NKG2D and DNAM-1 activating receptors and their ligands in NK–T cell interactions: role in the NK cell-mediated negative regulation of T cell responses

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The negative regulation of adaptive immunity is relevant to maintain lymphocyte homeostasis. Several studies on natural killer (NK) cells have shown a previously unappreciated immunomodulatory role, as they can negatively regulate T cell-mediated immune responses by direct killing and by secretion of inhibitory cytokines. The molecular mechanisms of T cell suppression by NK cells, however, remained elusive. Only in the last few years it has become evident that, upon activation, human T cells express MICA-B, ULBP1–3, and PVR, ligands of the activating receptors NKG2D and DNAM-1, respectively. Their expression renders T cells targets of NK cell lysis, representing a new mechanism taking part to the negative regulation of T cell responses. Studies on the expression of NKG2D and DNAM-1 ligands on T cells have also contributed in understanding that the activation of ATM (ataxia-telangiectasia, mutated)/ATR (ATM/Rad3-related) kinases and the DNA damage response is a common pathway regulating the expression of activating ligands in different types of cells and under different conditions. The functional consequences of NKG2D and DNAM-1 ligand expression on activated T cells are discussed in the context of physiologic and pathologic processes such as infections, autoimmunity, and graft versus host disease.

Keywords: NKG2D ligands, DNAM-1 ligands, NK–T cell cross-talk, DNA damage response, cell proliferation

Natural killer (NK) cells contribute to the suppression of T cell responses and to the maintenance of T lymphocyte homeostasis through the release of inhibitory cytokines, such as TGF-β and IL-10, which can inhibit dendritic cell (DC) maturation or T cell activation and functions, and/or through the direct elimination of antigen-presenting cells and activated T cells (Andoniou et al., 2005; Schrama et al., 2006; Galazka et al., 2007; Qiao et al., 2008), monocytes and macrophages (Hamerman et al., 2004; Nowbakht et al., 2005; Nedvetzki et al., 2007; Kloss et al., 2008; Schulz et al., 2010), B cells (Nowbakht et al., 2005), and T cells. In general, NKG2DLs are not expressed by resting T lymphocytes, but their expression can be induced by different stimuli (Table 1). The first evidence of NKG2DL expression on T cells came from a study by Molinero et al. (2002) indicating that human T cells can express MICA in response to alloantigen and to CD3/CD28 cross-linking. Furthermore, also other NKG2DLs namely MICA, MICB, and ULBP1–3, but not ULBP4, are detected on both CD4+ and CD8+ T lymphocytes following stimulation with alloantigens, SEB superantigen, a specific antigenic peptide or upon PMA/ionomycin treatment (Corboni et al., 2007a, 2009). As a consequence, activated T cells become susceptible to autologous NK cell lysis, with an NKG2D/NKG2DL-dependent mechanism (Corboni et al., 2007a). Nielsen et al. (2012) further demonstrated that NKG2D, LFA-1, and NKp46 are involved in NK cell degranulation triggered by activated autologous CD4+ T cells, with both subsets of human NK cells (CD56dim and CD56bright) equally cytotoxic. Expression of NKG2DLs was described also on regulatory T cells (Treg) in response to Mycobacterium tuberculosis and NK-cell mediated lysis of Treg involves both NKG2D and NKp46 (Roy et al., 2008). Expression of NKG2DLs was also reported on activated marine T cells. H60 is up-regulated on T cells upon in vitro stimulation with ovalbumin and T cell blasts become susceptible...
Table 1 | Different stimuli implicated in the induction or up-regulation of NKG2D and DNAM-1 ligands on activated T cells.

