Implications of NKG2A in immunity and immune-mediated diseases

Xiaotong Wang¹,², Huabao Xiong¹,²* and Zhaochen Ning¹,²*

¹Institute of Immunology and Molecular Medicine, Jining Medical University, Jining, China,
²Jining Key Laboratory of Immunology, Jining Medical University, Jining, China

In recent studies, NKG2A is revealed to be a key immune checkpoint for both natural killer (NK) cells and CD8⁺ T cells. It form heterodimer receptors with CD94, and targets the peptide-presenting human leukocyte antigen-E (HLA-E) molecules. Upon crosslinking, NKG2A/CD94 delivers inhibitory signals for NK cells and CD8⁺ T cells, while blocking NKG2A can effectively unleash functions of these cytotoxic lymphocytes. The interaction between NKG2A and HLA-E contributes to tumor immune escape, and NKG2A-mediated mechanisms are currently being exploited to develop potential antitumor therapeutic strategies. In addition, growing evidence shows that NKG2A also plays important roles in other immune-related diseases including viral infections, autoimmune diseases, inflammatory diseases, parasite infections and transplant rejection. Therefore, the current work focuses on describing the effect of NKG2A on immune regulation and exploring its potential role in immune-mediated disorders.

KEYWORDS
NKG2A, cancer immunotherapy, viral infections, autoimmune diseases, HLA-E

Introduction

NKG2A is a member of C-type lectin superfamily (1, 2). Its gene is localized in the natural killer (NK) complex on chromosome 12 and consists of seven exons (3). NKG2A is a single-pass type II integral membrane glycoprotein that contains the cytoplasmic, transmembrane as well as extracellular lectin-like domains (4). The intracellular portion has two ITIMs, which are involved in inhibitory signal transduction (5). NKG2A expression can be detected in cytotoxic lymphocytes, including most NK cells and a subset of CD8⁺ T cells (6). It is found to be expressed as a heterodimer with CD94, which also belongs to the C-type lectin superfamily (7). The ligands of NKG2A/CD94 heterodimeric receptor are non-classical MHC class I molecules, human leukocyte antigen (HLA)-E in humans and Qa-1 in mice (8). HLA-E is lowly expressed on almost all cell surfaces and displays limited polymorphism (9). Peptides that presented by HLA-E are derived from the leader sequences of the classical MHC class I molecules such
as HLAA, HLAB and HLAC (10). Engagement of NKG2A/CD94 receptor with peptide-presenting HLA-E results in the phosphorylation of ITIMs in NKG2A. Phosphorylated ITIMs are responsible for recruiting and activating intracellular phosphatase SHP-1 as well as SHP-2, thus suppressing the activation signals generated by activating receptors such as T cell receptor (TCR) and NKG2D (11). In contrast to classical HLA molecules, which are commonly lost (12), the expression of HLA-E is generally elevated within tumor cells (13). Similar to other immune checkpoint molecules, NKG2A is exploited by tumor cells to achieve immune evasion. In addition, disrupting the interaction of NKG2A with its ligands is shown to be effective in enhancing antitumor immune responses (6, 14, 15). The overexpression of HLA-E is also observed in viral-infected cells, and the NKG2A-HLA-E axis is proved to exert a vital role in viral infection (16). Notably, NKG2A expression is found to be correlated with disease severity in coronavirus disease 2019 (COVID-19) patients (17–20). Apart from that, NKG2A is also involved in the pathological process of other immune-mediated disorders, such as autoimmune diseases, inflammatory diseases, parasite infections and transplant rejection. These findings indicate that NKG2A is a new therapeutic target for managing a variety of immune-mediated disorders. Herein, we review the existing knowledge about NKG2A mediated immune regulation and discuss the implications of NKG2A-targeted immunotherapeutic strategies.

Effects of NKG2A in immunocytes

**NKG2A and NK cells**

Approximately half of the human peripheral blood NK cells display NKG2A expression (21–23). Its expression is mostly observed in CD56bright immature NK cells and is decreased with stepwise maturation of the NK cells (24). There exits a negative correlation between the expression of NKG2A and killer cell immunoglobulinlike receptors (KIRs), which is implicated in the differentiation process of NK cells (25, 26). Multiple cytokines including interleukin (IL)-21, IL-15, IL-12, IL-10 and transforming growth factor-β (TGF-β) are able to induce the expression of NKG2A in NK cells (27–30). Upon ligands binding, NKG2A/CD94 receptors deliver signals that suppress NK cell functions, while disrupting the interaction of NKG2A/CD94 with Qa-1 or HLA-E activates the cytotoxic activity of NK cells (31–33).

The inhibitory NK receptors for HLA act a pivotal part in the education of NK cells, thereby greatly affecting mature NK cell responsiveness (34). At least one inhibitory NK receptors specific for “self” HLA-I haplotype need to be expressed on mature NK cells for recognizing target cells as well as preventing the activation of NK cells against autologous cells (35). The lack of inhibitory NK receptors for HLA renders NK cells hyporesponsive (36), while educated NK cells that expressing these receptors show higher responsiveness (37). Several studies have shown that NKG2A is required for the education of NK cells (38–40). NKG2A-educated human NK cells were more effective at killing target cells and showed a more dynamic migration behavior (41). NKG2A-educated mouse uterine NK cells were found to be more functionally competent in response to NK1.1 crosslinking (42). Highton et al. reported that NKG2A-educated human NK cells displayed improved responsiveness and metabolic resilience compared to KIRs-educated counterparts (43).

NK cells must maintain an appropriate level of NKG2A expression on the cell surface so as not to destroy normal autologous cells (44). NKG2A can be reused through a relatively rapid recycling process, enabling continuous availability of NKG2A on the cell surface. This recycling process requires energy and the cytoskeleton, but does not require functional ITIMs (44). The interaction of NKG2A/CD94 receptor with its ligands does not affect this recycling process and the expression of NKG2A/CD94 within NK cells (25). According to the fluorescent recovery after photobleaching (FRAP) analysis, most NKG2A/CD94 molecules on the plasma membrane exist in a free-moving form. NKG2A/CD94 is enriched at the contact site after crosslinking, and this enrichment is achieved through lateral diffusion in plasma membrane rather than synthesis of new proteins (45).

