Review

The Regulatory Effect of Natural Killer Cells: Do "NK-reg Cells" Exist?

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The most important progress in immunology in the last decade is the description of regulatory lymphocytes, among which Treg cells and regulatory NKT cells are much attractive to not only immunologists but also almost all biomedical researchers. Meanwhile, it is noted that NK cells are not only "Killers" but also regulate innate and adaptive immunity, especially in early stage, by secreting cytokines and cell-cell contact. In this review, we are going to briefly summarize the progresses in regulatory lymphocytes including T cells (Treg, Tr1, Th3), NKT cells and NK cells, and then extensively introduce the positive regulatory function of NK cells in both normal immune response and in disease condition (tumor, infection and autoimmunity), and finally, to focus on the most latest progression in the negative regulatory effects of NK cells on normal and pathogenic immune response. In conclusion, we speculate that a "regulatory NK (NK-reg)" cell subset exist and need to explore. *Cellular & Molecular Immunology*. 2006;3(4):241-254.

Key Words: natural killer cell, regulatory T cell, innate immunity, immune regulation

Introduction

The immune system evolves to protect the host against the attack of foreign pathogens by recognizing self-antigens and non-self-antigens and to prevent the host from suffering autoimmune diseases *via* tolerance to self-antigens. Improper immune responses (e.g., immune response to self-antigens, immune tolerance or excessive immune response to foreign pathogens) may result in the damage to the host (1, 2). To sustain the immune homeostasis of internal environment, a complex immune regulatory system (e.g., the cytokine network, the idiotype and anti-idiotype network, the regulatory network among immune cells) has been developed during the evolutionary process of immune system. Induction and maintenance of the tolerance to peripheral antigen- specific T cells is crucial in preventing from autoimmune diseases, while the regulatory T cells (Treg cells) play a major role in controlling peripheral auto-reactive T cells. Other immune cells, such as NK cells, DCs, γδ T cells, NKT cells and cytotoxic T lymphocyte (CTL), also participate in the immune regulation. Recently, the regulatory effect of NK cells attracts a great deal of attention, but the mechanism is far from clear.

The positive regulatory effects of NK cells

NK cells constitute an important component of the innate immune system, providing surveillance against certain viruses, intracellular bacteria and transformed cells. Although NK cells represent only 5-10% of human peripheral blood mononuclear lymphocytes, they respond very rapidly to virus-infected or transformed cells and kill virus-infected or malignant transformed cells without pre-sensitization and restriction by major histocompatibility antigen (3-5). Therefore, NK cells are critical in early host defense against a variety of viral, bacterial, parasitic pathogens, and cancer. NK cells identify their targets through a set of activating or

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Abbreviations: NK, natural killer; Treg, regulatory T cell; DC, dendritic cell; Foxp3, forkhead box P3; GITR, glucocorticoid-induced TNFR; CTL, cytotoxic T lymphocyte; GM-CSF, granulocyte-macrophage-colony stimulating factor; KIR, killer cell immunoglobulin-like receptor; IFN, interferon; Con A, concanavalin A; NKT, natural killer T cell; Poly I:C, polyinosinic-polycytidylic acid; EAE, experimental autoimmune encephalomyelitis; PLP, proteolipid protein; MS, multiple sclerosis; uNK, uterus NK cell; inhKIR, inhibitory receptor of the KIR family; BCG, Bacillus Calmette-Guerin; NK-reg, regulatory NK cell; PHx, partial hepatectomy.

inhibitory receptors, which recognize pathogen-encoded molecules ("non-self recognition"), self proteins whose expression is up-regulated in transformed or infected cells ("stress induced-self recognition"), or self proteins that are expressed by normal cells but down-regulated by infected or transformed cells ("missing-self recognition") (6, 7). The dynamic balance between these activating and inhibitory signals controls NK cell activation (6-10). NK cells secret various cytokines (such as IFN-γ, GM-CSF and TNF-β) and chemokines and act to regulate innate and acquired immune responses (11). NK cells also influence B cell differentiation, specifically by producing IFN-γ that affects Ig isotype switching.

The regulatory effects of NK cells on DCs

DCs and their precursors are considered to be sentinels of the immune system. They play important roles as initiators of innate immunity and exhibit unique capacities to prime naïve T cells (12, 13). NK cells and DCs are two types of specialized cells of the innate immune system, the reciprocal interaction between these two types of cells results in a potent, activating cross-talk. They can potentially influence the maturation of each other (14-16). DCs act during the priming phase of NK cell activation and shape the magnitude of innate immune responses by modulating the cytolytic effect of NK cells on tumors, virus-, bacteria- or parasite-infected cells. NK cells can provide signals that favor the generation of mature DCs, promote DC maturation and cytokine production. *In vivo*, NK/DC interactions may occur in lymphoid organs as well as sites of inflammation or tumor tissues. The cross-talk between NK cells and DCs might take place at different stages of the innate and adaptive immune responses, which indicates the interaction of these cells plays a role in controlling of the links between innate and adaptive immunity. By inducing DC activation, NK cell activation induced by tumor cells can indirectly promote anti-tumoral T cell responses.

NK cells could profoundly influence DC functions by different mechanisms (15-19): 1) NK cell-mediated lysis of infected cells or tumor cells might release cell debris and microbial products that are then taken up by DCs, which enables cross-presentation of incoming antigens; 2) NK cell-mediated lysis of iDCs might maximize the efficiency of antigen presentation by "cleaning-up" iDCs that are unresponsive to particular infectious stimuli, thereby freeing up resources for reactive, maturing DCs and promoting the efficiency of antigen presenting; 3) Activated NK cells boost the antigen process and presentation of DCs and the polarization of Th1 cells by producing IFN-γ; 4) NK cells promote DC maturation and the production of IL-12, which in turn induces a more efficient CTL response; 5) NK cell-secreted granulocyte-macrophage-colony stimulating factor (GM-CSF) would promote DC survival and the differentiation of monocytic precursors into DCs.

