations expressing NK receptors straddle the innate-adaptive boundary with their innate-like features. Recent breakthrough technical advances in multi-omics analysis have enabled elucidation of the unique immunologic characteristics of these populations. However, studies have not yet fully clarified the heterogeneity and immunological characteristics of each CD8⁺ T-cell population expressing NK receptors. Here we aimed to review the current knowledge of various CD8⁺ T-cell populations expressing NK receptors, and to pave the way for delineating the landscape and identifying the various roles of these T-cell populations.

Keywords: CD8-Positive T-Lymphocytes; Natural Killer Cell Receptors; CD56 Antigen; Receptors, KIR; NKG2A Receptor; NKG2C Receptor

INTRODUCTION

Although both human NK and CD8⁺ T cells are representative cytotoxic lymphocytes, they have distinct characteristics as innate and adaptive immune cells, respectively. NK-cell activation is regulated by a balance between signals from germline-encoded activating and inhibitory NK receptors. Activating NK receptors—such as NKG2D, NKp44, NKp30, and NKG2C—recognize ligands that are mainly expressed on aberrant cells, e.g., virus-infected, transformed, or stressed cells. On the other hand, inhibitory NK receptors—such as killer cell immunoglobulin-like receptors (KIRs) and NKG2A—recognize MHC ligands that are expressed on normal healthy cells (1,2). As adaptive immune cells, CD8⁺ T cells are activated by TCRs that recognizes specific epitopes presented by MHC class I (MHC-I) molecules and exert effector functions (3). The CD8⁺ T-cell population exhibits a highly diverse TCR repertoire, enabling CD8⁺ T cells to respond against many different Ags.

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Abbreviations

COVID-19, coronavirus disease 2019; CMV, cytomegalovirus; ITAM, immunoreceptor tyrosine activation motif; ITIM, immunoreceptor tyrosine-based inhibitory motif; KIRs, killer cell immunoglobulin-like receptors; MHC-I, MHC class I; NCAM, neural cell adhesion molecule; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TEMRA, effector memory T; TRM, resident memory T; TVM, virtual memory T.

Author Contributions

Conceptualization: Koh JY, Kim DU, Moon BH, Shin EC; Data curation: Koh JY, Kim DU, Moon BH; Formal analysis: Kim DU, Moon BH; Funding acquisition: Shin EC; Investigation: Koh JY, Kim DU, Moon BH; Methodology: Koh JY, Kim DU, Moon BH; Project administration: Koh JY, Shin EC; Resources: Koh JY; Supervision: Shin EC; Validation: Shin EC; Writing - original draft: Koh JY, Kim DU, Moon BH, Shin EC.

Some subsets of T cells such as mucosal-associated invariant T cells, invariant natural killer T cells and γδ T cells express TCRs with limited diversity and exert innate-like functions. Apart from those subsets, $CD8^+$ T cells can express activating or inhibitory NK receptors, including KIRs, NKG2A, and NKG2C. However, studies have not yet comprehensively elucidated the immunological characteristics of $CD8^+$ T-cell subpopulations expressing each NK receptor.

In this review, we provide an overview of $CD8^+$ T-cell subpopulations expressing NK receptors. First, we describe $CD8^+$ T cells expressing CD56, with regard to their innateness and NK receptor expression. Next, we provide a structured review of $CD8^+$ T-cell subpopulations expressing KIR, NKG2A, or NKG2C. Finally, we discuss the physiological and pathological roles of $CD8^+$ T-cell subpopulations expressing NK receptors. We do not describe NKG2D because NKG2D is expressed by all types of human $CD8^+$ T cells, not by a $CD8^+$ T-cell subpopulation.

$CD8^+$ T CELLS EXPRESSING CD56

CD56—also known as neural cell adhesion molecule (NCAM)—is the first characterized immunoglobulin superfamily member engaged in cell adhesion (4). CD56 serves as a classical lineage marker for human NK cells, which are defined as $CD3^-CD56^+$ lymphocytes (5). Additionally, the CD56 expression level is used to define functionally distinct subsets of NK cells—with a $CD56^{bright}$ NK-cell subset showing elevated cytokine production (6,7), and a $CD56^{dim}$ NK-cell subset exhibiting enhanced cytotoxicity and a mature differentiation status (8).