**NKG2A and T cells**

NKG2A is also expressed in T cells, especially CD8+ T cells. NKG2A expression in CD8+ T cells is found to be highly regulated, differing from its expression pattern in NK cells. NKG2A is barely expressed in CD8+ T cells of healthy individuals, but upregulated in tumor lesions and during chronic viral infection (46, 47). The expression of NKG2A in CD8+ T cells can be modulated a number of cytokines such as IL-23, IL-21, IL-15, IL-10, IL-6, IL-4, IL-2 and TGF-β (48–51). In addition, NKG2A expression can be induced by TCR engagement, and is acquired after antigen encounter. Cytotoxic T lymphocyte (CTL) clones sharing the same antigen specificity have the same NKG2A expression pattern, indicating that TCR antigenic specificity dictates the expression of NKG2A (52). NKG2A marks a special CD8+ T cells subset harboring tissue-resident and terminally exhausted features (6, 53–55). Similar to its function in NK cells, NKG2A/CD94 receptor engagement delivers inhibitory signals to CD8+ T cells, thus inhibiting the cytotoxic activity (55). Besides, NKG2A has also been found to be expressed in human CD4+ T cells. The expression of NKG2A/CD94 was observed in anti-CD3 monoclonal antibody (mAb) activated CD4+ T cells under TGF-β and IL-10 treatment. Moreover, NKG2A/CD94 was functional in CD4+ T cells and could inhibit TCR mediated...
tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) secretion (56).

The functions of NKG2A in immunopathological settings

**NKG2A and tumors**

Overexpression of HLA-E is observed in various types of tumors, including solid tumors as well as hematological malignancies (57–63). Meanwhile, HLA-E overexpression predicts a poor prognostic outcome in patients with ovarian, liver, gynecologic, glioblastoma, colorectal, breast, gastric, kidney, esophageal, pancreatic, lung, and head and neck cancer (64–72). HLA-E overexpression may be caused by the interaction of tumor cells with tumor microenvironment (TME), and there was evidence that IFN-γ produced by tumor-reactive immunocytes contributed to the upregulation of HLA-E within tumor cells (73, 74). However, the underlying mechanism is not completely clear so far. Since overexpressed HLA-E functions to inhibit the cytotoxicity of cytotoxic lymphocytes, the blockade of NKG2A-HLA-E axis may possibly enhance the cell-based immunotherapeutic efficacy. In addition, according to multiple studies, NKG2A is also overexpressed in tumor-infiltrating cytotoxic lymphocytes in many types of tumors (55, 66, 75). The increase in the number of NKG2A+ tumor infiltrating lymphocytes (TILs) is correlated with a poor prognosis in patients undergoing colorectal, ovary and liver cancer (65, 72). Moreover, there is a growing body of evidence that NKG2A-HLA-E axis contributes to tumor immune escape. Sheu BC et al. found human cervical cancer cells could upregulate NKG2A expression in CD8+ T cells through an IL-15-dependent mechanism, thus abrogating the antitumor cytotoxicity of TILs (76). The cytotoxic effects of human NK cells and CD8+ T cells on HLA-E expressing B-lymphoblastoid cells were enhanced through RNAi-mediated inhibition of NKG2A expression (77). Kamiya and colleagues knocked out NKG2A protein expression in human peripheral blood NK cells achieved by retroviral transduction of NKG2A blocker, thus generating NKG2A−/− NK cells. They further found NKG2A−/− NK cells showed higher cytotoxic activity against HLA-E expressing tumor cells in immunodeficient mice (31). According to the results of the in vitro experiment, blocking NKG2A in human NK cells by the humanized anti-NKG2A antibody monalizumab was sufficient for improving the dysfunction of NK cells in chronic lymphocytic leukemia (CLL) (78). Salomé et al. showed that NKG2A was highly expressed in type 1 innate lymphoid cells (ILC1s) of acute myeloid leukemia (AML) patients. Moreover, the cytotoxicity of NKG2A+ ILC1s was impaired when encountering HLA-E-expressing leukemic targets (79). Collectively, the above results indicate that it is worthwhile to develop NKG2A blockade strategies for immunotherapy in cancer patients. However, clinical and preclinical studies showed that blocking NKG2A alone did not appear to be effective for tumor therapy. Monalizumab monotherapy showed very little clinical activity in patients with gynecologic cancers (80). Consistently, data from pre-clinical research suggested that anti-NKG2A mAb alone showed no effect on subcutaneous tumor xenografts in mice (14, 55). Regardless of the above drawbacks, monalizumab is still useful in combination with other immunotherapies. As demonstrated by preliminary data in microsatellite stable colorectal cancer (CRC) patients who typically do not respond to programmed death-ligand 1 (PD-L1)/programmed cell death-1 (PD-1)-based therapy, the combination of monalizumab and durvalumab (an anti-PD-L1 mAb) showed clinical efficacy and safety (81). Andre’ et al. also showed that combined blockade of PD-L1/PD-1 and NKG2A enhanced anticancer immunity in mouse lymphoma tumor models (14). According to the phase II trials interim results, the objective response rate (ORR) in head and neck squamous cell carcinoma (HNSCC) patients receiving monalizumab and cetuximab (an anti-EGFR blocking mAb) combination therapy was 31%, which was superior to previous data obtained from cetuximab monotherapy. The action of the above combinational therapy is probably mediated via NKG2A+ NK cells, rather than NKG2A+ CD8+ T cells (14). Additionally, according to van Hall’s group study based on four mouse models of solid tumors, the antitumor activity of CD8+ T cells responding to peptide vaccination was restored through blocking NKG2A-Qa-1 axis using blocking antibodies or genetic knockout (55). In addition, there are a number of ongoing clinical trials with monalizumab for the treatment of tumors, as shown in Table 1.

**NKG2A and viral infections**

Altering MHC molecules expression on the infected cell surface is one of the mechanisms that mediate viral immune escape. HLA-E and Qa-1 usually show overexpression on the virus infected cell surfaces and are able to bind peptides derived from viral proteins. HLA-E overexpression was observed in hepatic antigen-presenting cells (APCs) of hepatitis C virus (HCV) infected patients. HLA-E could bind to the viral peptide HCV core aa35–44 and present it on the cell surface, where it interacted with NKG2A/CD94 heterodimers, thereby resulting in immunosuppression (82). HCV infection induced Qa-1 expression in mouse hepatocytes. Abrogation of either NKG2A or Qa-1 signaling was shown to enhance NK function and promote NK cell-dependent HCV clearance (33). Similar findings were obtained during human cytomegalovirus (HCMV) infection. Glycoprotein UL40 encoded by HCMV could bind to HLA-E and interact with NKG2A/CD94 receptors, thereby inhibiting human NK cell activity and leading to immune...
evasion (83–85). HLA-E expression was enhanced in lymphocytes of human immunodeficiency virus (HIV) infected patients, and viral peptide HIV p24 aa14-22-loaded HLA-E could inhibit NK cell cytotoxic activity by binding to NKG2A (86). However, according to van Stigt Thans et al., HIV-1 downregulated the expression of HLA-E on the surface of infected primary human CD4+ T cells (87). During human papillomavirus (HPV) infection, the decreased expression of classical HLA class I molecules and overexpression of HLA-E were observed. In addition, HLA-E overexpression was associated with the decreased cytotoxicity of NK cells, which was most likely achieved through the interaction with NKG2A/CD94 receptors (88). Interestingly, a recent study showed that not all peptides presented by HLA-E could bind to NKG2A and thus exert inhibitory effects. As discovered by Mbiribindi B and colleagues, human NKG2A⁺ NK cells was able to recognize and respond to Epstein-Barr virus (EBV) infected autologous B cells. Further studies showed that EBV latent cycle protein-derived peptides impaired the recognition of NKG2A, despite being presented by HLA-E, thereby leading to the absence of inhibition (89).