| Stimulus | NKG2DLs | DNAM1Ls | T cell type | Reference |
|----------|----------|----------|-------------|-----------|
| Human anti-CD3 plus anti-CD28 | MICA/B, ULBP-1-3 | PVR | T cells | Molinero et al. (2002), Nielsen et al. (2012) |
| Superantigen, allosantigen, PMANonval Rivas et al. (2010), MICA/B, Maasho et al. (2005) | MICA/B, ULBP-1-3 | CD4+ T cells, CD8 T cells | Cerboni et al. (2007a), Cerboni et al. (2009) |
| Anti-CD3 plus IL-2 | MICA | CD8 T cells | Maaisho et al. (2005) |
| Superantigen, PVR, Nectin-2 | T cells | T cells | Ardolino et al. (2011) |
| PMA | PVR | CD4+ T cells | Cerboni et al. (2010) |
| History deacetylase inhibitors | MICA/B | Jurkat and activated T cells | Slow et al. (2005) |
| Propionic acid | MICA/B | Jurkat and activated T cells | Andersen et al. (2009) |
| M. tuberculosis | ULBR-1 | Treg | Roy et al. (2008) |
| HIV | MICA, ULBR-1, 2, 3 | Jurkat and activated CD4+ T cells | Cerboni et al. (2007a), Ward et al. (2007) |
| HIV | PVR | Activated CD4+ T cells | Matsuzaki et al. (2012) |
| Mouse mA antigen | H60, MULT1 | CD4+ T cells | Noval Rivas et al. (2010) |
| CeaA, PMA/Nonval Rivas, ovalbumin | H60 | T cells | Rabinovich et al. (2003) |

The table above lists various stimuli that have been shown to induce or up-regulate NKG2D and DNAM-1 ligands on activated T cells. These include human anti-CD3 plus anti-CD28 antibodies, superantigens, allosantigens, and PMAN. Other stimuli include PMA and history deacetylase inhibitors. The table also indicates the specific T cell type and reference for each stimulus.

**DNAM-1 AND ITS LIGANDS**

DNAM-1 is an activating receptor belonging to the Ig superfamily and is constitutively expressed by most NK cells, T cells, macrophages, and DCs. DNAM-1 interacts with LFA-1, required for its functional activity on both NK and cytotoxic T cells. Ligands for DNAM-1 (DNAM1Ls) include Nectin-2/CD112 and PVR/CD155, which are broadly distributed on hematopoietic, epithelial, and endothelial cells as well as on several tumors. PVR expression on activated T cells is also observed upon phagosome/autophagosome (PAM) stimulation or engagement of CD3/CD28 molecules. DNAM-1/PVR axis is involved in the NK cell-mediated lysis of allogeneic activated T cells (Ardolino et al., 2011), while in an autologous setting, NKG2D emerges as the dominant receptor (Rabinovich et al., 2003; Cerboni et al., 2007a; Nielsen et al., 2012).

**ROLE OF THE DDR IN THE REGULATION OF NKG2D AND DNAM-1 LIGANDS ON ACTIVATED T LYMPHOCYTES**

NKG2D and DNAM-1 ligands are induced in fibroblasts by genotoxic stress and stalled DNA replication, conditions known to activate the DNA damage response (DDR) initiated by ATM (ataxia-telangiectasia, mutated) or ATR (ATM/Rad3-related) kinases. Studies have shown that genotoxic stress can activate the DDR and stress pathways, via the HIV-1-encoded molecule Vpr (Ward et al., 2007), which regulates MICA expression on activated T lymphocytes by binding a specific sequence in the long intron 1 of the MICA gene (Molinero et al., 2004). NKG2DLs were found also on HIV-infected CD4+ T cells and their expression requires the activation of the DDR and stress pathways, via the HIV-1-encoded molecule Vpr (Ward et al., 2009; Richard et al., 2010; Pham et al., 2011), a potent activator of ATR and of a cell cycle arrest in G2 (He et al., 1995; Jowett et al., 1995; Re et al., 1995; Rohal et al., 2003). Similarly, oxidative stress and DDR strongly contribute to induce PVR expression on activated T cells (Ardolino et al., 2011). Thus, activation of ATM/ATR kinases and DDR could be a common pathway regulating the expression of different ligands on activated T cells.
activating ligands on T lymphocytes. Of note, we also found that genotoxic stress triggered ATM/ATR-dependent up-regulation of both DNAM1Ls and NKG2DLs on multiple myeloma cells (Soriani et al., 2009).