NK cells play a helper role in anti-tumor immune responses by interacting with DCs and promoting the induction of tumor-specific $CD4^+$ and $CD8^+$ T cell responses. Activated NK cells induce the maturation of DCs into type-1 polarized DCs (DC1), characterized by up to 100-fold enhanced ability of producing IL-12. This process depends on IFN-γ and TNF-α produced by NK cells (20-22). DC1 can produce high level of IL-12p70 even in the presence of immunosuppressive factors that abolish the IL-12p70 producing capacity of immature or mature DCs (21). In addition to the tumor cell-derived signal (such as NKG2D-MICA interaction), the helper role of NK cells requires additional signals from type-I IFNs, products of virally infected cells, or from IL-2, produced by activated $CD4^+$ Th cells. Other soluble factors, such as IL-18, exert synergistic effect with type-I IFNs or IL-2 during the process (20).

Efficient generation of CTLs from naïve $CD8^+$ T cells requires the helps from $CD4^+$ T cells, including the secretion of cytokines and CD40/CD40L interactions, which lead to an increased expression of co-stimulatory molecules on DCs and the induction of IL-12 (23-25). Interestingly, it was found that bone marrow-derived DCs caused rejection of A20 lymphoma and induced tumor-specific long-term memory, even if they were not loaded with tumor-derived antigen. Surprisingly, experiments using CD40 knock out mice and cell depletion indicated that this effect did not require the help from $CD4^+$ T cells (26). It was showed that the cross-talk between NK cells and DCs played key roles during this process. Activated NK cells stimulated by the expression of NKG2D ligands on tumor cells produced IFN-γ, which in turn induced the DC maturation. IL-12 produced by DCs primed CTL responses. The primary rejection of A20 cells following immunization with unplused DCs required NK cells and $CD8^+$ T cells, whereas long-term memories only required $CD8^+$ T cells (26, 27). Therefore, a novel pathway linking innate and adaptive immunity was suggested that the interplay between NK cells and DCs could completely replace the helps from $CD4^+$ T cell in the induction of $CD8^+$ CTLs.

The helper role of NK cells during the induction of CTL responses

NK cells fulfill essential accessory functions for the priming of antigen-specific CTLs. Kos and his colleagues first postulated that the generation of human alloantigen-specific $CD8^+$ T cells required the participation of $CD3^-CD16^+CD56^+$ NK cells but did not require $CD4^+$ T helper cells. Depletion of NK cells from responders abolished the induction of alloantigen-specific CTLs *in vitro* and *in vivo* (28, 29). On the basis of a NKG2D-ligand-positive tumor model, results were obtained that NK-mediated regulatory as well as NK-mediated cytolytic activities played major roles in the initiation and persistence of CTL activity. $CD8^+$ T-cell-dependent tumor rejection requires NK cell function *in vivo*, because tumors will progress both on the depletion of NK cells and in the absence of optimal NK activity (30). The absence of NK cells during subcutaneous tumor growth will abrogate generation of anti-tumor CTL responses. The accessory functions of NK cells in the initiation and persistence of CTL activity depend on the cross-talk between DCs and NK cells. In addition, interaction between CD27 on NK cells and CD70 on tumor cells promoted the rejection of

tumors by $CD8^+$ T cells, which depends on the production of IFN-γ (31). Wilcox RA and his colleages found that IL-2 and IL-15 induced NK cells to express CD137 and the ligation of CD137 stimulated NK cell proliferation and IFN-γ secretion. CD137-stimulated NK cells promoted the expansion of activated $CD8^+$ T cells *in vitro*, demonstrating the immuno-regulatory or helper activity at $CD8^+$ CTLs (32).

$CD4^+$ T cells and $CD8^+$ T lymphocytes are important for the elimination of intracellular pathogens. Limited information is available on the effect of NK cells on $CD8^+$ CTL responses. Depletion of NK cells by Abs to AsGM1 or NK1.1 suppressed the influenza virus-specific CTL responses, suggesting that NK cells are essential to initiation of CTL responses to infection (33, 34). Depletion of NK cells from PBMC of healthy tuberculin reactors reduced the frequency of *Mycobacterium tuberculosis (M. tb)*-responsive $CD8^+$ IFN-γ^+ T cells and decreased their ability to lyse *M. tb*-infected monocytes. Soluble factors secreted by activated NK cells can restore the frequency of $CD8^+$IFN-γ^+ T cells and this process depends on the presence of IFN-γ, IL-15 and IL-18 (35). Results showed that NK cells secreted IFN-γ, which stimulated monocytes to produce IL-15 and IL-18, which in turn facilitated the expansion of $CD8^+$ T cells that produce IFN-γ in response to *M. tb* infection. Meanwhile, the ability of NK cells to prime CTL activity was also dependent of cell-to-cell contact between NK cells and infected monocytes because this process was inhibited by anti-CD40 and anti-CD40L (35). NK cells link innate and adaptive immune responses by promoting of $CD8^+$ T cells to produce IFN-γ and to lyse infected cells, which is critical for protective immunity against *M. tb* and other intracellular pathogens.

NK cells enhance the function of $CD4^+$ T cells and promote the differentiation of Th1 cells by secreting IFN-γ

Previously, NK cells have been assumed to participate in adaptive immune responses by an indirect mechanism that involves their secretion of cytokines (such as IFN-γ, GM-CSF and TNF-α) and chemokines (MIP-1α, MIP-1β, RANTES, etc.) (3, 4, 11). Recently, increasing evidence indicates that the direct cell-to-cell contact between NK cells and T cells also plays potential roles. Phillips and his colleagues first found that activated human NK cells expressed MHC class II molecules (36). Later, Roncarolo and his colleagues demonstrated that NK cells up-regulated the expression of MHC class II molecules and presented antigen to $CD4^+$ T cells (37). More recently, Zingoni showed that human NK cells activated by innate cytokine, IL-12 and IL-15, expressed CD86 (a B7 family member and a ligand of co-stimulatory receptor CD28). The ligation of activating NK receptors (e.g., CD16, NKG2D) induced the expression of OX40 ligand (OX40L) on activated NK cells, while OX40 is induced by TCR/CD3 signals and is mostly present on activated $CD4^+$ T cells. They further demonstrated that receptor-activated NK cells could co-stimulate TCR-induced proliferation and cytokine production of autologous $CD4^+$ T cells and that this process required OX40-OX40L and CD28-B7 interaction (38, 39). This interaction might happen in liver and secondary lymphoid organs. These findings suggest a novel link between natural and adaptive immune responses, providing direct evidence for cross-talk between human $CD4^+$ T cells and NK receptor-activated NK cells.