In this background, early investigators used the term "natural T cells" to describe CD56-expressing T cells (9-11). This $CD56^+$ natural T-cell population comprises heterogeneous T-cell subsets, including γδ T cells and $CD4^+$ T cells, but mainly $CD8^+$ T cells with conventional TCRs (11,12). $CD56^+$ T cells are distinguished from $CD56^-$ T cells and invariant T cells, in terms of TCR clonality, surface protein phenotypes, and genome-wide transcriptional patterns. Compared with $CD56^-$ T cells, $CD56^+$ T cells exhibit higher expressions of NK-cell-related molecules (e.g., CD16, CD94/NKG2, NKG2D, CD122, and DNAM-1) and granzyme B (12). With regards to TCR diversity, $CD56^+$ T cells exhibit a considerably restricted TCRVβ spectrum compared to $CD56^-$ T cells, but a more diverse spectrum than invariant T cells. $CD56^+$ T cells expand in response to IL-2 synergized with IL-12 (13). They also exhibit a potent capacity for T helper 1 cytokine production, and exert TCR-independent cytotoxicity following stimulation with mitogen and IL-2 (10). Based on these innate-like features, it has been suggested that $CD56^+$ T cells may contribute to rapid immune responses against viruses, like innate immune cells. $CD56^+$ T cells have been reported to inhibit hepatitis C virus replication in hepatocytes (14). The frequency of $CD56^+$ T cells in peripheral blood is higher among patients with cytomegalovirus (CMV) infection compared to healthy donors (15).

Our research group recently identified a distinct $CD8^+$ T-cell subpopulation showing high CD56 expression without CD161 expression ($CD56^{hi}CD161^-CD8^+$ T cells), which is characterized by high expression of NK-related molecules and a uniquely restricted TCR repertoire (**Fig. 1**). The frequency of these cells within the liver sinusoidal $CD8^+$ T-cell population is significantly increased among patients with hepatitis B virus (HBV)-related chronic liver disease (16). $CD56^{hi}CD161^-CD8^+$ T cells mainly exhibit a $CCR7^-CD45RA^-$ effector memory phenotype, and include a higher frequency of $CD69^+$ cells, which are tissue resident memory T (T_{RM}) or T_{RM}-like cells, compared to other effector memory $CD8^+$ T cells.

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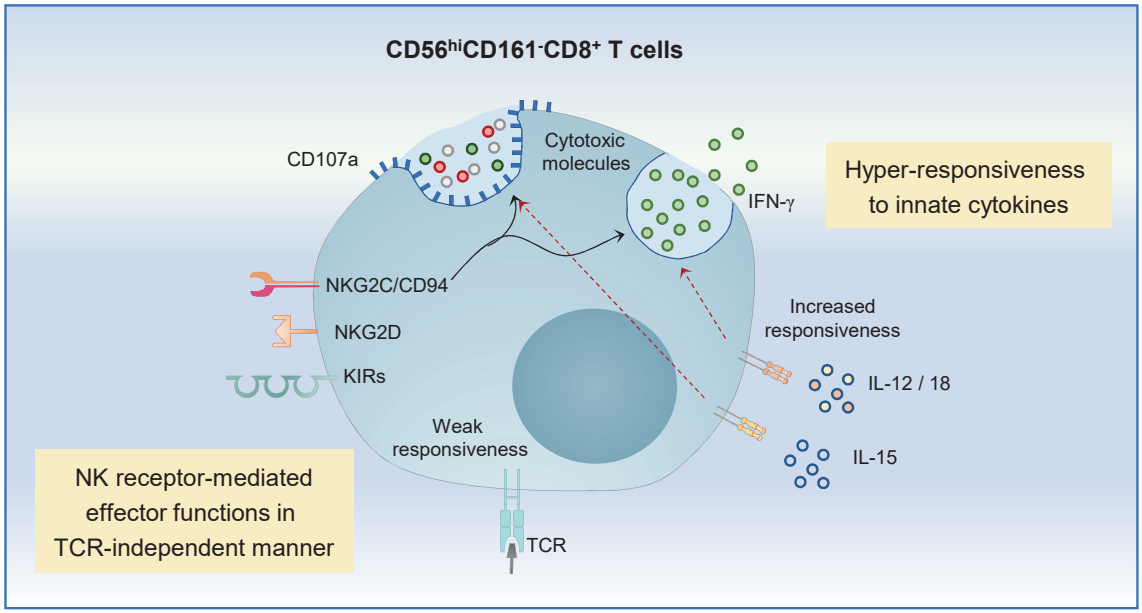