Increasing evidences show the involvement of DDR in many physiological processes, such as mitosis (Orcchio et al., 2006), insulin response (Yang and Kastan, 2000), V(D)J recombination (Chen et al., 2000) or after lipopolysaccharide stimulation in macrophages (Eissmann et al., 2010). In addition, up-regulation of ATM protein levels was observed in BMMCs (peripheral blood mononuclear cells) in response to mitogenic stimuli (Fukao et al., 1999). Increased phosphorylation of either ATM or one of its substrates, the histone H2AX, was described on T cells upon CD3 triggering, PHA or SEB stimulation (Cerboni et al., 2007a; Tanaka et al., 2007; Ardolino et al., 2011). Remarkably, PVR and NKG2DLs expression was mainly observed on T cells that had gone through at least one mitosis (Cerboni et al., 2007a, 2009; Ardolino et al., 2011). This is only one of the numerous examples showing a correlation of either NKG2DL or PVR expression with cell proliferation. In murine bone marrow grafts, Rae-1 was detected on donor proliferating hematopoietic cells in the spleen of the transplant recipients rather than on the long-term hematopoietic stem cells (Ogasawara et al., 2005). The presence of MIC molecules on rheumatoid arthritis synoviocytes was strongly associated with the expression of the nuclear Ki-67 proliferation marker (Groh et al., 2003) and MIC gene promoter contains elements for cell proliferation-associated transcriptional activation (Venkataraman et al., 2007). A preferential expression of PVR on proliferating rat hepatocytes during liver regeneration and acute injury was previously described (Erickson et al., 2006). These authors also reported that PVR expression in epithelial cells was tightly regulated by changes in cell density. NK cells react more efficiently to concanavalin A-stimulated, proliferating MHC class I-deficient target cells than to non-activated cells in vitro and in vivo (Correa et al., 1994) and proliferating T cells become more susceptible to NK cell killing (Ardolino et al., 2011). In line with these results, Davis’s group reported that human NK cells bound to cells in mitosis more effectively than the same cells in other phases of the cell cycle (Nolte-’t Hoen et al., 2007). Thus, we envisage that the expression of PVR and NKG2DLs on proliferating T lymphocytes is a possible mechanism used by NK cells to restrict the expansion of activated/proliferating T cells (Figure 1).

**FIGURE 1** | NKG2D and DNAM-1 ligands are expressed on activated/proliferating T cells. Resting T cells do not express ligands of the activating receptors NKG2D and DNAM-1 and are resistant to NK cell-mediated killing. However, upon T cell activation triggered by different stimuli (listed in Table 1), as well as upon HIV-1 infection, MICA/B, ULBP1–3, and PVR become detectable on the cell surface, preferentially on T lymphocytes that were undergone at least one cell division. The signaling pathways regulating the expression of NKG2D and DNAM-1 ligands involve the activation of ATM/ATR and of their substrates (e.g., phosphorylation of the histone H2AX). The final outcome is the direct elimination of activated/proliferating T lymphocytes by NK cells.
IN VIVO RELEVANCE FOR NK–T CELL INTERACTION

VIRAL INFECTIONS

A plethora of studies analyzed the role of NKG2D/NKG2DL axis by looking at infected cells, which very often express one or more ligands. These studies have demonstrated that NKG2D plays an important role in anti-viral immunity, via a direct NK cell-mediated lysis of infected cells. This evidence is also underscored by the countermeasure taken by viruses to avoid NKG2D-mediated triggering (Lanier, 2008; Rossini et al., 2012). However, NK cell contribution to anti-viral immunity can be seen also from another point of view: NK cells might restrain anti-viral T cell responses, thus promoting the return to T cell homeostasis. In vivo depletion studies established that NK cells act to negatively regulate CD4+ and CD8+ T cell dependent IFN-γ production and proliferation during murine cytomegalovirus infection, and they can mediate a similar effect on CD4+ T cell responses during lymphocytic choriomeningitis virus (LCMV) infection in β2-microglobulin deficient mice (Su et al., 2001). Accordingly, a more recent study showed that perforin-deficient mice chronically infected with LCMV contain greater numbers of activated anti-viral T cells compared to control animals. The accumulation of activated CD8+ T cells resulted in mortality within 2–4 weeks, an event which is rarely seen following an i.p. injection with LCMV of normal mice (Matsuhashi et al., 1999). It was described also a three-way of NK–T cell interaction, where NK cells directly eliminate activated CD4+ T cells (via a perforin-dependent pathway), thereby affecting CD8+ T cell function with beneficial or detrimental effects depending on the viral dose. However, no role for NKG2D/NKG2DLs could be observed (Waggoner et al., 2011). In another study, NK cell depletion promoted LCMV-induced CD8+ T cell immunity with the involvement of both perforin and NKG2D (Ling et al., 2012). Altogether, these studies show that NK cells can be crucial in controlling viral infections not only by a direct elimination of infected cells, but also by altering the number and functions of virus-specific T cells. However, the role of NKG2D and other activating receptors awaits a better elucidation.