The expression of NKG2A in NK cells is also generally increased during viral infection. The dysfunction of NK cells and T cells was observed in chronic hepatitis B (CHB) patients, along with the overexpression of inhibitory receptors including PD-1 and NKG2A (90). Hepatitis B e-antigen (HBeAg) was able to induce IL-10 secretion within regulatory T cells (Tregs), thus upregulating NKG2A expression in NK cells of CHB patients (91). The overexpressed NKG2A severely impaired the cytotoxicity of NK cells during HBV infection, which could be restored through the blockade of NKG2A-HLA-E axis (90, 91). Among the EBV reactivation and EBV-chronic graft-versus-host disease (GvHD) patients after hematopoietic stem cell transplantation (HSCT), the frequency of NKG2A⁺CD56dim NK cells was significantly increased in peripheral blood (92). According to Hendricks et al., the coinfection of cytomegalovirus (CMV) and EBV led to NKG2A⁺CD56dim NK cell expansion (93). Interestingly, there was a study reveal an innovative viral immune evasion mechanism. According to Wang et al., rodent herpesvirus Peru could counteract mouse NK cell activation by encoding a Qa-1 like protein via RNA splicing (94).

### TABLE 1 Ongoing clinical trials with monalizumab for the treatment of tumors.

| Clinical trial | Phase | Drug | Disease | Participants | Status | First Posted |
|---------------|-------|------|---------|--------------|--------|--------------|
| NCT05414032  | II    | Monalizumab, Cetuximab | Locoregionally advanced HNSCC | 200 | Not yet recruiting | June 10, 2022 |
| NCT05221840  | III   | Monalizumab, Durvalumab, Oleclumab, Placebo | Non-small cell lung cancer (NSCLC) | 999 | Recruiting | February 3, 2022 |
| NCT05061550  | II    | Monalizumab, Durvalumab, Oleclumab, Placebo | NSCLC | 140 | Recruiting | September 29, 2021 |
| NCT04590963  | III   | Monalizumab, Cetuximab | HNSCC | 624 | Recruiting | October 19, 2020 |
| NCT04307329  | II    | Monalizumab, Trastuzumab | Breast cancer | 38 | Recruiting | March 13, 2020 |
| NCT03834440  | II    | Monalizumab, Durvalumab, Oleclumab, Ceralaserib, Docetaxel | NSCLC | 120 | Recruiting | February 7, 2019 |
| NCT03822351  | II    | Monalizumab, Durvalumab, Oleclumab | Stage III NSCLC | 188 | Active, not recruiting | January 30, 2019 |
| NCT03088059  | II    | Monalizumab, Afatinib, Palbociclib, Durvalumab, Niraparib, INCAGN01876 standard of care | Recurrent or metastatic HNSCC | 340 | Recruiting | March 23, 2017 |
| NCT02921685  | I     | Monalizumab, Cetuximab | Hematologic malignancies | 18 | Unknown | October 3, 2016 |
| NCT02643550  | I/II  | Monalizumab, Cetuximab, Anti-PD(L)1 | Recurrent or metastatic HNSCC | 143 | Active, not recruiting | December 31, 2015 |
In addition to NK cells, NKG2A also has an impact on CD8\(^+\) T cell-mediated antiviral immunity. During polyoma virus infection in mice, NKG2A expression was enhanced in antiviral CD8\(^+\) T cells, thereby leading to the decrease of antigen-specific cytotoxicity in the process of virus-mediated oncogenesis and viral clearance (95). During ectromelia virus infection, NKG2A functioned intrinsically within mouse virus-specific CD8\(^+\) T cells for limiting excessive activation (96). However, NKG2A does not appear to affect CD8\(^+\) T cell-mediated antiviral immunity in all types of viral infections. Miller et al. found NKG2A/CD94 heterodimers showed no inhibitory effect on CD8\(^+\) T cell activity during lymphocytic choriomeningitis virus (LCMV) infection in mice (97).

Significantly, recent studies have highlighted a key role of NKG2A in the infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The expression of NKG2A was enhanced in peripheral NK cells and CD8\(^+\) T cells of COVID-19 patients and was correlated with disease severity (17–20). Interestingly, the NKG2A\(^+\) cytotoxic lymphocytes proportion was reduced among recovered patients (17). Further research has shown that the NKG2A expression is found to be regulated by SARS-CoV-2 spike 1 protein (SP1). The results of in vitro experiments showed that coculture with SP1-transfected lung epithelial cells led to NKG2A overexpression and reduced degranulation in NK cells (98). In addition, NKG2A was also overexpressed in NK cells isolated from bronchoalveolar lavage fluid (BALF) of COVID-19 patients with acute respiratory distress syndrome (ARDS), and the expression level was even higher than that in blood cells (19). In general, the NKG2A-HLA-E axis can be exploited by viruses to limit the activity of cytotoxic lymphocytes, thereby contributing to viral immune escape (Table 2).

### NKG2A and autoimmune diseases

NK cells are able to eliminate autoreactive T cells, while NKG2A expressed within NK cells functions to prevent this process (99–101). Hence the blockade of NKG2A-ligand interaction is an efficient approach to treat autoimmune diseases. NKG2A/CD94 receptor has been found to exert a critical influence on experimental autoimmune encephalomyelitis (EAE) by modulating T cell activity. Typically, the interaction of NKG2A with its ligands was essential for immunologic memory development and clonal expansion of autoreactive T cells, as well as contributed to the protection of activated CD4\(^+\) T cells from lysis by NKG2A\(^+\) NK cell. The blockade of NKG2A-Qa-1 axis could effectively promote the elimination of autoreactive T cells mediated by NK cells, thereby alleviating EAE in mice (102, 103). Consistently, in comparison with CD4\(^+\) T cells obtained from Qa-1 wild type mice, NK cells showed higher cytotoxic activity against activated CD4\(^+\) T cells isolated from Qa-1 deficient mice (102). As observed from the rheumatoid arthritis (RA) mouse model, blocking NKG2A accelerated NK cell mediated elimination of pathogenic T helper 17 (Th17) cells as well as follicular helper T (Tfh) cells, thus arresting disease progression (104).