By high-throughput proteomic analysis of NK cell membrane-enriched fractions and flow cytometry, Hanna J and his colleagues showed that activated NK cells expressed significant levels of MHC class II molecules and ligands for TCR co-stimulatory molecules (e.g., B7-H3 and CD70). Incubation of activated NK cells resulted in a dose-dependent enhancement of $CD4^+$ T cell proliferation and secretion of IL-2 and IFN-γ. NK cells possess multiple independent unique pathways for antigen uptake. The ligation of activating receptors (NKp30, NKp46, NKG2D and CD16) on NK cells and their ligands leads to lysis of target cells, and then NK cells become activated and obtain the ability to process pathogen-derived antigen and stimulate $CD4^+$ T cells. They also showed that NK cells isolated from inflamed tonsils expressed significant levels of HLA-DR, DP, DQ, CD86, CD70, OX40L, which indicated that human NK cells acquire APC-like phenotype *in vivo* in inflamed lymphoid organs (40). These observations offer new insights into the direct interactions between NK and T cells and suggest novel APC-like properties of human NK cells.

Activated NK cells could boost the ongoing adaptive responses by producing IFN-γ, which promotes the Th1 of antigen-specific T cells. IL-12 plays an important role in promoting the production of Th1 type cytokines and inhibiting the production of Th2 type cytokines in antigen-specific adaptive immune responses. Activated NK cells produce IFN-γ, which in turn activates macrophages to secrete IL-12. Both IFN-γ and IL-12 can induce the differentiation of Th1 cells (15, 16). Normal BALB/c mice are sensitive to *Leishmania major* infection and undergo fatal visceral dissemination when infected. During early phase of infection, injection of IL-12 decreased the mortality rate and mice obtained the capacity to resist to re-challenging with *Leishmania major*. However, depletion of NK cells abolished this effect of IL-12 and did not result in Th1 cytokine responses. Normal CH3 mice are resistant to *Leishmania major* infection and sustain a type 1 cytokine status *in vivo*. Depletion of NK cells resulted in a type 2 cytokine status and disseminating lethal infection in liver and in lung (41). Similar results were also obtained in mice with *B. pertussis* infection (42). Meanwhile, the type 2 cytokine status was observed in NK-deficient tumor-bearing mice, which affect the activity of CTL and suppress subsequent memory CTL restimulation (30). Increasing evidence indicated that the predominant effect of IL-12 on Th1 status depends on the presence of NK cells and the importance of NK cells in promoting the differentiation of Th1 cells and in generation and persistence of adaptive immune responses. When the immune system tends to be type 2 oriented, NK cells can drive an efficient type 2 to type 1 switch in the population of antigen-presenting cells and Th cells to provide signaling for the generation of CTLs.

NK cells improve γδ T cell response to pathogen

Tuberculosis remains one of the worldwide infection diseases. The decrease in NK cell activity and the loss of γδ T cells in active pulmonary tuberculosis patient have been reported (43, 44), but the relationship between the changes of NK cells and γδ T cells is unclear. Considering the immune regulation function of NK cells, we presume that NK cells might be involved in the immune regulation on γδ T cells in response to *M. tb* and the loss of γδ T cells might be the result of the decrease in NK cells activity. The proliferating response of γδ T cells to the supernatant from heat-treated *M. tb* H37Ra (SHT *M. tb*) was used as a good model in γδ T cell research. By using this model, we found that NK cells were essential in the proliferating response of γδ T cells to SHT *M. tb* by selectively depleting NK cells from PBMC before culturing. NK cells, which were specifically activated by SHT *M.tb*, promoted the immune response of γδ T cells to SHT *M.tb* by CD54-mediated cell contact and the soluble factors IL-12, GM-CSF and TNF-α, but not IFN-γ (45, 46). These results demonstrated that NK cells positively regulate γδ T cells in response to *M. tb*.

The negative regulatory effects of NK cells

NK cells exert negative regulatory effects in order to maintain immune homeostasis in some physiological and pathological conditions. A recent research found that a small NK cell subset that expresses CD94/NKG2A, but not killer Ig-like receptors (KIRs) in lymph nodes was capable of killing not only immature DCs but also mature DCs in order to prevent the overactivation of DCs (47). The CD94/ $NKG2A^{+}$ KIR^{-} NK cell phenotype is consistent with that of most $CD56^{bright}$ NK cells. By limiting the supply and recruitment of iDCs, activated NK cells exert the ability to control the subsequent innate and adaptive immune responses. The cross-talk between activated NK cells and iDCs acts as a control/switch for immune system. At low NK:DC ratio (1:5), the DC/NK interaction dramatically enhances DC cytokine production (IL-12, TNF-α) in a cell to cell contact- dependent manner and DC maturation which depends on endogenously produced TNF-α. While at high NK:DC ratio (5:1), inhibition of DC functions is the dominant feature due to the direct NK cell killing of immature DCs (14-16, 18, 19). NK cells may also play an important role in maintaining immune homeostasis by directly regulating clonal expansion of activated T cells. The role of NK cells in down-regulation of T cell responses has been implicated in several studies. Trivedi PP and his colleagues found that NK cells inhibit syngeneic T cell proliferation *via* up-regulation of the cell cycle inhibitor, p21, resulting in a G0/G1 stage cell cycle arrest. The inhibition is cell-cell contact dependent, reversible, and Ag nonspecific (48). Their results suggest that the novel mechanism of T cell regulation by NK cells provides insight into NK cell-mediated regulation of adaptive immunity and provides a mechanistic link between NK cell function and suppression of T cell responses.