Considering HIV-1, a virus replicating (among other cell types) in CD4+ T lymphocytes, we face a situation where NK cell targeting of activated T cells via NKG2D means, at the same time, eliminating the infected cell. In fact, expression of several NKG2DLs was observed on HIV-1 infected CD4+ T cells, with increased susceptibility to NK lysis (Cerboni et al., 2007b; Ward et al., 2007; Fogli et al., 2008; Richard et al., 2010). However, HIV-1 has also evolved its own countermeasures as it can also down-regulate NKG2DLs via Nef and Vif proteins (Cerboni et al., 2007b; Norman et al., 2011). Thus, regulation of NKG2DL expression by Vpu, Nef and possibly other viral proteins might have different impacts on NK cell recognition of infected CD4+ T cells. The role of DNAM-1 and its ligands in the context of NK–T cell interactions during viral infections has been less investigated. Recently, PVR was detected on HIV-1 infected CD4+ T cells, and when the NKG2D pathway was inhibited, additional blocking of DNAM-1 strongly impaired the capacity of NK cells to kill HIV-1-infected cells, indicating the involvement of both receptors (Matusali et al., 2012). However, expression of PVR on CD4+ T cells might also be responsible for the down-regulation of DNAM-1 on CD8+ T cells observed in chronic HIV-1 infection (Cella et al., 2010).

AUTOIMMUNITY

The mechanisms by which NK cells modulate adaptive immune responses in the course of autoimmune diseases have been addressed by a large number of in vivo and in vitro studies. However, depending on the model system, NK cells might either promote or inhibit the generation and proliferation of autoreactive T cells (French and Yokomasa, 2004; Shi and Van Kaer, 2006; Flodström-Tullberg et al., 2009; Lunemann et al., 2009).

Thinking in terms of negative regulation of (autoreactive) T cell responses, NK cells might exert a direct effect on activated, autoantigen-specific T cells. In experimental autoimmune encephalomyelitis (EAE), in vivo depletion of NK cells exacerbated demyelination and the clinical features of EAE; in addition, in vitro studies have shown that direct NK–T cell contact inhibited T cell proliferation and cytokine production triggered by myelin-derived peptides (Zhang et al., 1997; Matsumoto et al., 1998; Smeltz et al., 1999; Xu et al., 2001). NK cells might thus ameliorate the course of EAE by limiting the expansion of myelin-reactive T cells in the periphery and in the absence of their suppressive action, central nervous system inflammation became more marked. However, these studies are in conflict with another report showing that NK cell depletion resulted in less severe clinical scores (Shi et al., 2000). In an in vivo model of colitis, NK cell-depleted animals developed accelerated disease, and it was suggested that NK cells inhibited effector CD4+ T cells in a perforin-dependent manner (Fort et al., 1998; Yamaji et al., 2012). Such a protective effect also occurred in Staphylococcus aureus- and collagen-induced arthritis (CIA; Nilsson et al., 1999; Leavenworth et al., 2011), as well as in NOD mice (Lee et al., 2004).

A number of studies have identified the cytolytic mechanism underlying NK cell-mediated killing of autoreactive T cells, and the NK cell-mediated immunoregulatory activity was shown to be perforin-dependent in animal models of colitis, EAE, and CIA (Fort et al., 1998; Lu et al., 2007; Leavenworth et al., 2011). Thus, the receptor/ligand interactions triggering a perforin-mediated cytotoxicity play a key role in controlling T cell responses, and NKG2D might be part of the picture, since it plays a major role in NK cell lysis of autologous activated T cells (Rabinovich et al., 2003; Cerboni et al., 2007a; Nielsen et al., 2012). Moreover, NK cells can lyse autologous DCs, that under certain circumstances – including EAE – express NKG2DLs (Imashiki et al., 2003a,b; Andoniou et al., 2005; Schrama et al., 2006; Galata et al., 2007; Qiao et al., 2008). These data, together with NKG2DL expression also on activated macrophages and monocytes, bone marrow cells and microglia (Lunemann et al., 2008), indicate that this receptor/ligand pair might play a more general immunoregulatory role besides killing autoreactive T cells, e.g., by eliminating macrophages and other antigen-presenting cells or their precursors under inflammatory conditions, as a feedback mechanism to silence uncontrolled antigen-specific immune responses.