The expression profile of NKG2A within NK cells varies among different autoimmune diseases. Compared with NK cells from healthy individuals, NK cells from systemic lupus erythematosus (SLE) patients showed lower cytotoxicity with enhanced NKG2A expression (105, 106). On the contrary, a decrease in NKG2A expression was observed in NK cells of Graves’ disease (57) and new-onset psoriasis (107) patients. There were reports that the expression of NKG2A in T cells was decreased in SLE patients (108) and rheumatoid arthritis.

| TABLE 2 Roles of NKG2A-HLA-E axis in viral infections. |
|---------------------------------------------------------|
| **Condition**                                           | **Roles of NKG2A-HLA-E axis** |
| HCV (Core aa35-44)                                       | HCV infection induced-Qa-1 expression in mouse hepatocytes. Blocking NKG2A-Qa-1 axis was able to restore the function of NK cells and promote virus clearance (33). |
| HCMV                                                     | HCMV-encoded glycoprotein UL40 could bind to HLA-E and interact with NKG2A/CD94 receptors, thereby inhibiting NK cell activation (83–85). |
| HIV                                                      | HIV p24 aa14-22-loaded HLA-E impaired NK cell function by binding to NKG2A (86). |
| HPV                                                      | HLA-E overexpression was observed in cervical biopsies of women infected with HPV and was associated with the inhibition of NK cell cytotoxicity (88). |
| EBV                                                      | EBV latent cycle protein-derived peptides could bind to HLA-E, but impair the recognition of NKG2A expressed by NK cells, thereby leading to the absence of inhibition (89). In EBV reactivation and EBV-chronic GvHD patients after HSCT, the frequency of NKG2A\(^+\)CD56\(^{dim}\) NK cell population was increased in peripheral blood (92). |
| HBV                                                      | NKG2A overexpression was observed in NK cells of CHB patients and severely impaired the cytotoxicity of NK cells during HBV infection (90, 91). |
| Polyoma virus                                            | NKG2A overexpression impaired the cytotoxicity of antiviral CD8\(^+\) T cells in mice (95). |
| LCMV                                                     | NKG2A/CD94 heterodimers showed no inhibitory effect on CD8\(^+\) T cell activity in mice (97). |
| SARS-CoV-2                                               | NKG2A expression was increased in peripheral cytotoxic lymphocytes of COVID-19 patients and was correlated with the severity of disease (17–20). |
(RA) patients who flared (109), indicating that lack of inhibitory signals might lead to T cell hyperactivation and the immunological disorders. However, this conclusion is not applicable for CD8+ Tregs. CD8+ Tregs function to suppress self-reactive CD4+ T cells activity, thereby alleviating EAE. Upon Binding to Qa-1, NKG2A/CD94 receptor functioned to inhibit CD8+ Tregs activity. Disrupting the interaction of NKG2A/CD94 with Qa-1 unleashed CD8+ Tregs activity and abolished EAE progression in mice (110). Besides, the overexpressed NKG2A in CD8+ Tregs of patients with relapsing multiple sclerosis (MS) may function to limit CD8+ Tregs activity and contribute to disease progression (111).

NKG2A and other immune-related diseases

In addition to tumors, viral infections and autoimmune diseases, NKG2A is also involved in the pathological process of other immune-related diseases including inflammatory diseases, parasite infections and transplant rejection. NKG2A generally exerts immunosuppressive effects in inflammation. As reported by Hall and colleagues, NK cells inhibited the pro-inflammatory function of activated neutrophils through NKG2A-dependent mechanism in a DSS-induced colitis mouse model. Therefore, NKG2A played a protective role by inhibiting inflammation, while blocking NKG2A aggravated neutrophil-induced inflammation and tissue damage (112). In line with this, Zou and colleagues showed that the overexpressed NKG2A in NK cells exerted a vital function in suppressing neutrophil activation, thus alleviating DSS-induced colitis in mice (113). In celiac disease (CD) patients, CD-associated inflammation was marked by a decreased frequency of NKG2A+ natural killer T cells (NKT) and NKG2A+ NK cells, which might be involved in CD-associated tissue damage mediated by cytotoxic lymphocytes (114). Synovial NK cells from arthritis patients exhibited an activated phenotype and were capable of producing TNF-α and IFN-γ. Further, the secretion of these pro-inflammatory cytokines was increased under NKG2A blocking condition as well as proliferation in T cells, indicating that the reduction in NKG2A+ NK cells is most likely the cause, rather than the result, of GvHD. The above evidence highlights the importance of NKG2A+ NK cells in limiting GvHD by suppressing activated self-reactive T cells (124). In line with this, Kordelas et al. also found a reduction of NKG2A+ NK cells in the peripheral blood of GvHD patients after HSCT (125).

Perspectives

A large number of studies have highlighted the critical role of NKG2A in tumors as well as viral infections. It is worth noting that NKG2A is involved in the pathological process of COVID-19 (17–20). The antiviral activity of circulating NK cells and CD8+ T cells is markedly decreased during SARS-CoV-2 infection, which leads to severe impairment of the host immune function (126–128). In COVID-19 patients, NKG2A expression is found to be correlated with the severity of disease (17–20). Therefore, anti-NKG2A mAb monalizumab could represent a possible solution for treating COVID-19 patients. Immune checkpoint blockade is one of the most promising ways to activate antitumor immunity. Unlike other known checkpoint molecules such as cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and PD-1, NKG2A shows selective expression in cytotoxic lymphocytes including NK cells and CD8+ T cells. This suggests that the NKG2A-HLA-E axis does not appear to affect the initiation or regulation of anti-tumor immunity, but primarily functions in the final stages of tumor killing. Compared with HLA-E, NKG2A is more suitable as the blockade target of NKG2A-HLA-E axis. Apart from NKG2A, HLA-E also binds to NKG2C. NKG2C is...
expressed in both NK cells and T cells (129–132), and functions as an activating receptor by associating with the DNAX activation protein of 12 kDa (DAP12) signaling adapter (133) (Figure 1). NKG2C and NKG2A recognize mostly overlapping, but partially distinct epitopes on HLA-E (134). Although both NKG2A and NKG2C target HLA-E, the activating receptor shows a much lower affinity for its ligand. Compared with NKG2A, there are some amino acid differences in NKG2C protein, resulting in a 6-fold lower affinity for HLA-E (135, 136). Further, unlike HLA-E, which is expressed on almost all cell surfaces, NKG2A is mainly expressed in tumor lesions. Therefore, blocking NKG2A is more specific. Though NKG2A blockade shows limited effects as a stand-alone therapy, the NKG2A blocking antibody has synergistic effects with other tumor immunotherapies. A central paradigm in current tumor immunotherapy is “combination”, and NKG2A, a modulator of both adaptive and innate immunity, could be an important candidate.

**Author contributions**

XW and ZN are responsible for preparation of the published work. HX and ZN are responsible for supervision, review, editing and funding acquisition. All authors contributed to the article and approved the submitted version.

