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Natural killer cells in rejection and tolerance of solid organ allografts

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Abstract

Purpose of review—A series of recent papers defy conventional wisdom by showing that NK cells exert a powerful and long lasting influence on the immune response to whole organ allografts. The early activation of NK cells following transplantation is associated with killing of allogeneic target cells and release of immunomodulatory chemokines and cytokines, which can contribute to either rejection or tolerance. Here, we review findings describing NK cell receptors, potential mediators and mechanisms underlying the dual influence of NK cells in solid organ transplantation.

Findings—New studies show that NK cells can discriminate between self and foreign tissues and play a key role in the initiation and regulation of adaptive immune responses after solid organ transplantation. Depending upon the types of NK cell receptors engaged and the nature of cytokines released, early NK cell activation can promote either acute rejection or tolerance.

Summary—Solid organ transplantation is associated with the early activation of NK cells, which are then licensed to kill allogeneic target cells directly or via ADCC and release various chemokines and immunomodulatory cytokines. Depending upon the nature of NK cell subsets activated and their ability to kill allogeneic target cells and release certain types of cytokines, NK cells can promote the activation/expansion of pro-inflammatory Th1 cells or regulatory Th2/Treg cells thus tilting the balance of alloimmunity towards rejection or tolerance. An in-depth understanding of these mechanisms will be necessary in order to design therapies targeting NK cells in human transplantation.

Keywords

NK cells; solid organ transplantation; transplant rejection; transplant; tolerance; innate immunity; chronic allograft vasculopathy

Introduction

Traditionally, natural killer (NK) cells have been considered a central component of the innate immune system since they are developmentally programmed to destroy targets either directly or via antibody-dependent cellular cytotoxicity (ADCC) in the absence of antigen priming [1,2]. While NK cells do not express germline-encoded antigen receptors, they can discriminate between cells of self and non-self origins. Indeed, peripheral NK cells express clonotypic receptors specific for self-MHC class I molecules [2]. Following interaction with self-MHC class I, engagement of inhibitory receptors prevents autoimmune destruction of autologous cells by NK cells [2–5]. In contrast, lack or suboptimal self-MHC class I

recognition by NK cells results in NK cell activation, cytokine release and cytotoxicity [6–8], a phenomenon referred to as “missing self” [9–11]. NK cells are known for their ability to kill virally-infected cells and tumor cells in a MHC class I-dependent fashion [1,12–14]. Likewise, NK cells can recognize transplanted tissues containing cells lacking self-MHC class I molecules including skin grafts from $\beta 2m$ KO mice and semi-allogeneic F1 donors [15,16]. While the involvement of NK cells in skin and bone marrow transplantation is firmly established [17], their contribution to the rejection of organ allografts has long been considered negligible. This conclusion derives in part from studies showing that NK cell depletion fails to prevent or delay the rejection of skin and heart allografts [18–20]. However, recent studies indicate that this prevailing dogma needs to be reassessed.

Following allorecognition, activated NK cells acquire cytolytic effector functions and release a series of pro-inflammatory cytokines including γ IFN and TNF α and thus, develop the potential of contributing to the rejection of solid organ allografts directly and/or indirectly by enhancing Th1-mediated adaptive alloimmunity [21,22]. Indeed, these cytokines are known to induce/upregulate MHC class II expression by APCs [23] and promote the processing and presentation of alloantigens by dendritic cells. Therefore, NK cells can potentially promote allograft rejection by enhancing the alloreactivity of alloantigen-specific proinflammatory Th1 cells [24,25]. There is also accumulating evidence showing that some NK cell subsets possess a memory phenotype which could play a role in a host's sensitization to donor antigens and the maintenance of anamnestic alloimmunity after transplantation [26]. In contrast, there is accumulating evidence showing that NK cells are involved in induction and maintenance of tolerance. NK cells appear to promote the acceptance of allografts by killing donor professional APCs [27,28] and by secreting immunoregulatory IL-10 cytokine thereby promoting activation of Th2 and/or regulatory T cell responses [29]. In addition, a recent report indicates that NK cells can promote tolerance of allogeneic transplants by downregulating the homeostatic proliferation of CD8⁺ memory T cells [30]. Therefore, contrary to previous beliefs, NK cells appear to play an essential role in the initiation and regulation of alloimmune responses and in the rejection or tolerance of organ allografts. The mechanisms by which activated NK cells influence antigen presentation by APCs and the adaptive immune responses by T cells are poorly understood. It is clear, however, that the nature of the “NK cell effect” may vary depending upon the type of NK cell subset activated and its stage of differentiation. In addition, engagement of different inhibitory or stimulatory receptors on NK cells governs the nature of NK cell effector functions which in turn determines the influence of NK cells on adaptive alloimmunity.

Contribution of NK cells to alloimmunity and organ allograft rejection

A number of recent studies demonstrate beyond doubt that NK cells play a pivotal role in acute and chronic rejection of solid organ allografts.