The role of NKG2D/NKG2DLs in autoimmunity has been addressed also from another point of view. In fact, endogenous cells and/or tissues can aberrantly express NKG2DLs (as shown in...
particular for MICA and MICB in humans and Rae-1 in mice), promoting activation of autoreactive infiltrating NKG2D+ T cells, leading to tissue destruction. Examples of this condition can be found in human type 1 diabetes and in NOD mice, in patients with rheumatoid arthritis, Crohn’s disease, celiac disease, and in a mouse model of autoimmune vitiligo. These aspects are however reviewed elsewhere (Shi and Van Koot, 2006; Van Belle and van Herrath, 2009).

Regarding DNAM-1, despite the expression of PVR on activated T cells (Cella et al., 2010; Ardolino et al., 2011; Nielsen et al., 2012), its role was not evident in autologous NK–T combinations (Ardolino et al., 2011; Nielsen et al., 2012), while it was relevant in allogeneic settings (Ardolino et al., 2011), suggesting that DNAM-1 might not be involved in autoimmune reactions.

GRAFT VERSUS HOST DISEASE

Allogeneic bone marrow transplantation (BMT) was estimated to be an effective treatment for hematologic malignancies and some solid tumors. However, the high incidence of graft versus host disease (GVHD) mediated by the activation and proliferation of alloreactive T cells leads to severe host tissue damage. Previous studies demonstrated that donor NK cells are able to suppress the development of GVHD through the killing of host antigen-presenting cells which are essential for donor T cell activation (Buggeri et al., 2002). More recently, several in vivo studies in the mouse showed a direct effect of donor NK cells on GVHD-inducing T cells. Allogeneic T cells and NK cells trafficked similarly after BMT (Olson et al., 2009) and donor NK cells limited the expansion of syngeneic donor T cells through different mechanisms mediated by perforin and Fas-FasL interaction (Olson et al., 2010). Similarly, in a model of chronic GVHD, both donor NK cell killing and non-killing mechanisms downstream of TLR-4 stimulation on human-activated T lymphocytes and mDCs show a direct effect of donor NK cells (Ruggeri et al., 2002). More recently, several studies have reported the role of donor NK cells in the prevention of chronic GVHD, through the regulation of the activating receptor NKG2D and the immunoregulatory activity of NK cells was inhibited by injection of antibodies directed to NKG2D (Novak Rivas et al., 2010). In humans, a fraction of KIR2DS1+ NK cells can mediate strong alloreactivity against both mDCs and activated T lymphocytes and DNAM-1 and NKp30 were shown to be involved in this process, supporting an important role of NK cells in the prevention of GVHD (Sovori et al., 2011).

CONCLUSION

In summary, a central role for NK cell killing in mediating immunoregulatory effects is emerging. Studies of different conditions (infections, autoimmune, transplants) indicate that NK cytotoxicity of activated T cells, as well as of all cells of the immune system, is important in immune regulation. The involvement of NKG2D and DNAM-1 receptors may represent the “tip of the iceberg,” with significant effects on the negative regulation of adaptive T cell responses, resulting in increased viral burdens, viral persistence, and/or inflammation. The locations where these events take place, and which are the NK cell subsets involved are still rather obscure parts of the picture.

ACKNOWLEDGMENTS

The authors are supported by grants of the Italian Ministry of Health (Giovanni Ricerctor n. 0003577 to Alessandra Zingoni), the Italian Association for Cancer Research (AIRC), AIRC 5x1000, and the “Sapienza” University of Rome. Michele Ardolino is a recipient of a fellowship from Istituto Pasteur-Fondazione Cenci Bolognetti.

REFERENCES

Andolino, C. A., van Duinzenen, S. L., Vogt, V., Andersson, D. M., Berard, G., Ausina-Pattier, C., et al. (2009). Immunological dendritic cells and natural killer cells are integral to the activation of effective antiviral immunity. Nat. Immunol. 10, 1011–1019.

Andolina, C. E., Castiglione, A. D., and DiGiulio, M. A. (2008). Killers and beyond: NK-cell-mediated control of immune response. Eur. J. Immunol. 38, 2947–2954.

Andolina, L., Hansen, K. A., Jensen, H., Peterkin, S. F., Stroggaard, P., Hämmerling, G. J., et al. (2009). Non-cytotoxic acid secreted from probiotic bacteria induces NKG2D ligand expression on human T-lymphocyte subsets. J. Immunol. 183, 5775–5785.