**Funding**

The present study was funded by the National Natural Science Foundation of China (No. 82003027), Doctoral Startup Fund of Jining Medical University (No. 2017YQD24) and Innovation training program for college students of Jining Medical University (No.cx2021065).

**Conflict of interest**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher’s Note**

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.
highly activated. J Immunol (2021) 207(4):1099–111. doi: 10.4049/jimmunol.2100446

11. Andre P, Brunet G, Guia S, Gallais H, Sampol J, Vivier E, et al. Differential regulation of killer Ig-like receptors and CD94 lectin-like dimers on NK and T lymphocytes from HIV-1-infected individuals. Eur J Immunol (1999) 29(4):1076–85. doi: 10.1002/(sici)1521-4141(199904)29:4<1076::aid-immunol>3.0.co;2-z

12. Mahapatra S, Mace EM, Minor GD, Forbes LR, Varghese-Hernandez A, Duryea TK, et al. High-resolution phenotyping identifies NK cell subsets that distinguish healthy children from adults. PLoS One (2017) 12(8):e0181134. doi: 10.1371/journal.pone.0181134

13. Manners AR, Uhrberg M. Age-related changes in natural killer cell repertoires: impact on NK cell function and immune surveillance. Cancer Immunol Immunother (2016) 65(4):417–26. doi: 10.1007/s00262-015-1750-0

14. Britaz V, Desours B, Parizot C, Debré P, Vieillard V. NK cell terminal differentiation: correlated stepwise decrease of NGK2A and acquisition of KIRs. PLoS One (2010) 5(8):e11966. doi: 10.1371/journal.pone.0011966

15. Faurier C, Andersson S, Bjerklund AT, Carlsten M, Møller B, Bjørkstøe NK, et al. Estimation of the size of the alloreactive NK cell repertoire: studies in individuals homozygous for the KIR haploype. J Immunol (2008) 181(9):6010–9. doi: 10.4049/jimmunol.181.9.6010

16. Bjerklund NK, Ruse P, Heuts F, Andersson S, Faurier C, Iverson MA, et al. Expression patterns of NGK2A, KIR, and CD57 define a process of CD56dim NK-cell differentiation uncoupled from NK-cell education. Blood (2010) 116(19):3853–64. doi: 10.1182/blood-2010-04-281675

17. Sun G, Zhao X, Li M, Zhang C, Jin H, Li C, et al. CD4 derived double negative T cells prevent the development and progression of nonsclerotic steatohepatitis. Nat Commun (2021) 12(1):650. doi: 10.1038/s41467-021-20941-x

18. Morgan DJ, Davis DM. Distinct effects of dexamethasone on human natural killer cell responses dependent on cytokines. Front Immunol (2017) 8:432. doi: 10.3389/fimmu.2017.00432

19. Brady J, Hayakawa Y, Smyth MJ, Nutt SL. IL-21 induces the functional maturation of murine NK cells. J Immunol (2004) 172(4):2048–58. doi: 10.4049/jimmunol.172.4.2048

20. Mingari MC, Vitale C, Cantoni C, Bellomo R, Ponte M, Schiaffetti F, et al. Interleukin-15 induced maturation of human natural killer cells from early thymic precursors: selective expression of CD94/NKG4A as the only HLA class I specific inhibitory receptor. Eur J Immunol (1997) 27(6):1374–80. doi: 10.1002/(sici)1521-4141(199706)27:6<1374::aid-immunol>3.0.co;2-z

21. Kamiya T, Seow SY, Wong D, Robinson M, Campana D. Blocking expression of inhibitory receptor NGK2A overcomes tumor resistance to NK cells. J Clin Invest (2019) 129(5):2094–106. doi: 10.1172/jci123955

22. Wang X, Cui Y, Luo Q, Wang Q, Hu J, He W, et al. Activated mouse CD4(+)-Fas(+) T cells facilitate melanoma metastasis via qa-1-dependent suppression of NK cell cytotoxicity. Cell Res (2021) 32(2):1696–706. doi: 10.1038/s41422-020-0328-5

23. Zhang C, Wang XM, Li SR, Twelkmeyer T, Wang WH, Zhang SY, et al. NGK2A is a NK cell exhaustion checkpoint for HCV persistence. Nat Commun (2019) 10(1):1507. doi: 10.1038/s41467-019-09212-y

24. Elliott JM, Yokoyama WH. Unifying concepts of MHC-dependent natural killer cell education. Trends Immunol (2011) 32(8):364–72. doi: 10.1016/j.it.2011.06.001

25. Zegh E, Calvi M, Marcenaro E, Mulero D, Di Vito C. Targeting NGK2A to elucidate natural killer cell ontogenesis and to develop novel immune-therapeutic strategies in cancer therapy. J Leukoc Biol (2019) 105(6):1243–51. doi: 10.1002/JLB.0719-500R

26. Anfossi N, Andre P, Guia S, Fall CS, Roetynck S, Stewart CA, et al. Human NK cell education by inhibitory receptors for MHC class I. Immunity (2006) 25(2):31–42. doi: 10.1016/j.immuni.2006.06.013

27. Kim S, Poursine-Laurent J, Truscott SM, Lybarger L, Song YJ, Yang L, et al. Licensing of natural killer cells by host major histocompatibility complex class I molecules. Nature (2005) 436(7051):709–13. doi: 10.1038/nature04387

28. Zhang X, Feng J, Chen S, Yang H, Dong Z. Synergized regulation of NK cell education by NGK2A and specific Ly49 family members. Nature Commun (2019) 10(1):5010. doi: 10.1038/s41467-019-13032-5

29. Lunemann S, Langenecker AE, Matruss G, Hess LU, Salzerberger W, Ziegler AE, et al. Human liver-derived CXC(6)+ cells are predominantly educated through NGK2A and show reduced cytokine production. J Leukoc Biol (2019) 105(6):1331–40. doi: 10.1002/JLB.M1118-428R

30. Anfossi N, Andre P, Guia S, Fall CS, Roetynck S, Stewart CA, et al. Human NK cell education by inhibitory receptors for MHC class I. Immunity (2006) 25(2):31–42. doi: 10.1016/j.immuni.2006.06.013
Cell proliferation and increased associated with increased target cell conjugation and probability of killing compared to cd56dimcd57(-) nk cells. J Immunol (2015) 195(7):3374–81. doi: 10.4049/jimmunol.1500171

Shreve N, Depierreux D, Hawkes D, Traherne JA, Sovic U, Huhn O, et al. The CD94/NKG2A inhibitory receptor educates uterine NK cells to optimize pregnancy outcomes in humans and mice. Immunity (2021) 54(6):1231–1244 e4. doi: 10.1016/j.immuni.2021.03.021