The negative regulatory effects of NK cells in autoimmune hepatitis induced by NKT cells

Hepatitis is a common worldwide disease with high mortality. Several hepatitis models have been reported by different groups to study hepatitis, mainly including concanavalin A (Con A)-induced hepatitis (49-52) and LPS-induced liver injury (53). The former was a well-described mouse model of T cell-dependent liver injury *via* intravenous injection with T cell mitogen Con A, which can cause fulminant hepatitis (49-52). The latter was considered to be associated with macrophages and was septic hepatitis (53, 54). Activation of T cells or macrophages is one of the initial events in these two hepatitis models in which activated T cells and macrophages are directly cytotoxic against hepatocytes or indirectly release proinflammatory cytokines, which mediate hepatocyte damage (55, 56). Recently, it has been reported that natural killer T (NKT) cells，a population of T cells, play a key role in Con A-induced hepatitis *via* releasing a wide variety of cytokines and direct cytotoxicity against hepatocytes (57, 58). In contrast to T cells, NKT cells and macrophages or Kupffer cells, which have been shown to play an important role in hepatitis, the role of NK cells in liver injury remains obscure although the antiviral activity of NK cells has been well documented.

Recent researches revealed that NK cell involves in the pathogenesis of some autoimmune diseases (e.g., diabetes, multiple sclerosis) (59-61). Presently, although hepatitis is thought to be a kind of autoimmune diseases, whether NK cells involve in its pathogenesis is still unclear. It is found that the amount and proportion of NK cells in HBV or HCV-infected liver increased significantly and the liver injury is also related to NK cell activation (62-64). Polyinosinic-polycytidylic acid (poly I:C) is an artificial mimic of viral RNA and mimics the immune response during viral infection and can induce the activation of NK cells *in vivo* and *in vitro* (65). In our laboratory, Dong Z found that injection with poly I:C preferentially induces accumulation and activation of NK cells in the liver (66, 67). Administration of poly I:C induces a slight elevation of ALT/AST, mild inflammation and focal necrosis in the liver. Poly I:C-induced liver injury is much weaker than fulminant hepatitis caused by Con A injection. Depletion of NK cells by anti-AsGM1 antibody markedly attenuates poly I:C-induced liver injury. They further demonstrated that Poly I:C-induced liver injury is dependent of NK cells, but independent of T, B and NKT cells and independent of IFN-γ, TNF-α and IL-6 by using gene knock out mice (66). These poly I:C-induced liver injury model indicated the involvement of NK cells in autoimmune hepatitis. Interestingly, injection mice with sub-dose of Con A (inducing NKT activation but without liver injury) followed by poly I:C lead to severe liver injury, which indicated that NKT cells up-regulate the function of NK cells. However, when the mice were injected with low dose of poly I:C followed by giving Con A, there is not any injury in liver, which indicated that poly I:C pretreatment protected against T cell-mediated hepatitis, as evidenced by decreased mortality, hepatic necrosis, serum transaminase levels and inflammatory cytokines (IL-4, IFN-γ). The protective effect

of poly I:C was diminished in NK-depleted mice, which could be partially restored by adoptive transfer of NK cells. Administration of poly I:C caused NKT and T cell apoptosis *via* enhancing expression of Fas protein on these cells and expression of Fas ligand on NK cells (68). These findings suggest that activation of NK cells by poly I:C prevents Con A-induced T cell-hepatitis *via* down-regulation of T/NKT cells and subsequent reduction of inflammatory cytokines. Injected mice with low dose of Con A leaded to no liver injury, but severe liver injury occurred when it was given to HBsAg-transgenic mice (NK cell deficient), which demonstrated that malfunction of NK cells in HBsAg-transgenic mice lost the negative effect on NKT cells (69).

In the mouse model of DDC-induced liver fibrosis, activated NK cell by poly I:C induced cell death to activated hepatic stellate cells and attenuated the severity of liver fibrosis. The protective effect was diminished through either depletion of natural killer cells or by disruption of the IFN-γ gene. Meanwhile, high levels of retinoic acid early inducible 1 (RAE-1), the NKG2D ligand, were found on activated hepatic stellate cells, which correlated with the increased susceptibility of activated hepatic stellate cells to natural killer cell lysis. Treatment with poly I:C or IFN-γ enhanced the cytotoxicity of NK cells against activated hepatic stellate cells and increased the expression of NKG2D and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) on liver natural killer cells. Blocking NKG2D or TRAIL with neutralizing antibodies markedly diminished the cytotoxicity. This demonstration suggests that NK cells ameliorate liver fibrosis by killing activated hepatic stellate cells *via* RAE-1/NKG2D-dependent and TRAIL-dependent mechanisms (70).

NK cells and NKT cells constitute about 13% and 30%, respectively, of lymphocytes in murine livers and are key players in innate immune responses against tumors and pathogens in the liver (71, 72). Increasing evidence suggests that NK and NKT cells also play critical roles in hepatocellular injury induced by Con A (58), α-galactosylceramide (73), and viral infection (63). Recently, Sun R found that NK cells were activated after partial hepatectomy (PHx) (74). Infection with MCMV or injection of poly I:C further activated NK cells to produce IFN-γ and attenuated liver regeneration in the PHx model. Depletion of NK cells or disruption of either the IFN-γ gene or the IFN-γ receptor gene enhanced liver regeneration and partially abolished the negative effects of MCMV and poly I:C on liver regeneration, whereas NKT cells may only play a minor role in suppression of liver regeneration. Adoptive transfer of IFN-$\gamma^{+/+}$ NK cells, but not IFN-$\gamma^{-/-}$ NK cells, restored the ability of poly I:C to attenuate liver regeneration in NK-depleted mice. These results demonstrated that NK cells negatively regulated liver regeneration in the partial hepatectomy model and that MCMV infection and poly I:C suppressed liver regeneration *via* NK/IFN-γ-dependent mechanisms (74).

It has been shown that the proportion of NKT cells in the liver is significantly elevated after PHx (75, 76), and NKT cells appear to be involved in hepatocellular injury during liver regeneration (76). However, the role of NKT cells in hepatocyte replication during liver regeneration when infected with HBV has not been clearly explored. On one hand, activated NKT cells triggered by α-Galcer, a specific NKT cell activator, could inhibit HBV replication by releasing IFN-γ (77). On the other hand, there were many activated non-classical NKT cells in the liver of HBV-tg mice, and transfer with these cells could give rise to prolonged liver injury in recipient mice (78). In our laboratory, using a murine model of HBV infection, Dong Z found that partial hepatectomy induced CD1d over-expression on hepatocytes of HBV-tg mice, which contributed to NKT cell activation. Activated NKT cells dramatically retarded liver regeneration through inhibiting hepatocyte proliferation, instead of direct cytotoxicity. Blockade of CD1d-NKT interaction restored the impaired liver regeneration in HBV-tg mice caused by NKT cells (our unpublished data). The results firstly documented the negative regulation of NKT cells on liver regeneration of HBV-tg mice, an alternative mechanism involving HBV pathogenesis.