Ardolino, M., Zingoni, A., Cerboni, C., Caccio, F., Sotiari, A., Amantea, M. L., et al. (2011). DNAM-1 ligand expression on Ag-stimulated T lymphocytes is mediated by β2 integrin-dependent activation of DNA-damage response; relevance for NK–T cell interaction. Blood 117, 4778–4786.

Bottino, C., Cattinoni, B., Pende, D., Rivera, P., Nanni, M., Carassiti, A., et al. (2003). Identification of PVR (CD155) and Nectin-2 (CD112) as ligands for the human DNAM-1 (CD226) activating molecule. J. Exp. Med. 198, 557–567.

Cella, M., Prat, R., Voron, V., Laven- dos, K., Turnbull, E., Ohlssonsoo- jambor, C., et al. (2010). Loss of DNAM-1 contributes to CD8+ T-cell exhaustion in chronic HIV-1 infection. Eur. J. Immunol. 40, 549–554.

Carbone, C., Zingoni, A., Cippittelli, M., Poscil, M., Frati, L., and Santoni, A. (2007). Antigen-presenting human T lymphocytes express cell-surface PVR (CD155) and Nectin-2 (CD112) at very high density. Eur. J. Immunol. 37, 2957–2964.

Carbone, C., Zingoni, A., Cippittelli, M., Poscil, M., Frati, L., and Santoni, A. (2007a). Antigen-activated human peripheral blood mononuclear cells express the ligands of the activating receptor NKG2D and inhibit natural killer cell-mediated cytotoxicity. J. Gen. Virol. 88, 242–250.

Carbone, C., Arduolo, M., Santoni, A., and Zingoni, A. (2009). Down- regulating CD94 T lymphocytes by down-regulation of the activating receptor NKG2D role of NKG2D ligands released by activated T cells. Blood 113, 2957–2964.

Chen, H. T., Bhakdi, A., Dilliparan- tio, M. J., Zhu, J., Brown, M. I., Dai, X., et al. (2008). Response to RAG-mediated V(D)J cleavage by NBS1 and γ-H2AX. Science 290, 1962–1965.

Corsa, L., Corel, L., and Raulet, D. H. (1994). Multiple natural killer cell-activating signals are inhibited by major histocompatibility complex class I expression in target cells. Eur. J. Immunol. 24, 1523–1531.

Eagl, R. A., and Teneinde, L. (2007). Pseudomonas and the single recepto- r: NKG2D. Nat. Rev. Immunol. 7, 737–744.

Eisermann, F., Erano, J. H., Mebiato, M., Roche, E. L., Nederstijt, S., and Darn, D. M. (2010). Multiple machineries downstream of TLR-4 stim- ulation allow expression of NKG2D ligands to facilitate macrophage/NK cell cross-talk. J. Immunol. 184, 6901–6908.

Ericksen, B. M., Thompson, N. L., and Hissin, D. C. (2006). Tightly regulated induction of the adhesion molecule n-cadherin during rat liver regeneration and acute liver injury. Hepatology 43, 325–334.

Friederlein-Tullberg, M., Bryson, Y. T., Shi, P. D., Hoogland, P., and Tum- gern, H. G. (2009). Natural killer cells in human autoimmunity. Curr. Opin. Immunol. 21, 636–640.

Fogli, M., Marzio, D., Brambilla, E., Vochten, M., Azu, A., Roby, G., et al. (2008). Loss of endogenously infected CD8+ T cells is the result of 2-activated autologous natural killer cells from HIV-infected seronegative individuals. PLoS Pathog. 4, 7. doi: 10.1371/journal.ppat.1000101.

Forti, M., Lead, M. W., and Remick, D. M. (1998). A role for NK cells as regulators of CD4+ T-cells in a trans- fer model of colitis. J. Immunol. 161, 3226–3231.

French, A. R., and Yokoyama, W. M. (2004). Natural killer cells and autoimmunity. Arthritis Res. Ther. 6, 8–14.
Jowett, J. B., Planelles, V., Poon, B., Jinushi, M., Takeda, T., Tatsumi, H., Hamerman, J. A., Ogasawara, K., and Groh, V., Bruhl, A., El-Gabalawy, H., Gasser, S., Orsulic, S., Brown, E. J., and Fukao, T., Kaneko, H., Birrell, G., Zingoni et al. NK cell negative regulation of T cell responses. Virol. 69, 6705–6711.