Figure 1. Innate-like features of the CD56^{hi}CD161^{-}CD8^{+} T-cell population. Our group recently reported a CD8^{+} T-cell population marked with high CD56 expression without CD161 expression (CD56^{hi}CD161^{-}CD8^{+} T cells). These CD56^{hi}CD161^{-}CD8^{+} T cells are distinguished from other CD8^{+} T cells in terms of their innate-like features. This CD8^{+} subpopulation exhibits high expressions of various NK receptors, and exerts NK-receptor mediated effector functions in a TCR-independent manner. Additionally, these CD56^{hi}CD161^{-}CD8^{+} T cells show increased responsiveness to stimulation with innate cytokines, including IL-12/18 and IL-15.

CD56^{hi}CD161^{-}CD8^{+} T cells exhibit weak responsiveness to TCR stimulation, but they show high expression of various NK receptors (e.g., CD94, KIRs, and NKG2C) and exert NKG2C- or NKG2D-mediated effector functions even in the absence of TCR stimulation. Additionally, CD56^{hi}CD161^{-}CD8^{+} T cells are highly responsive to innate cytokines (e.g., IL-12/18 and IL-15) in the absence of TCR stimulation. The CD56^{hi}CD161^{-}CD8^{+} T-cell population resembles previously described CD161^{-}CD56^{+} regulatory CD8^{+} T cells (17). Further studies are needed to elucidate the roles of CD56^{hi}CD161^{-}CD8^{+} T cells in immune responses to microbial pathogens or immunopathology.

CD8^{+} T CELLS EXPRESSING KIRs

Virus-infected or transformed host cells tend to lose their MHC-I expression (termed "missing-self"). These aberrant cells with MHC-I downregulation are targeted by NK cells. When target cells express sufficient levels of MHC-I, inhibitory KIRs (receptors for MHC-I) deliver inhibitory signals to NK cells, which does not occur when target cells lose MHC-I expression (18). KIRs are polygenic and polymorphic Ig superfamily receptors, which can recognize distinct MHC-I molecules that are also polygenic and polymorphic. Inhibitory KIRs contain immunoreceptor tyrosine-based inhibitory motifs (ITIMs) in their cytoplasmic domains, which suppress signaling delivered by activating receptors (19,20).

KIRs can be expressed on TCRαβ^{+}CD8^{+} T cells as well as NK cells (21), and can exert a suppressive function in both cell types. Engagement of KIRs with MHC-I ligands reduces the TCR-mediated phosphorylation of ZAP-70 and LAT and downstream signaling pathways (22). This decreases the TCR-triggered effector functions of CD8^{+} T cells, in terms of cytokine secretion (23,24) and cytotoxicity (24-26). On the other hand, KIRs might contribute to CD8^{+} T-cell survival by suppressing activation-induced cell death (27,28). Furthermore, several

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studies suggest that KIR$^+$CD8$^+$ T cells show intrinsic functional impairment, at least against TCR stimulation. Impairment of proliferation and cytokine secretion have been reported even in the absence of KIR engagement (29-31).

KIR$^+$CD8$^+$ T cells exhibit the surface phenotypes of CCR7$^-$CD45RA$^+$ effector memory T (T_{EMRA}) cells, known as terminally differentiated T cells (32,33), and CD28$^-$CD57$^+$ replicative-senescent T cells (30,34). They also express high levels of cytotoxic molecules, such as perforin (29) and granzyme B (35). KIR$^+$CD8$^+$ T cells exhibit an increasing frequency with age (31,36) and have a restricted TCR repertoire (26,30,37).