The role of NK cells in other autoimmune diseases

The role of NK cells in autoimmunity is attracting increased attention, although NK cells play seemingly opposite roles in autoimmune diseases and function as both regulators and inducers of autoimmune diseases (59-61, 79). The role of NK cells depends on which cells become targets for NK cell attack. If the targets are non-transformed or stressed organized tissues, NK cells might participate in their destruction in the initial stage of autoimmune diseases. If the targets are anto-reactive immune cells, NK cells can act as regulators by killing the inflammatory cells mediating autoimmune diseases.

NK cells have been shown to regulate autoimmune responses by inhibiting the auto-reactive T lymphocytes under some experimental conditions in animals. The mechanism of NK cell regulatory role in experimental autoimmune encephalomyelitis (EAE) was studied in animal models. Smeltz RB et al. showed that rat bone marrow-derived NK cells exhibited potent inhibitory effects on T cell proliferation to Con A as well as the central nervous system Ag myelin basic protein, which indicated that NK cells may play an important role in regulating both normal and autoimmune T cell responses by exerting a direct effect on activated, autoantigen-specific T cells (80). Furthermore, *in vivo* experiments showed that NK cell depletion by anti-NK1.1 monoclonal antibody treatment enhanced EAE in mice. To investigate the mechanism, proteolipid protein (PLP) 136-150 peptide-specific, encephalitogenic T cell lines, which were used as the NK cell target，were cultured. The results showed that NK cells exert a direct cytotoxic effect on autoantigen-specific, encephalitogenic T cells. Furthermore, using enriched NK cells as effector cells enhanced cytotoxicity to PLP-specific, encephalitogenic T cell lines (81). The results indicate that NK cells play a regulatory role in EAE through killing syngeneic T cells, which include myelin antigen-specific, encephalitogenic T cells, and thus ameliorate EAE.

Takahashi K and his colleagues found that NK cells from $CD95^{+}NK^{high}$ multiple sclerosis could inhibit the antigen-driven secretion of IFN-γ by autologous MBP-specific T cell clones *in vitro*, which indicated that NK cells may regulate activation of autoimmune memory T cells in an antigen non-specific fashion to maintain the clinical remission in $CD95^{+}NK^{high}$ multiple sclerosis (MS) patients (82). Meanwhile, the type 2 cytokines, such as IL-5, secreted by NK cells (NK2 cells) also play a role in maintaining the remission of MS, while NK cells lose the NK2-like property when relapse of MS occurs, but regain it after recovery. It has been found that NK2 cells induced *in vitro* inhibited induction of Th1 cells, suggesting that the NK2-like cells *in vivo* may also prohibit autoimmune effector T cells (83).

In vivo blockade of the human IL-2R by mAb has been used for immunosuppression in transplantation, therapy for leukemia, and autoimmune diseases. During the course of treatment of uveitis patients, it was found that administration of a humanized IL-2R blocking Ab induced a 4- to 20-fold expansion of $CD56^{bright}$ regulatory NK cells. The induced $CD56^{bright}$ regulatory NK cells from patients exhibited similar phenotype as those naturally occurring $CD56^{bright}$ cells. Patients with active uveitis had a significantly lower level of $CD56^{bright}$ NK cells compared with normal donors. In addition, the induced $CD56^{bright}$ cells could secrete large amounts of IL-10 whereas $CD56^{dim}$ NK cells could not, suggesting that the induction of the $CD56^{bright}$ cells may have a beneficial effect on the remission of active uveitis (84). This observation may have implications to IL-2R blockade therapy and for the potential role of $CD56^{bright}$ regulatory NK cells in autoimmune diseases.

Type 1 diabetes is an autoimmune disease in which pancreatic islet β cells are destroyed by the cellular immune system, leading to β cell loss, insulin deficiency, and hyperglycemia (85, 86). Much of the understanding of the pathogenesis of β cell destruction in type 1 diabetes has been obtained through the study of disease in the nonobese diabetic (NOD) mouse (87, 88). Although some researches found that depletion of NK cells prevented the loss of β cells following infection and indicated that NK cells induced the progression of type 1 diabetes by stimulating auto-reactive T and B cells (89, 90), some conflicting outcomes obtained in other researches. Previous studies have shown that a single injection of CFA prevents diabetes in NOD mice, but the mechanisms of protection remain unknown. Lee and his colleagues showed that this reduced incidence was associated with a decrease in the number of β cell-specific, auto-reactive CTL. Moreover, removal of NK cells abolished the protective effects of CFA while restoration of NK cells returned its protective effects, indicating that NK cells mediate protection from diseases (91). Targeting NK cells represents a novel approach to the prevention of type 1 diabetes.

The regulatory effects of uterus NK cells: predominant expression of inhibitory receptors

NK cells constitute 50-90% of lymphocytes in human uterine decidua in early pregnancy. These cells derive predominantly from a subset of peripheral blood NK cells, which gets recruited to the uterus under hormonal influence (92-94). Thus, human uterine decidual NK cells have been thought to play a role in implantation and pregnancy, at least in early pregnancy. The phenotypes and function of uterus NK (uNK) cells are different from that of peripherial blood NK cells and the precise role of uNK cells in pregnancy, embryo implantation, sterility, and recurrent spontaneous abortion has not been clarified.