Fukui, T., Kaneko, H., Berrett, G., Taatia, H., Yoshida, T., Cross, S., et al. (2018). ATM is upregulated during the mitotic response in peripheral blood mononuclear cells. Blood 134, 1998–2006.

Galadari, G., Jouni, A., Olszewski, O., Steculof, M., Brocass, C. F., Barnett C. S., et al. (2007). EAE induction with Mycobacterium leprae complex depends on H90 and NKG2D activity. J. Immunol. 178, 4503–4512.

Gassiot, S., Orvedl, S., Beven, E. J., and Rauter, D. H. (2003). The DNA damage phosphorylation-related innate immune system ligands for the NKG2D receptor. Nat. Immunol. 4, 1106–1110.

Godzik, V., Brede, A., Elgabaly, H., Nilsson, J. L., and Spaar, T. (2015). Stimulation of T cell autoactivity by abnormal expression of NKG2D and its MHC ligands in rheumatoid arthritis. Proc. Natl Acad. Sci. U.S.A. 110, 8942–8947.

Hamerman, J. A., Ogawa, K., and Luan, L. L. (2004). Toll-like receptor signaling in macrophages induces ligands for the NKG2D receptor. J. Immunol. 172, 2507–2515.

He, L., Cho, S., Walker, B., Di Mattia, P., Morgan, D. O., and Landau, N. R. (2001). IL-15 is required for a type I IFN-mediated dendritic cell expression of chronic hepatitis C virus infection. J. Immunol. 170, 1249–1255.

Jimbo, M., Takehara, T., Tatsumi, T., Kato, T., Godzik, V., Spice, T., et al. (2005a). Critical role of MHC class I 1-liganded M and B expression on IFN-α-stimulated dendritic cells in the regulation of chronic hepatitis C virus infection. J. Immunol. 175, 532–538.

Kneba, K., Oropou-Anane, J., Matsunawa, A., Kohlmann, J. E., and Borgo, E. (2005). NKG2D is a costimulator for human non-chromatid T cells. J. Immunol. 174, 5783–5788.

Matsunawa, M., Sunohara, M., Glass, A., Galvan, M., Chou, K., Whitmire, J. K., et al. (1999). A role for perforin in degranulating T cell responses during autoimmunity. J. Exp. Med. 190, 2527–2536.

Matsui, Y., Kobayashi, T., Akaike, Y., Shin, T., Koyama, Y., Suzuki, Y., et al. (1998). Role of natural killer cells and T cell-mediated cytotoxic function in acute autoimmune encephalomyelitis. Eur. J. Immunol. 28, 1641–1646.

Matsuki, Y., Poter, M., Santoni, A., Colbin, C., and Doria, M. (2010). The human immunodeficiency virus type 1 Nef and Vpr proteins downregulate the natural killer cell-activating ligand PIR. J. Virol. 86, 4496–4504.

Molinet, L. L., Fauret, M. B., Rabino-vich, G. A., Faubonin, L., and Zwiers, N. W. (2002). Activation-induced expression of MIIR on T lymphocytes involves engagement of CD2 and CD28. J. Leukoc. Biol. 71, 791–797.

Molinet, L. L., Fauret, M. B., Girard, M. V., Faubonin, L., Rabnitzovich, G. A., Coste, M. A., et al. (2004). Nef-B regulates expression of the MHC class I-related chain A gene in activated T lymphocytes. J. Immunol. 175, 5585–5590.

Nobič, S., Sovocool, S., Espla, R. A., Harris, J., Vily, E., Pende, D., et al. (2007). Reciprocal regulation of human natural killer cells and macrophages associated with distinct immune responses. Blood 109, 3779–3785.

Nohno, S., Okum, N., Irie, B., Lanzé, L. L., and Sipe, P. (2012). Cytotoxicity of CD8/CD4 T cells towards autologous activated CD4+ T cells is mediated through NKG2D. J. Leukoc. Biol. 89, 259–268.

Olsson, J. A., Lessov-SỘ cooper, D. B., Baker, J., Bedrick, A., and Negri, R. S. (2010). Tissue-specific homing and expansion of donor NK cells in allogeneic bone marrow transplantation. J. Immunol. 185, 3239–3248.

Olsson, J. A., Lessov-Sompson, D. B., Bakken, J., Bedrick, A., and Negri, R. S. (2010). NK cells mediate reduction of GVHD by inhibiting activated, autoreactive T cells while retaining GVT effects. Blood 115, 4393–4391.