Highton AJ, Dierscik BP, Mock F, Martrus G, Sauter J, Schmidt AH, et al. High metabolic function and resilience of nkg2a+ nk cells. Front Immunol (2020) 11:559576. doi: 10.3389/fimmu.2020.559576

Borrego F, Kabat I, Sanni TB, Coligan JE. NK cell CD49D/NKG2A inhibitory receptors are internalized and recycle independently of inhibitory signaling processes. J Immunol (2002) 169(11):6102–11. doi: 10.4049/jimmunol.169.11.6102

Sanni TB, Malsamani M, Kabat J, Coligan JE. Borrego F. Exclusion of lipid rafts and decreased mobility of CD94/NKG2A receptors at the inhibitory NK cell synapse. Mol Biol Cell (2004) 15(7):3210–23. doi: 10.1091/mbc.e03-11-0779

Borst L, van der Burg SH, van Hall T. The NKG2A-HLA-A e-axis as a novel checkpoint in the tumor microenvironment. Clin Cancer Res (2020) 26(21):5549–55. doi: 10.1158/1078-0432.CCR-20-0875

van Hall T, Andre P, Horowitz A, Ruan DF, Borst L, Zerbib R, et al. Monalizumab inhibiting the novel immune checkpoint NKG2A. J Immunother Cancer (2019) 7(11):263. doi: 10.1186/s40425-019-0761-3

Cho HJ, Kim HO, Webster X, Palmarida H, Bahn K, Kim KS, et al. Calcineurin-dependent negative regulation of CD94/NKG2A expression on naive CD8+ T cells. Blood (2011) 118(11):1168–72. doi: 10.1182/blood-2010-11-317396

Kim HJ, Cantor H. Regulation of self-tolerance by qa-1-regulated CD8(+). Semin Immunol (2011) 23(6):446–52. doi: 10.1016/j.smim.2011.06.001

Bertone S, Schiavetti F, Bellomo R, Vitale C, Moretta L, et al. Transforming growth factor-beta-induced expression of CD94/NKG2A inhibitory receptors in human T lymphocytes. Eur J Immunol (1999) 29(1):23–9. doi: 10.1002/(sici)1521-4141(19990129)29:1<0.0001::aid-immun33.0.co;2-y

Derre L, Covaisse M, Pandolfino MC, Diez E, Jotereau F, Gervois N. Expression of CD94/NKG2A on human T lymphocytes is induced by IL-12: implications for adoptive immunotherapy. J Immunol (2002) 168(10):4864–70. doi: 10.4049/jimmunol.168.10.4864

Jabri B, Selby JM, Negulescu H, Lee L, Roberts AI, Beavis A, et al. TCR dependency of IL-12-induced expression of CD94 and NKG2 molecules on human CD4(+) T cells in response to CD3- to innate immunity. J Mol Med (Berl) (2015) 24(1):133–43. doi: 10.1007/s00109-014-1752-7

Romero P, Ortega C, Palma A, Molina IJ, Peña J, Santamarina N. High metabolic function and resilience of nkg2a+ nk cells. Front Immunol (2010) 131(4):855–63. doi: 10.3389/fimmu.2010.00269

Levy EM, Bianchini M, Von Eue EM, Barrio MM, Bravo AL, Furman D, et al. Human leukocyte antigen-e protein is overexpressed in primary human colorectal cancer. Int J Oncol (2008) 32(3):633–41. doi: 10.3892/ijool.2007.363

Kren L, Slaby O, Muckova K, Liczaraova E, Sova M, Vyhalov V, et al. Expression of immune-modulatory molecules HLA-G and HLA-E by tumor cells in glioblastomas: an unexpected prognostic significance? Neuropathology (2011) 31 (2):129–34. doi: 10.1111/j.1440-1789.2010.01149.x

Wolpert F, Roth P, Lamskus Z, Tabatabai G, Weller M, Eisele G. HLA-E contributes to an immune-inhibitory phenotype of glioblastoma stem-like cells. J Neuroimmunol (2012) 250(1–2):27–34. doi: 10.1016/j.jneuroim.2012.05.010

Gooden M, Lampen M, Jordanova ES, Neffs N, Triminos JB, van der Burg SH, et al. HLA-E expression by gynecological cancers restrains tumor-infiltrating CD8(+) T lymphocytes. Proc Natl Acad Sci U.S.A. (2011) 108(26):10656–61. doi: 10.1073/pnas.1103340108

Johansson D, Forslund E, Sohlberg E, Enqvist M, Olofsson PE, Malmberg KJ, Önfelt B. Impaired function of NK cells in patients with new onset of graves disease. J Autoimmun (2015) 51(3):140–6. doi: 10.1016/j.jaut.2014.09.001

Figueiredo C, Seltsam A, Blasczyk R. Permanent silencing of NKG2A (CD395) by lentiviral delivery impairs IFN-γ production and reduces NK cell cytotoxicity. J Clin Invest (2015) 125(3):1134–46. doi: 10.1172/jci83539

Ferns DM, Heeren AM, Samuels S, Bleeker MCG, de Gruijl TD, Kenter GG, et al. First-in-human dose escalation of monalizumab plus durvalumab, with expansion and cohort-expansion study of monalizumab (iph2201) in patients with advanced gynecologic malignancies: a trial of the canadian cancer trials group (cctg). Oncotarget (2020) 11(20):16052–60. doi: 10.18632/oncotarget.29378

Gustafson KS, Kand G. Interferon-gamma induction of the human leukocyte antigen-e gene is mediated through binding of a complex containing STAT1alpha to a distinct interferon-gamma-responsive element. J Biol Chem (1996) 271(33):20305–6. doi: 10.1074/jbc.271.33.20305

Li Q, Cai S, Li M, Zhou X, Wu G, Kang K, et al. Natural killer cell exhaustion in lung cancer. Int Immunopharmacol (2021) 96:107764. doi: 10.1016/j.intimp.2021.107764

Sheu BC, Chiu SH, Lin HH, Chow SN, Huang SC, Ho CN, et al. Up-regulation of inhibitory natural killer receptors CD94/NKG2A with suppressed intracellular perforin perform expression of tumor-infiltrating CD8(+) T lymphocytes in human cervical carcinoma. Cancer Res (2005) 65(7):2921–9. doi: 10.1158/0008-5472.can-04-2108

Figueredo C, Seltzam A, Blaszyk R. Permanent silencing of NKG2A expression for cell-based therapeutics. J Mol Med (Berl) (2009) 87(2):199–210. doi: 10.1007/s00109-008-0417-0

McWilliams EM, Mele JM, Cheney C, Timmerman EA, Fiazuddin F, Strattan EL, et al. Therapeutic CD94/NKG2A blockade improves natural killer cell dysfunction in chronic lymphocytic leukemia. Oncoimmunology (2016) 5(10):e102670. doi: 10.1080/21624089.2016.126270