In mice, uNK cells play an important role in the development of placental vasculature (95). The role of these cells in human pregnancy is still not definitively established; however, they are believed to promote placental and trophoblast growth and provide immunomodulation at the maternal-fetal interface. Human peripherial blood NK cells comprise two different subsets, the predominant $CD56^{dim}$ NK cell subset (90-95%) and the much smaller $CD56^{bright}$ NK cell subset (5-10%). However, the pattern of predominant human uterine decidual NK cells is $CD56^{bright}CD16^{-}$ with expression of inhibitory NK cell receptors CD94/NKG2A and KIRs (92, 93, 96). $CD56^{bright}$ NK cell is now thought to be an important NK cell subset for exerting immuno-regulatory effect. The $CD56^{bright}CD16^{-}$ NK cells with expression of inhibitory NK cell receptors in uterus may play major regulatory effect in preventing the attack of NK cells on trophoblast cells and in promoting the implanting and growth of plancenta and trophoblast. It is found that aborting women usually have a limited repertoire of inhibitory receptors of the KIR family (inhKIR), and that many of them lack inhKIRs specific for the fetal HLA-Cw antigens, which indicated that a limited maternal inhKIR repertoire and a lack of maternal inhKIR-fetal HLA-C epitope matching may be cause of recurrent spontaneous abortion (97). The $CD56^{bright}CD16^{-}$ uNK cells also exert regulatory effect at the maternal-fetal interface *via* secreting various kinds of cytokines including IL-10, TNF-α, GM-CSF, TGF-β, IL-1β and IFN-γ. Recently, we found that $CD56^{bright}CD16^{-}$ uNK cells in C57BL/6J mice produced more IFN-γ and TNF-α than other organ-derived NK cells, and secreted minor amount of IL-4 and IL-5. The IFN-γ and TNF-α produced by uNK cells may contribute to a successful pregnancy progress (98).

Human NK cell subsets and the "regulatory" function

While many immune cells have been conveniently divided up into subsets (such as Th1 and Th2, Tc1 and Tc2, DC1 and DC2) associated with different functional types of adaptive immune responses (99, 100), the situation of NK cells remains less clear. There are several pieces of data that indicate the presence of different subsets of NK cells dependent on either the pattern of cytokines they produced or expression of cell surface markers and activating or inhibitory receptors.

$CD56^{bright}$ and $CD56^{dim}$ subsets

Human NK cells can be distinguished as $CD56^{bright}$ and

$CD56^{dim}$ subsets by expression of CD56 surface density. The majority (approximately 90%) of human NK cells are $CD56^{dim}$ that express high levels of FcγRIII (CD16), whereas a minority (approximately 10%) are $CD56^{bright}$ and $CD16^{dim/neg}$. $CD56^{bright}$ and $CD56^{dim}$ NK cells differ in their proliferative response to IL-2, intrinsic cytotoxic capacity, NKR repertoire, and adhesion molecule expression (101, 102). $CD56^{bright}$ NK cells constitutively express the high- and intermediate-affinity IL-2 receptors and expand *in vitro* and *in vivo* in response to low doses of IL-2. In contrast, resting $CD56^{dim}$ NK cells express only the intermediate affinity IL-2 receptor and proliferate weakly in response to high doses of IL-2 *in vitro*, even after induction of the high-affinity IL-2 receptor. Resting $CD56^{dim}$ NK cells are more cytotoxic against NK-sensitive targets than $CD56^{bright}$ NK cells. All resting $CD56^{bright}$ NK cells have high expression of CD94/NKG2 C-type lectin receptors. A small percentage (less than 10%) expresses killer cell immunoglobulin-like receptors (KIR), while most (more than 85%) resting $CD56^{dim}$ NK cells are KIR^{+} and have low expression of CD94/NKG2. $CD56^{bright}$ NK cells express a functional CC-chemokine receptor 7 (CCR7) and had high-level expression of CXC-chemokine receptor 3 (CXCR3) and strong chemotactic responses to the ligands for these receptors. By contrast, $CD56^{dim}$ NK cells lack expression of CCR7 but had high levels of expression of CXCR1 and CX3C-chemokine receptor 1 (CX3CR1), and show functional responses to IL-8 and fractalkine. $CD56^{bright}$ NK cells produce significantly greater levels of IFN-γ, TNF-β, GM-CSF, IL-10, and IL-13 protein in response to monokine stimulation than $CD56^{dim}$ NK cells, which produce negligible amounts of these cytokines (101-104).

The developmental relationship between $CD56^{bright}$ and $CD56^{dim}$ NK cells has not been clarified. It is commonly accepted that $CD56^{bright}$ NK cells can be induced by IL-15 from NK cell precursors and then may differentiate into $CD56^{dim}$ NK cells (101, 102). However, it cannot be excluded the existence of a unique $CD56^{dim}$ NK-cell precursor or an alternate signal (e.g., a novel cytokine) that could induce the differentiation of $CD56^{dim}$ cells from a common NK-cell precursor. Recently, we found that both IL-2 and IL-15 support differentiation of NK cells from cord blood mononuclear cells. IL-15 maintained the differentiation or survival of both subsets of NK cells, but IL-2 only stimulated $CD56^{bright}$ NK cells proliferation. And the $CD56^{dim}$ NK cells were lost after several cycles of division in IL-2 culture (105). The results revealed that IL-15, but not IL-2, maintained terminal differentiation and survival of $CD56^{dim}$ NK cells from intermediate NK progenitor or precursor cells.

Previous studies demonstrated that AIDS patients and some cancer patients had lower percentage of $CD56^{dim}$ NK-cell subset with decreased natural cytotoxicity (106, 107). It is also noted that NK cells in immune-tolerance organ, such as human uterine and liver, were mostly compose of $CD56^{bright}$ NK cell subset with a relative fewer $CD56^{dim}$ NK cell subset (92, 95, 108). These results raise a possibility that $CD56^{dim}$ cells play an important role in innate immunity against virus and cancer, and $CD56^{bright}$ cells possibly negatively affect immune response.

Recently, Batoni G found that human $CD56^{bright}$ and $CD56^{dim}$ NK cell subsets respond differentially to direct stimulation with *Mycobacterium bovis Bacillus Calmette-Guerin* (BCG) (109). $CD56^{bright}$ cells were mainly involved in IFN-γ production in response to BCG. In contrast, the $CD56^{dim}$ subset contained higher levels of perforin and granzyme A, two key molecules for exocytosis-mediated cytotoxicity, than the $CD56^{bright}$ subset. These results demonstrate that $CD56^{bright}$ and $CD56^{dim}$ human NK-cell subsets exert different functional activities in response to a live bacterial pathogen.