Infection with CMV, one of the most prevalent latent viruses in human beings, is associated with expansion of the KIR$^+$CD8$^+$ T-cell population. Chan et al. (12) demonstrated that CMV-seropositive individuals have higher frequencies of KIR$^+$CD56$^+$ T cells compared to CMV-seronegative individuals. Moreover, CMV reactivation is associated with expansion of the KIR$^+$CD56$^+$ T-cell population in bone marrow transplant recipients. It was hypothesized that the KIR$^+$ T cells in CMV-seropositive individuals are specific to CMV Ags. However, Björkström et al. (30) demonstrated that KIR expression is much lower (or virtually absent) on CMV pp65-specific CD45RA$^+$CD57$^+$CD8$^+$ T cells compared to on the non-specific population. On the other hand, a recent report described KIR expression on the vast majority of HLA-E-restricted CMV UL40-specific CD8$^+$ T cells (38).

Besides in CMV infection, the KIR$^+$CD8$^+$ T-cell population expands in patients with HIV infection (39) and psoriasis (40). Additionally, the MHC allele-dependent expansion of KIR$^+$CD8$^+$ T-cell populations has been reported in cancer patients (41,42). It remains unknown whether Ag recognition by TCR is required for expansion of the KIR$^+$CD8$^+$ T-cell population in patients with inflammation or infection.

Recent studies have reported that KIR$^+$CD8$^+$ T cells function in regulating immune responses (**Fig. 2**). In 2021, Pieren et al. (31) reported that KIR$^+$CD45RA$^+$CD8$^+$ T cells are regulatory CD8$^+$ T cells, as was previously described in mice (43). Similar to CD4$^+$ Tregs, KIR$^+$CD45RA$^+$CD8$^+$ T cells exhibit high expressions of Helios and TIGIT. These cells also show upregulation of CD122, which is associated with CD8$^+$ Tregs in mice. Pieren et al. (31) also demonstrated that KIR$^+$CD45RA$^+$CD8$^+$ T cells can dose-dependently regulate the proliferation of KIR$^-$ NKG2A$^-$ conventional CD8$^+$ T cells. More recently, Li et al. (37) also reported that KIR$^+$CD8$^+$ cells act as CD8$^+$ Tregs. They found increased frequencies of KIR$^+$CD8$^+$ T cells in patients with autoimmune diseases and infections, such as celiac disease and coronavirus disease 2019 (COVID-19). When gliadin-specific CD4$^+$ T cells from patients with celiac disease were stimulated with Ag, KIR$^+$CD8$^+$ T cells suppressed pathogenic CD4$^+$ T-cell responses by killing pathogenic cells, without harming non-pathogenic CD4$^+$ T cells. RNA sequencing of KIR$^+$CD8$^+$ T cells further revealed that human KIR$^+$CD8$^+$ T cells are the analogous population of mouse Ly49$^+$CD8$^+$ T cells (CD8$^+$ Tregs). Further studies are required to elucidate how the KIR$^+$CD8$^+$ T-cell population size is regulated, and how these cells recognize pathogenic T cells.

CD8$^+$ T CELLS EXPRESSING NKG2A

A member of the lectin family, NKG2A is an ITIM-bearing inhibitory receptor (44). NKG2A forms a heterodimer with CD94, and binds to HLA-E, which is expressed on most human tissues and complexed with peptides derived from the leader sequence of classical MHC-I