Romero P, Ortega C, Palma A, Molina IJ, Peña J, Santamarina N. High metabolic function and resilience of nkg2a+ nk cells. Front Immunol (2010) 131(4):855–63. doi: 10.3389/fimmu.2010.00269

Sollone B, Gomez-Cadena A, Loyon R, Sulfitti M, Salvestrini V, Wys W, et al. CD56 as a marker of an ILC1-like population with NK cell properties that is impairing CD8(+). J Mol Med (2016) 94(1):133–9. doi: 10.1007/s00109-015-1312-6

Segal N, Naidoo I, Curigliano G, Patel S, Sahajbhim S, Papadopoulos K, et al. First-in-human dose escalation of monalizumab plus durvalumab, with expansion...
in patients with metastatic microsatellite-stable colorectal cancer. J Clin Oncol (2018) 36:3543–9. doi:10.1200/JCO.2018.36.15_suppl.3540

Nattermann J, Nischalke HD, Hofmeister V, Ahlenstiel G, Zimmerman H, Leifeld L, et al. The HA-A2 restricted T cell epitope HCV core 35-44 stabilizes HLA-e expression and inhibits cytolysis mediated by natural killer cells. Am J Pathol (2005) 166(2):449–53. doi:10.1016/s0002-9440(10)6238-5

Ulrich M, Martinou S, Greczuk M, Hengel H, Elbert W, Pfa M, et al. Cutting edge: the human cytomegalovirusUL16gene product contains a ligand for HLA-e and prevents NK cell-mediated lysis. J Immunol (2000) 164(10):5309–22. doi:10.4049/jimmunol.164.10.5309

Tomasec P, Braud VM, Rickards C, Powell MB, McSharry BP, Gadola S, et al. Surface expression of HLA-e, an inhibitor of natural killer cells, enhanced by human cytomegalovirusgpUL40. Science (2000) 287(5455):1031. doi:10.1126/science.287.5455.1031

Wang EC, McSharry B, Retiere C, Tomasec P, Williams S, Borysiewicz LK, et al. UL40-mediated NK evasion during productive infection with human cytomegalovirus. Proc Natl Acad Sci USA (2002) 99(11):7570–5. doi:10.1073/pnas.112060099

Nattermann J, Nischalke HD, Hofmeister V, Kupfer B, Ahlenstiel G, Feldmann G, et al. HIV-1 infection leads to increased HLA-e expression resulting in impaired function of natural killer cells. Antivir Ther (2005) 10(1):95–107. doi:10.1177/135965350501001017

van Stigt Thans T, Akko J, Niehrs A, Garcia-Beltran WF, Richert L, Sturzel CM, et al. Primary HIV-1 strains use nef to downmodulate HLA-e surface expression. J Viral (2019) 93(20):e00719-19. doi:10.1128/JVI.00719-19

Gonçalves MA, Le Disordec M, Simões RT, Rabureau M, Soares EG, Donadi EA, et al. Classical and non-classical HLA molecules and p16(INK4a) expression in precancerous lesions and invasive cervical cancer: Eur J Obstet Gynecol Reprod Biol (2008) 141(1):70–4. doi:10.1016/j.ejogrb.2008.06.010

Mribindilibon P, Pena JK, Arvedson MP, Moreno Romero C, McCarthy SR, Davis DM, et al. Classical and non-classical HLA molecules and p16(INK4a) expression in precancerous lesions and invasive cervical cancer: Eur J Obstet Gynecol Reprod Biol (2008) 141(1):70–4. doi:10.1016/j.ejogrb.2008.06.010

Jin X, Yan ZH, Lu L, Lu S, Zhang G, Lin W. Peripheral immune cell exhaustion and functional impairment in patients with chronic hepatitis B. Front Immunol (2020) 11:281–8. doi:10.3389/fimmu.2020.02705

Ma Q, Dong X, Liu S, Zhong T, Sun D, Zong L, et al. Hepatitis b antigen induces nkg2a(+)/nkg2e(+) natural killer cell dysfunction via regulatory T cell-mediated interleukin 10 in chronic b virus infection. Front Cell Dev Biol (2020) 8:421. doi:10.3389/fcell.2020.00421

Iwasiw SR, Bhakuni P, Bhagwati G, Aiyar HM, Chakrabarti A, Chakrabarti J, et al. Activating and inhibitory receptors on synovial inflammatory autoimmune diseases. J Immunol (2020) 195(1-2):121–34. doi:10.4049/jimmunol.1905105

Correa J, Villa A. Isolation and characterization of cd8(+) regulatory T cells in multiple sclerosis. J Neuroimmunol (2008) 195(1-2):121–34. doi:10.4049/jimmunol.1905105

Hall LJ, Murphy CT, Quinnan G, Hurley G, Shanahan F, Nally K, et al. Natural killer cells protect mice from dsd-induced colitis by regulating neutrophil function via the NKG2A receptor. Mucosal Immunol (2013) 6(6):1510–26. doi:10.1038/mi.2012.140

Zou Z, Zhao D, Yang J, Fan H. The ANXA1 released from intestinal epithelial cells in the hepatic cystic echinococcosis microenvironment. Infection (2017) 45(3):511–8. doi:10.1007/s10795-016-2584-9

Abulizi A, Xiao S, Bai Y, Tu L, Zong C, Zhang A, et al. Echinococcus multilocularis inoculation induces NK cell functional decrease through high expression of NKG2A in C57BL/6 mice. BMC Infect Dis (2019) 19:1. doi:10.1186/s12879-019-4417-1

Yasen A, Sun W, Aini A, Aji T, Shao Y, Wang H, et al. Single-cell rna sequencing reveals the heterogeneity of infiltrating immune cell profiles in the hepatic cystic echinococcosis microenvironment. Infect Immun (2021) 89(12):e029721. doi:10.1128/IAI.02972-21

Artsanis-Takonas K, Eleme K, McQueen KL, Cheng NW, Parham P, Davis DM, et al. Activation of a subset of human NK cells upon contact with the bacterial pathogen via NKG2A expression in human natural killer cells. Biochim Biophys Acta. (2017) 1867(1):213–20. doi:10.1016/j.bbamcr.2016.07.066

Marafini I, Monteleone I, Di Fusco D, Sedda S, Cuppi ML, Fina D, et al. Celiac disease-related inflammation is marked by reduced expression of nkp44/nkp46+-double positive natural killer cells. PloS One (2013) 8(11):e71822. doi:10.1371/journal.pone.0071822

Lu L, Kim HJ, Werneck MB, Cantor H. Regulation of CD8+ T cells: Interruption of the NKG2A-Qa-1 interaction allows robust suppressive activity and resolution of autoimmune disease. Proc Natl Acad Sci USA (2008) 105(19):7420–5. doi:10.1073/pnas.0709178105