NK1 and NK2 subsets

It has been shown that human NK cells can differentiate into NK1 and NK2 subsets, similar to the Th1 and Th2 subsets of $CD4^{+}$ T cells (110). In the presence of IL-12, NK cells produce IL-10 and IFN-γ (NK1), whereas in the presence of IL-4, NK cells produce IL-5 and IL-13 (NK2). Later, the *in vivo* existence of human NK1 and NK2 subsets similar to the Th1 and Th2 cells was demonstrated in freshly isolated IFN-γ-secreting and IFN-γ-nonsecreting NK cells (111). Both subsets may exhibit regulatory properties in the immune network with secreted cytokines and may display provocative and counter-regulatory roles in allergic and normal immune responses.

Loza et al. proposed that these two different lineages do not develop individually in response to various stimuli, but instead that NK1 and NK2 cells exist as two different developmental stages in a linear differentiation model. They present data supporting the hypothesis that NK2 cells are immature NK cells and able to proliferate in the presence of IL-4. These cells then differentiate into NK0 cells, which can produce both IL-13 and IFN-γ, and finally differentiate into fully mature NK1 cells that produce IFN-γ and are fully cytotoxic (112, 113). Evidence of the presence of these NK cell subsets was also supported in mice, which showed that mouse IL-2-activated NK cells can be subdivided based on expression of high or low levels of the IL-12Rβ2 (114).

It is well known that Th2 cells and the cytokines (e.g. IL-4 and IL-5) they secreted play a pivotal role in the pathogenesis of human asthma (115-117). Owing to the fact that type 2 cytokines are not only produced by $CD4^{+}$ T cells but also by $CD8^{+}$ T cells, DCs, and NK cells, whether other type II cells involved to the pathogenesis of human asthma is still not known. Recently, we observed that the ratio of $IL\text{-}4^{+}CD56^{+}$ NK2 cells in PBMCs of 8 asthmatic patients were higher than that in healthy individuals. The average mean of the relative intensity of PCR products for type 2 cytokines in NK cell clones significantly increased in the asthmatic patients. Signal transducer and activator of transcription 6, a key transcript factor of type 2 phenotype, was constitutively activated in NK2 clones from asthmatic patients. The content of $IL\text{-}4^{+}$ NK2 cells from asthmatic patients was significantly decreased after cocultured with

Table1. Characteristics of regulatory T cells

	$CD4^+CD25^+$ Treg	Tr1	Th3	Regulatory NKT (126, 129)
Phenotype				
CD25	++	+	+	
GITR	++	–	?	TCR Vα14Jα281 in mice
CTLA-4	+++	+	++	TCR Vα24Jα18 in humans
Foxp3	++	?	?	
Cytokine secretion				
IL-10	+/–	+++	+	
TGF-β	+/–	+	+++	Th1 and Th2
Function-related cell-surface molecules	TGF-β CTLA-4	?	?	CD40L FasL
Differentiation factors	IL-2 Foxp3 B7	IL-10 IFN-α	TGF-β IL-4	IL-15, lymphotoxin, fyn, Ets, AP-1, NF-κB, CD1d antigen, cathepsin L, AP-3, saposins
Regulatory mechanisms	Cell-cell contact IL-10, TGF-β	IL-10, TGF-β	TGF-β	IL-4, IL-10, TGF-β, IFN-γ; cytotoxicity
In vivo function	Prevention of a variety of autoimmune diseases; regulation of allograft rejection; immune response to pathogens	Control the activation of naïve and memory T cells; suppress Th1- and Th2-mediated immune responses to pathogens, tumors and alloantigens.	Suppress Th1- and Th2-mediated immune responses; immune regulation and T cell homeostasis	Destruction of tumors and pathogens; regulations of Th1-mediated autoimmune diseases

IFN-γ and anti-IL-4 antibody in the presence of IL-15. Interestingly, NK2-biased status in asthmatic patients was reversed when patients recovered from regular therapy. The results suggest that the NK2 cell subset is involved in the pathogenesis of asthma (118).

It has been found that type II cytokines (such as IL-4, IL-5, IL-10, IL-13) are dominant in tumor microenvironment and suppress the host cellular immune responses (119-121). We first confirmed the predominance of type two cytokines in syngeneic B16 tumor-bearing mice and found that the declining degrees of IFN-γ-producing NK cells (NK1) were much greater than those of IFN-γ-producing $CD4^+$ T cells at early tumor stage (day 10) or tumor-advanced stage (day 20). The increasing degrees of IL-10-producing NK cells and IL-4-producing NK cells (NK2) by percentage or the absolute amounts were also much greater than those of $CD4^+$ T cells (122). Our results demonstrated that the imbalance of NK1 and NK2 cells might account for the predominance of type II cytokines in tumor microenvironment and that the NK1 or NK2 cells were possibly more sensitive to tumor progression. It is also showed that the NK1/NK2 and NKT1/NKT2 cell ratios in peripheral blood lymphocyte populations were significantly decreased in normal pregnancy compared with non-pregnant and pre-eclamptic women, while there were no changes in the Th1/Th2 or Tc1/Tc2 cell ratios between them. The results also suggest a dominant role of the innate (esp. NK cells) rather than the adaptive immune system in immuno-regulation during pregnancy (123).

Do "NK-reg cells" exist?

The regulatory T-cell populations

Treg cells may be defined as $CD4^+$ T cells that inhibit immunopathology or autoimmune disease *in vivo*. Specifically, Treg cells include those able to suppress naïve T-cell proliferation *in vitro* and to control $CD4^+$ or $CD8^+$ T-cell numbers *in vivo*, in lymphopenic hosts (120-122). The regulatory T cells can be divided into several subsets, such as the $CD4^+CD25^+$ T cells, Tr1 and Th3 cells，depending on their surface phenotypes, the variety of secreted cytokines and their effective mechanisms (Table 1).