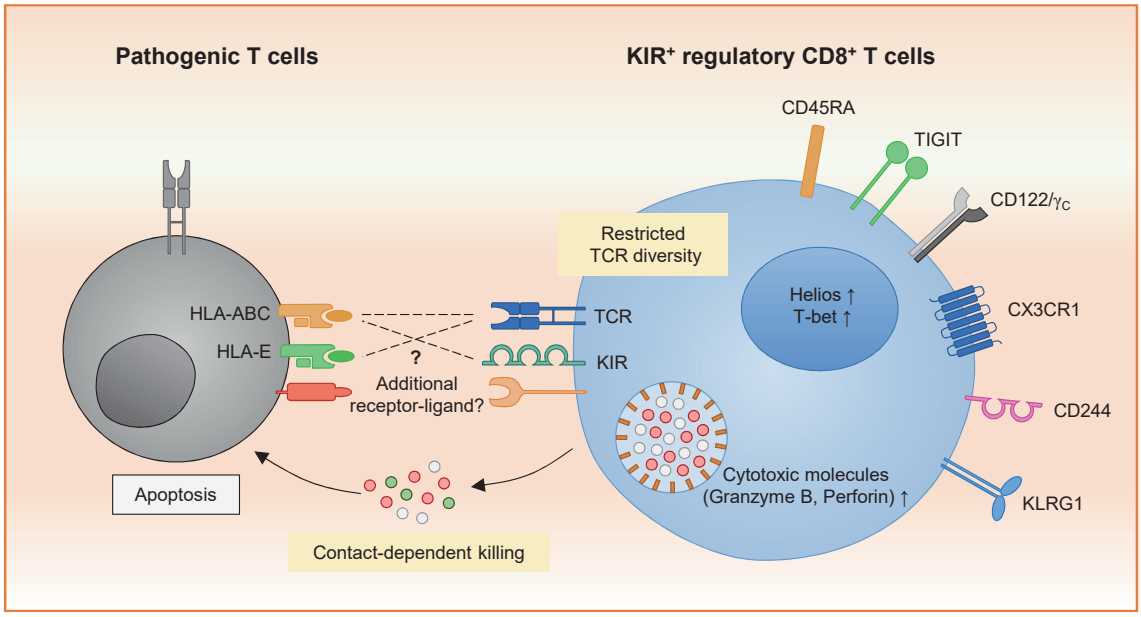

Figure 2. KIR$^+$CD8$^+$ T cells as a regulator of immune responses. KIR$^+$CD8$^+$ T cells have been reported to be human CD8$^+$ T_{REG} cells, which can regulate or kill pathogenic T cells. Similar to CD8$^+$ T_{REG} cells of mice, human KIR$^+$CD8$^+$ T cells exhibit high expressions of the transcription factor Helios and IL-15 receptor β chain (CD122). They contain high amounts of cytotoxic molecules (perforin and granzyme B), and show restricted TCR usage. The mechanisms of how KIR$^+$CD8$^+$ T cells originate, and how they recognize pathogenic T cells, remain unknown.

(45-47). NKG2A is typically expressed on NK cells, but can also be expressed on CD8$^+$ T cells (48-50). TCR stimulation induces NKG2A expression on CD8$^+$ T cells in a manner synergized with cytokines, such as IL-12, IL-15, and TGF (51-55). NKG2A engagement suppresses effector functions of CD8$^+$ T cells (49), as also observed in NK cells, and blockade of NKG2A or CD94 increases the cytotoxic activity of NKG2A-expressing CD8$^+$ T cells (53).

NKG2A has recently attracted attention as an immune checkpoint, similar to the well-known checkpoint receptors PD-1, TIGIT, and TIM-3 (56,57). An anti-NKG2A monoclonal Ab, called monalizumab, has been developed (58,59). Clinical trials investigating concomitant use of anti-PD-1/PD-L1 treatment and monalizumab have shown better clinical results in diverse cancers, including bladder cancer, non-small-cell lung cancer, and colorectal cancer (56,60,61). Chronic antigenic stimulation and persistent exposure to various cytokines in the tumor microenvironment reportedly induce NKG2A expression on tumor-infiltrating CD8$^+$ T cells (51). Monalizumab reinvigorates the cytotoxic function of NKG2A$^+$CD8$^+$ T cells by blocking the interaction of NKG2A with HLA-E expressed on cancer cells. It has also been found that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) specific CD8$^+$ T cells from patients with severe COVID-19 express high NKG2A levels, and exert reduced effector functions (62).

NKG2A and/or KIRs have been proposed as unique markers of human virtual memory T (T_{VM}) cells, which are T cells featuring memory phenotypes even in neonatal cord blood (63). Human T_{VM} cells express high levels of eomesodermin, CD62L, and CD122; exhibit a CCR7$^-$ CD45RA$^+$ T_{EMRA} phenotype; and show increased responsiveness to innate cytokines, such as IL-12, IL-15, and IL-18 (63,64). However, a recent study demonstrated that CD45RA$^+$CD8$^+$ T cells expressing NKG2A versus KIR are distinct subsets (31). Compared to KIR$^+$CD45RA$^+$CD8$^+$ T cells, NKG2A$^+$CD45RA$^+$CD8$^+$ T cells exhibit downregulated transcripts related to senescence, exhaustion, and regulatory functions. Moreover, the relative proportion of NKG2A$^+$CD45RA$^+$CD8$^+$ T cells declines with age.