Hervier B, Bezaiz V, Haroche J, Mathian A, Lebon P, Ghillani-Dalbin P, et al. Phenotype and function of natural killer cells in systemic lupus erythematosus: excess interferon-γ production in patients with active disease. Arthritis Rheum (2011) 63(6):1698–706. doi:10.1002/art.30313

Sen SW, Kim EO, Ryu ES, Kim TJ, Kim JN, Choi JE, et al. Upregulation of fas and downregulation of CD94/NKG2A inhibitory receptors on circulating natural killer cells in patients with new-onset psoriasis. Br J Dermatol (2009) 161(2):88–92. doi:10.1111/j.1365-2133.2009.09178.x

Wang L, Kang N, Zhou J, Guo Y, Zhang X, Cui L, et al. Downregulation of CD94/NKG2A inhibitory receptor on decreased B7 T cells in patients with systemic lupus erythematosus. Scand J Immunol (2012) 76(1):62–9. doi:10.1111/j.1365-3083.2012.07205.x

Kucuksezer UC, Aktas Cetin E, Leven K, Aldeniz N, Gelmez MY, et al. The role of natural killer cells in autoimmune diseases. Front Immunol (2021) 12:62306. doi:10.3389/fimmu.2021.622306

Lu L, Iliazova K, Hu D, Werneck MB, Wucherpfennig KW, Cantor H. Regulation of activated CD4+ T cells by NK cells via the qa-1/NKG2A inhibitory pathway. Immunity (2007) 26(5):593–604. doi:10.1016/j.immuni.2007.03.017

Leavenworth JW, Schallack C, Kim HJ, Li L, Spee P, Cantor H. Analysis of the cellular mechanism underlying inhibition of EAE after treatment with anti-NKG2A Fab(‘)2. Proc Natl Acad Sci USA (2010) 107(26):16–25. doi:10.1073/pnas.0914715107
natural killer cells. *PloS One* (2013) 8(2):e55432. doi: 10.1371/journal.pone.0055432

121. Khetsuphan T, Chaisri U, Dechkhajorn W, Benjathummarak S, Dekumyoy P, Ampawong S, et al. Effects of *Gnathostoma spinigerum* infective stage larva excretory-secretory products on NK cells in peripheral blood mononuclear cell culture: focused on expressions of IFN-gamma and killer cell lectin-like receptors. *Parasitol Res* (2020) 119(3):1011–21. doi: 10.1007/s00436-019-06093-3

122. Li L, Cha H, Yu X, Xie H, Wu C, Dong N, et al. The characteristics of NK cells in *Schistosoma japonicum*-infected mouse spleens. *Parasitol Res* (2015) 114(12):4371–9. doi: 10.1007/s00436-015-4674-4

123. Cha H, Qin W, Yang Q, Xie H, Wang M, et al. Differential pulmonic NK and NKT cell responses in *Schistosoma japonicum*-infected mice. *Parasitol Res* (2017) 116(2):599–67. doi: 10.1007/s00436-016-5320-y

124. Hu LJ, Zhao XY, Yu XX, Lv M, Han TT, Han W, et al. Quantity and quality reconstitution of nkg2a(+) natural killer cells are associated with graft-versus-host disease after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant* (2019) 25(1):1–11. doi: 10.1016/j.bbmt.2018.08.008

125. Kordelas L, Steckel NK, Horn PA, Beelen DW, Rebmann V. The activating nkg2c receptor is significantly reduced in NK cells after allogeneic stem cell transplantation. *Blood* (2016) 127(9):3624–31. doi: 10.1182/blood-2015-09-6828

126. Qin R, He L, Yang Z, Jia N, Chen R, Xie J, et al. Identification of parameters representative of immune dysfunction in patients with severe and fatal COVID-19 infection: a systematic review and meta-analysis. *Clin Rev Allergy Immunol* (2022) 1-33. doi: 10.1007/s12016-021-08908-8

127. Zhang S, Gan J, Chen BG, Zheng D, Zhang JG, Lin RH, et al. Dynamics of peripheral immune cells and their HLA-G and receptor expressions in a patient suffering from critical COVID-19 pneumonia to convalescence. *Clin Transl Immunol* (2020) 9(5):e1128. doi: 10.1002/clit.1128

128. Zidi I. Puzzling out the COVID-19: Therapy targeting HLA-G and HLA-e. *Hum Immunol* (2020) 81(12):697–701. doi: 10.1016/j.humimm.2020.10.001

129. Gümüş M, Angulo A, Vilches C, Gómez-Lozano N, Malats N, Lipers-Botet M. Immunoregulation of human cytomegalovirus infection on the NK cell receptor repertoire. *Blood* (2004) 104(12):3664–71. doi: 10.1182/blood-2004-05-2058

130. Gümüş M, Budi M, Sáez A, Beckalo T, Hengel H, Angulo A, et al. Expansion of CD94/NKG2C+ NK cells in response to human cytomegalovirus-infected fibroblasts. *Blood* (2006) 107(9):3624–31. doi: 10.1182/blood-2005-09-3682

131. Rölle A, Pollmann J, Ewen EM, Le VT, Hählenius A, Hengel H, et al. IL-12-producing monocytes and HLA-e control HCMV-driven NKG2C+ NK cell expansion. *J Clin Invest* (2014) 124(12):5305–16. doi: 10.1172/jci77440

132. Marshall NR, Vong AM, Devarajan P, Brauner MD, Kuang Y, Nayar R, et al. NKG2C/E marks the unique cytotoxic CD4 T cell subset, Tc2IL, generated by influenza infection. *J Immunol* (2017) 198(3):1142–55. doi: 10.4049/jimmunol.1601297

133. Lanier LL, Corliss B, Wu J, Phillips JH. Association of DAP12 with activating CD94/NKG2C NK cell receptors. *Immunity* (1998) 8(6):693–701. doi: 10.1016/s1074-7613(00)80574-9

134. Wada H, Matsumoto N, Maenaka K, Suzuki K, Yamamoto K. The inhibitory NK cell receptor CD94/NKG2A and the activating receptor CD94/NKG2C bind the top of HLA-e through mostly shared but partly distinct sets of HLA-e residues. *Eur J Immunol* (2004) 34(1):81–90. doi: 10.1002/eji.200344332

135. Kaiser BK, Barahmand-Pour F, Paulsen W, Medley S, Geraghty DE, Strong RK. Interactions between NKG2x immunoreceptors and HLA-e ligands display overlapping affinities and thermodynamics. *J Immunol* (2005) 174(5):2878–84. doi: 10.4049/jimmunol.174.5.2878

136. Kaiser BK, Pizarro JC, Kern J, Strong RK. Structural basis for NKG2A/NKG2D interactions. *Proc Natl Acad Sci USA* (2008) 105(18):6696–701. doi: 10.1073/pnas.0802736105