The $CD4^+CD25^+$ T cell subset represents 5-10% of the $CD4^+$ T lymphocytes in healthy adult mice and humans and is thought to perform a specialized role in controlling both the innate and the adaptive immune systems. $CD4^+$ $CD25^+$ Tregs are characterized by the constitutive expression of several activation markers including glucocorticoid-induced TNFR (GITR) family-related protein, OX40 (CD134), L-selectin (CD62L), CTLA-4 (CD152) or intracellular expression of the transcriptional repressor Foxp3 (forkhead box P3) (124-126). CD25 is not a definitive marker of natural regulatory T cells. Foxp3 seems to be the most promising marker of natural regulatory T cells, and was shown to be specifically expressed by $CD25^+$ Treg cells. This transcription factor is thought to program the development and function of this subset and so far is the most unambiguous marker available to identify naturally occurring Treg cells. Loss-of-function mutations in this gene, in both

Table 2. Characterizations of human regulatory NK cell subsets

	NK Subset		$CD56^{bright}$ NK Subset		
	$CD56^{bright}$	$CD56^{dim}$	NK1	NK2	"NK-reg"?
% of NK cells	10 %	90 %			
Classic NK Phenotype					
CD56	+++	+	+++	++	++?
CD16	+/–	+++	+	–	–?
CD94/NKG2A	+++	+	+	–	+++?
KIR	+	+++	+	–	+?
Cytokine Receptor					
c-kit (SCF-R)	+	–			
IL-2Rα	+	–		+	
IL-15Rα					
IL-2/15Rβγ	+	+	±	+	
Adherent Molecules					
PEN5	-	+++			
CD62L	+++	–			
LFA-1	+	+++			
CCR7	+++	–			
CXCR1	–	+			
FasL	++	+	++	-	
TRAIL	++	+	–	++	
Cytokine Production					
IFN-γ	+++	±	+++	–	+++?
TNF-α	+++	–	+	+	+?
TNF-β	+++	–			
IL-4				±	
IL-5				+++	
IL-10	+++	–	+	–	+++?
IL-13	+++	–	–	+++	+++?
GM-CSF	+++	–	+	+	+?
Response to Cytokines					
IL-2	Growth ↑	Killing ↑	No Change	No Change	Growth ↑?
IL-4			Growth ↓	Growth ↑	Growth ↑?
IL-12	IFN-γ ↑	No Change	Maturation ↑	Differentiation ↑	Differentiation↑?
IL-15	Growth ↑ Differentiation ↑ Cytokine secretion ↑ Killing ↑	Growth ↑			
Cytotoxicity					
ADCC	+	+++	+	+	±?
LAK	+++	+++			
K562 Killing	+	+++	+	+	±?

"?": estimation of possibility under investigation.

humans and mice, caused the absence of Treg cells (but, importantly, not of other $CD25^+$ activated T cells) and a prominent phenotype that includes autoimmune endocrinopathy, early onset type 1 diabetes, thyroiditis and, in some cases, severe atopy and food allergy (124-127).

In addition to naturally occurring Treg cells, two types of secondary T regulatory cells, Tr1 and Th3 cells, also play important roles in immuno-regulation. Tr1 cells are defined by their ability to produce large amounts of IL-10 and low to moderate levels of TGF-β, whereas Th3 cells produce

Table 3. Comparison between "NK-reg cells" and Treg cells

	Treg	"NK-reg"
Phenotype		
CD4	+	-?
CD25	++	++?
CD56	–	+++?
CD16	–	+/–?
CD94/NKG2A		+++?
KIR		+?
Functional Markers		
Foxp3	++	+?
CTLA-4	+++	+?
GITR	++	
CD134 (OX40)	++	
CD62L (L-selectin)	+	+++?
Cytokine Receptor		
c-kit (SCF-R)	+	++?
IL-2Rα	++	+?
IL-2/15Rβγ	+	+++?
IL-15Rα	+	+++?
Regulatory Cytokine		
IL-10	+	+++?
TGF-β	+/–	+?
IL-13	+	++?
Regulation		
in vitro	Cell-to-cell	Cell-to-cell ?
in vivo	Cell-to-cell IL-10, TGF-β	Cell-to-cell? IL-10?, TGF-β?

"?": estimation of possibility under investigation.

preferentially TGF-β. Antigen induced IL-10-secreting Tr1 cells produce IL-10, some IL-5, and IFN-γ, with or without TGF-β, but showed only marginal or no IL-2 and IL-4 production. Tr1 cells inhibit Th1 and Th2 responses *via* IL-10-dependent mechanisms, and emerge *in vitro* and *in vivo* following chronic antigen exposure or in the presence of specialized antigen-presenting cells (128). Tr1 cells also develop alongside Th1 cells in several chronic infectious diseases (126). Tr1 can control the activation of naïve and memory T cells both *in vitro* and *in vivo* and suppress Th1- and Th2-mediated immune responses to pathogens, tumors, and alloantigens. Furthermore, supernatants of activated Tr1 cells strongly reduce the capacity of DCs to induce alloantigen-specific T cell proliferation. The suppressive effects of Tr1 cells are reversed by blocking Abs against IL-10, showing that the inhibitory capacity of Tr1 cells is mainly mediated through production of immuno-suppressive IL-10.

Th3 cells are a unique T cell subset induced by orally administered Ag *in vivo* and triggered in an Ag-specific fashion. They provide help for IgA production and have suppressive properties for Th1 and Th2 cells. However, the suppressive effects of Th3 cells are Ag nonspecific and mediated as bystander suppression through secretion of TGF-β. Because TGF-β is broadly expressed and influences the functional activity of multiple cell types, TGF-β-secreting Th3 cells probably have a major role in many aspects of immuno-regulation and T cell homeostasis (124-127).

Comparison of "NK-reg cells" to Treg cells

More and more evidence has been obtained that NK cells play positive or negative immune regulatory effect by secreting various cytokines or cell-to-cell contact and maintain immune homeostasis (Table 2). The malfunction or loss of NK cells is involved in the pathogenesis of many diseases (e.g., tumor, autoimmune diseases, infection, sterility, and recurrent spontaneous abortion). Therefore, we propose that there exists a "regulatory NK cell subset (NK-reg subset)", which exerts important regulatory effect on innate and adaptive immunity. To validate this hypothesis, many questions are to be explored. For example, as speculately summarized in Table 3, whether $CD56^{bright}$ NK cells or NK2 cells contain regulatory NK cells similar to Treg cells? How many similarities in phenotype and function between "NK-reg cells" and Treg cells? What are the working mechanisms of "NK-reg cells"? Are "NK-reg cells" implicating in designing novel biotherapy strategies? We speculate that these questions will be resolved one by one in the near future.

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