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CD8⁺ T CELLS EXPRESSING NKG2C

NKG2C also forms a heterodimer with CD94. The NKG2C/CD94 heterodimer binds to HLA-E, similar to NKG2A but with lower affinity, and transduces signals through the immunoreceptor tyrosine activation motif (ITAM)-bearing adaptor molecule DAP12 (65,66). Like NKG2A, NKG2C is mainly expressed on NK cells, but can also be expressed on some subsets of CD8⁺ T cells (50,67). NKG2C⁺CD8⁺ T-cell populations have been reported to expand under several pathologic conditions, including CMV infection, Stevens-Johnson syndrome, toxic epidermal necrolysis, and celiac disease (68-70). Two studies have described NKG2C-mediated CD8⁺ T-cell activation. Co-stimulation with anti-CD94 and anti-CD3 Abs strengthens the lytic function of NKG2C-expressing CD8⁺ T cells (50). Even in the absence of TCR stimulation, NKG2C ligation itself can activate T cells to proliferate and kill HLA-E-transfected target cells that do not express the other MHC-I molecules (71). This finding reveals that NKG2C signaling could be a potential alternative to TCR-mediated activation of CD8⁺ T cells.

Recent studies have also examined and characterized NKG2C-expressing CD8⁺ T cells (**Fig. 3**). One study identified NKG2C as an important marker for potent antimicrobial T cells against *Mycobacterium leprae* (72). Compared with other CD8⁺ subsets, CD8⁺ T cells that express granulysin, perforin, and granzyme B exert superior effector functions against *M. leprae*-