Oroszcz, E., Sadowski, C, Jociad, S., Soddu, S., and Cantad, E. (2006). ATM is activated by default in mitosis, localizes at centromeres and monitors mitotic spindle integrity. Curr. Biol. 16, 48–52.

Pende, D., Castriconi, R., Romagnani, P., Spaggiari, G., Marziano, S., Dehner, C., et al. (2006). Expression of the DNAM-1 ligands, Nectin-1 (CD110) and poliovirus receptor (CD155), on dendritic cells: relevance for natural killer-cell dendritic cell interaction. Blood 107, 2038–2046.

Pham, T. N., Gerard, F. C., Poen, C., and Cohen, E. A. (2011). Modulation of NKG2D-mediated cytotoxic functions of natural killer cells by viral protein B from HIV-1 primary isolates. J. Virol. 85, 12256–12261.

Peggy, A., Poens, C., Masur, A., Murgui, S., Umans, S., Perez, H., et al. (2012). Interaction between human NK cells and bone marrow stromal cells induces NK cell triggering: role of NKG2D and NKG2D receptors. J. Immunol. 188, 6352–6360.

Qiao, Y., Liu, B., and Li, Z. (2008). Activation of NK cell by extracellular heat shock protein 70 through induction of NKG2D ligands on dendritic cells. Cancer Immunol. Immunother. 57, 259–266.

Rabinovich, G. A., Li, J., Shannon, J., Huran, C., Lopez-Ibor, J., and Cordon, D., et al. (2002). Activated but not resting T cells can be recognized and killed by syngeneic NK cells. J. Immunol. 169, 3572–3576.

Rao, F., Brunner, D., Frank, R. M., and Jakob, J. (1995). Human immunodeficiency virus type 1 Vpr arrests the cell cycle in G2 by inhibiting the activation of p38 and cyclin B1. J. Virol. 69, 8679–8684.

Richard, J. B., Snell, K., Pham, T. N., Boland, J. C., and Cohen, E. A. (2010). HIV-1 Nef up-regulates expression of the activating NKG2D receptor and promotes NKG2D-mediated killing. Blood 115, 3579–3583.

Roshal, M. K., Zhu, T., Bhn, P., and Plumbley, V. (2005). Activation of
of the ATR-mediated DNA damage response by the HIV-1 viral protein R. J. Biol. Chem. 276, 29479–29486.

Romani, G., Cerbone, C., Santoni, A., Landini, M., F. Landoni, S., Gatti, D., et al. (2012). Interplay between human cytomegalovirus and intrin-
sic/intracellular host responses: a complex bidirectional relationship. Mol. Immunol. 52, 1–6.

Roy, S., Barua, P. F, Garg, A., Wu, S., Cooman, D., and Varki-Arapany, R. (2008). NK cell‐ induced T cell regulatory cells that expand in response to an intra-
cellular pathway. J. Immunol. 180, 1729–1736.

Bargi, S., Capuani, M., Uribani, E., Perroncito, R., Shimokawa, W. D., Trent, A., et al. (2002). Effectiveness of donor natural killer cell alloreact-
ity in mismatched hematopoietic transplants. Science 295, 2097–2100.

Schott, E., Bonatto, R., and Plohog, H. L. (2003). Elimination of in vivo developing T cells by natural killer cells. J. Exp. Med. 196, 1213–1224.

Schrama, D., Trapenier, P., Otto, K., Kammenieu, U., Brückner, E., Lülling, E., et al. (2006). Expression of the NKG2D ligand UL16 bind-
ing protein-1 (ULBP-1) on dendritic cells. Eur. J. Immunol. 36, 65–72.

Schulz, U., Krause, M., Muthhoff, G., Stöckler, B., Köhler, M., Andreesen, R., et al. (2010). Interleukin-10 promotes

monocyte NK cell killing of autologous tumor cells by stimulating expres-

sion of NKG2D ligands. Scand. J. Immunol. 72, 319–331.

Shi, F. D., Takeda, K., Akira, S., Sarvet-Ruggeri, L., Capanni, M., Urbani, E., Shibuya, A., Campbell, D., Hannum, C.,

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any com-

mercial or financial relationships that could be construed as a potential con-

flict of interest.

Received: 30 November 2012; paper pending publication: 21 December 2012; accepted: 9 January 2013.

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