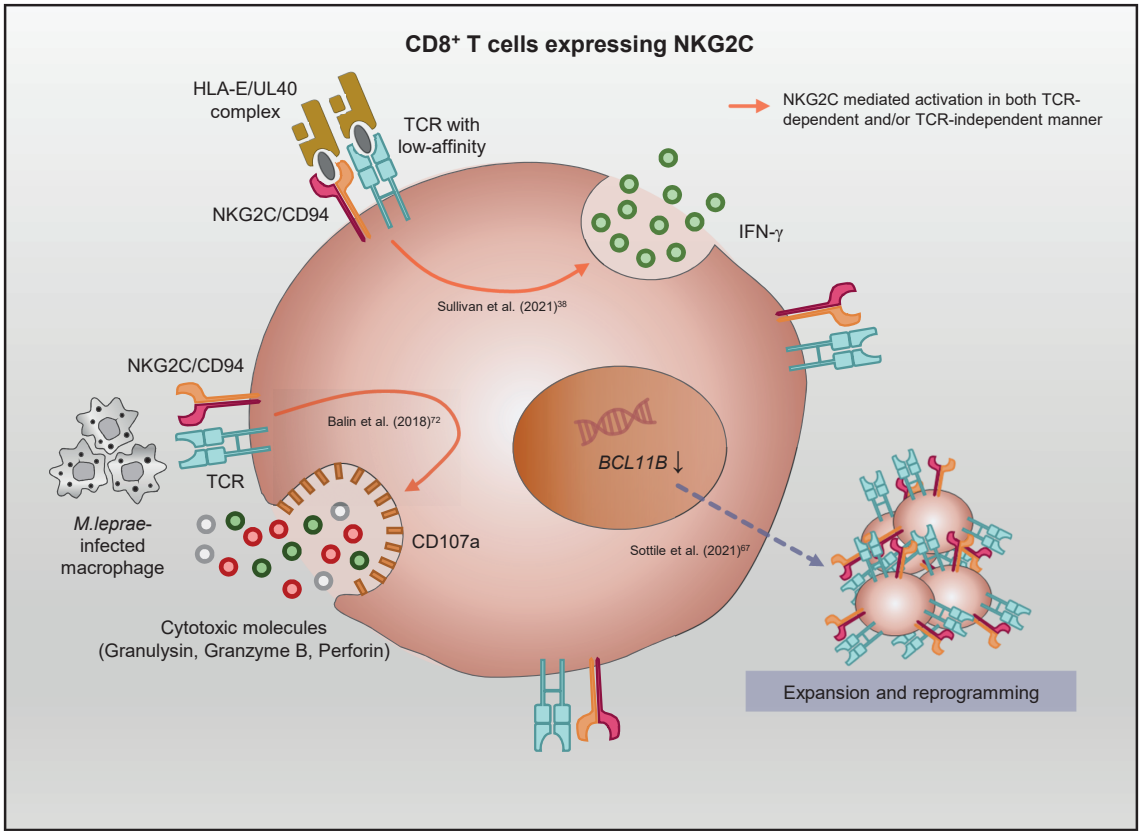

Figure 3. Characteristics of CD8⁺ T cells expressing NKG2C. Balin et al. (72) reported that NKG2C is an important marker for CD8⁺ T cells expressing granulysin, perforin, and granzyme B (tri-cytotoxic CD8⁺ T cells), and having greater antimicrobial activity against *Mycobacterium leprae*. NKG2C ligation activates tri-cytotoxic CD8⁺ T cells to release cytotoxic proteins. Sottile et al. (67) described downregulation of *BCL11B* in NKG2C⁺CD8⁺ T cells. The loss of *BCL11B* triggers NK-cell-like reprogramming and induces the generation of NKG2C⁺CD8⁺ T cells. Sullivan et al. (38) reported that HLA-E-restricted CD8⁺ T cells with a TRBV14 repertoire have a low affinity for HLA-E/UL 40 complexes, and express high levels of NKG2C. NKG2C ligation increases the production of IFN-γ and TNF-α from these CD8⁺ T cells, indicating that NKG2C can compensate for a weak TCR signal.

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infected macrophages, and these cells typically express NKG2C. Functionally, anti-CD94 Ab enhances the release of cytotoxic molecules from anti-CD3-stimulated NKG2C$^+$CD8$^+$ T cells.

HLA-E serves as a ligand of both CD94/NKG2C and CD94/NKG2A, complexed with peptides derived from the leader sequence of classical MHC-I (73). In CMV infection, CMV-encoded UL40, which mimics the leader sequence of classical MHC-I, enables CMV-infected cells to evade NK cell-mediated immune responses by engaging NKG2A (74). On the other hand, NKG2C on NK cells can recognize the HLA-E/UL40 complex, and NKG2C$^+$ NK cells exert cytotoxic functions against CMV-infected cells (75). Furthermore, these NKG2C$^+$ NK cells undergo clonal-like expansion against UL40, similar to the memory response of CD8$^+$ T cells. The NKG2C$^+$CD8$^+$ T-cell population also expands in CMV-infected patients (76). Sottile et al. revealed a mechanism for CD8$^+$ T-cell expansion and reprogramming in CMV-infected patients (67). Bulk RNA-sequencing analysis of the NKG2C$^+$CD8$^+$ T-cell population revealed downregulation of *BCL11B*. The loss of *BCL11B* triggers NK-cell-like reprogramming of T cells, and induces the generation of NKG2C$^+$CD8$^+$ T cells under HLA-E ligand stimulation. Additionally, TCR analysis reveals that most NKG2C$^+$CD8$^+$ T cells in CMV-seropositive individuals exhibit narrow TCR Vβ-chain usage, mainly TRBV-14, while NKG2C$^+$CD8$^+$ T cells in CMV-seronegative individuals are more polyclonal. This restricted TCR diversity in CMV-seropositive donors indicates that NKG2C$^+$CD8$^+$ T cells undergo clonal expansion.

HLA-E is recognized not only by NKG2A and NKG2C, but also by TCRs of CD8$^+$ T cells that are restricted by HLA-E. HLA-E-restricted CD8$^+$ T cells have been investigated in several diseases, including CMV, HIV, Epstein-Barr virus, *Mycobacterium tuberculosis*, and *Salmonella typhi* infection (74,77,78). Interestingly, HLA-E-restricted CD8$^+$ T cells reportedly exert regulatory properties in tuberculosis infection by inhibiting the proliferation of CD4$^+$ T cells, and patients with autoimmune type I diabetes exhibit a decreased frequency of HLA-E-restricted CD8$^+$ T cells (79,80). Sullivan et al. (38) examined whether NKG2C played a role in the activation of HLA-E-restricted CD8$^+$ T cells in CMV infection, and demonstrated that NKG2C on HLA-E-restricted CD8$^+$ T cells could co-stimulate CD8$^+$ T cells by compensating for the relatively weak signal intensity of TCRs.

CONCLUSION

In the late 1990s, researchers reported CD56$^+$ T cells (termed "natural T cells") and demonstrated that this T-cell subpopulation exhibits distinct immunologic features, in terms of the expressions of many NK receptors and innate-like features, compared to their CD56$^-$ T-cell counterparts. Since those initial descriptions, there have been sporadic reports of CD8$^+$ T-cell populations expressing various NK receptors (**Table 1**). Some act as co-stimulatory or inhibitory molecules, while others stimulate CD8$^+$ T cells to exert effector functions in a TCR-independent manner. Recent breakthrough technical developments in multi-omics analysis have enabled us to explore the heterogenous subpopulations of CD8$^+$ T cells expressing NK receptors, and to reveal the unique immunologic characteristics of these populations (16,37). The CD8$^+$ T-cell populations expressing NK receptors execute unique functional roles—for example, regulatory roles—distinct from the conventional CD8$^+$ T-cell population. However, studies have not yet fully clarified the heterogeneity of CD8$^+$ T-cell populations expressing NK receptors. Further studies are needed to delineate the heterogeneity of CD8$^+$ T-cell populations expressing NK receptors, and to elucidate their molecular characteristics and roles in physiologic and pathologic conditions.

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Table 1. Featured characteristics of human $CD8^+$ T cells expressing NK-associated surface proteins

	Immunophenotype	Immunologic features	Clinical significance	Ref.
$CD56^+CD8^+$	T_{EM} ($CCR7^-CD45RA^-$) and T_{RM}-like ($CD69^+$) in liver sinusoid (16)	· High expression of various NK-related molecules, e.g., CD16, CD94/NKG2, NKG2D, CD122, and DNAM-1 (11,12) · Expands with IL-2 stimulation synergized with IL-12 stimulation (13) · Potent capacity for Th1 cytokine production (10) · TCR-independent cytotoxicity upon stimulation with mitogen and IL-2 (13) · Restricted TCR diversity (16)	· Exert anti-viral effects, such as in chronic hepatitis C infection (9) · Expanded in CMV and chronic hepatitis B infection (15,16)	(9-16)
KIR^+CD8^+	T_{EMRA} ($CCR7^-CD45RA^+$) Replicative-senescent T cells ($CD28^-CD57^+$) (30)	· KIR-dependent inhibition of TCR signaling (22) · Intrinsic functional impairment against TCR stimulation (29-31) · High expression of cytotoxic molecules, e.g., perforin and granzyme B (29,35) · Exert regulatory functions against pathogenic $CD4^+$ T cells (37) · Restricted TCR diversity (26,30,37)	· Increased frequency with aging (31,36) · Expanded in CMV and HIV infection and psoriasis (12,39,40)	(12,22,26,29-31,35-37,40)
$NKG2A^+CD8^+$	Similar to effector memory T cells ($CD45RA^-CD45RO^+CD28^+CD27^+CCR7^-CD57^-$ $IL7R^+$) (67)	· NKG2A-dependent negative regulation of effector function (49) · Expanded with TCR stimulation synergized with cytokines (51,52)	· NKG2A is targeted by immune check point inhibitor (monalizumab) (51,58,59) · Expanded in severe COVID-19 infection (62)	(49,51,52,58,59,62,67)
$NKG2C^+CD8^+$	Similar to T_{EMRA} cells ($CD45RA^+$ $CD45RO^-CD28^-$ $CD27^-CCR7^-CD57^+IL7R^{low/-}$) (67)	· Exert TCR-independent effector function (71) · High expression of cytotoxic molecules, e.g., granulysin, perforin, and granzyme B (72) · NKG2C on HLA-E restricted $CD8^+$ T cells compensates for the relatively weak TCR signal intensity (38) · Restricted TCR diversity in CMV-seropositive donors (67)	· Expanded in several diseases, e.g., CMV, leprosy, Stevens-Johnson syndrome, toxic epidermal necrolysis, and celiac disease (67-70,72)	(38,67-72)

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