Role in acute rejection

Based upon NK cell depletion studies, it has been long accepted that NK cells do not contribute to the early acute rejection of solid organ allografts [18,19]. Indeed, depletion of these cells failed to impact the kinetics of rejection, while elimination of T lymphocytes usually resulted in delayed graft rejection or transplant tolerance [20,31,32]. However, it has become increasingly clear that studies relying exclusively on depletion of discrete cell subsets and on mice with selected knocked out genes often lead to simplistic and erroneous conclusions. This is due in part, to the presence of biological mechanisms designed to compensate for the lack of particular cells or molecules in order to ensure critical immune functions such as rejection of foreign tissues in transplantation. While useful in some

situations, depleting strategies have sometimes led to misleading results. Indeed, in contradistinction to earlier studies, recent findings show that NK cells become activated early after organ transplantation and can contribute to the cell-mediated alloresponse and acute rejection process [21,22,33–35]. In the first few days after transplantation of cardiac allografts in rodents, the majority of infiltrating lymphocytes were found to be NK cells [36]. It is noteworthy that early NK cell activation and graft infiltration is only observed in recipients of allogeneic but not syngeneic organ transplants [37]. This suggests that NK cells become activated following direct recognition of alloantigens. It is likely that NK cell activation is associated with both the recognition of stress ligands (stimulatory receptors) and the lack of self-MHC class I recognition on donor cells (inhibitory receptors such as KIR in humans and Ly49 in mice and presumably other inhibitory receptors including ILT1) [38–41]. Additionally, it is possible that NK cell activation is boosted by positive signals delivered by activated dendritic cells producing IL-12 and Th1 cells producing IL-2 and γ IFN. These activated NK cells display an enhanced ability to kill allogeneic target cells in vitro through perforin, granzymes, FasL and TRAIL pathways [42–45]. In mouse models, acute rejection of cardiac allografts is consistently associated with expression of the NK cell activating receptor NKG2D and its ligands, including retinoic acid early inducible (Rae-1) and minor histocompatibility antigen H60 [46]. Furthermore, the expression of NKG2D ligands MICA/MICB (MHC class I chain-related genes) on kidney and pancreatic allogeneic transplants as well as circulating anti-MICA antibodies has been associated with acute rejection in patients [47–49]. Conversely, the presence of shed NKG2D ligands is known to preserve graft integrity presumably by preventing NK cell activation [49]. It is likely that activated NK cells contribute to the acute rejection process by secreting proinflammatory cytokines including γ IFN and TNF α . The production of γ IFN by NK cells is likely to induce and upregulate expression of MHC molecules and costimulatory receptors on APCs thus promote the maturation efficacy of professional APCs (DCs and B cells) and presumably nonprofessional APCs (endothelial cells) [33] which enhance direct and indirect alloresponses by T cells [50–54]. In addition, it is established that graft infiltrating NK cells are predominantly responsible for initial release of chemokines such as MIP-1 α , MIP-1 β , CXCL1, CCL3, CXCL10 and CX3CL1 which play a critical role in the acute rejection process [55,56].

A series of studies using costimulation-deficient (CD28^{-/-}) mice has provided direct evidence of the contribution of NK cells to acute rejection of cardiac allografts in mice. It was observed that inhibition of CD28-B7 costimulatory signaling using anti-CD154 monoclonal antibodies (mAbs) led to tolerance of fully allogeneic cardiac transplants, while CD28-deficient mice rejected these cardiac allografts through a CD8-mediated process [57]. Strikingly, CD28 KO mice whose NK1.1⁺ T cells had been depleted accepted cardiac allografts indefinitely [58]. Furthermore, a blockade of the activating receptor NKG2D with specific Abs induced long-term survival of cardiac allografts (> 70 days) [59]. In this model, NK cells became activated secondary to the lack of self-MHC class I on donor cells (missing self). Activated alloreactive NK cells were able to restore T cell help in CD28KO mice (i.e. direct activation of T cells recognizing donor antigens through their TCRs leads to subsequent acute cellular rejection of cardiac allografts). This exemplifies the role of NK cells as a link between innate and adaptive immunity in solid organ transplantation [21]. Collectively, these studies support the view that while NK cells can recognize alloantigens directly, they promote the rejection process by enhancing immune responses by T lymphocytes. However, evidence that NK cells can reject an allograft *directly* was recently provided in a skin allograft model. Rag KO mice lacking T and B cells could reject skin allografts upon activation of NK cells exposed to IL-15 [60]. In contrast, IL-15 failed to induce rejection in RAG KO gc-deficient mice lacking NK cells. Therefore, under appropriate circumstances, NK cells are capable of ensuring acute rejection of allografts in the absence of adaptive alloimmunity.

Role in chronic rejection

Prevention of acute rejection using calcineurin inhibitors has rendered possible large-scale clinical transplantation of allogeneic kidneys, livers and hearts. However, a significant proportion of these organ transplants ultimately succumb to chronic rejection, a slow process involving perivascular inflammation, fibrosis and arteriosclerosis associated with intimal thickening and subsequent luminal occlusion of graft vessels [61–65]. The mechanisms underlying the initiation and perpetuation of chronic rejection are still largely unknown. Some evidence has shown that indirectly activated CD4⁺ T cells play a key role in this process by promoting the production of allo- and presumably auto-antibodies by B cells. However, it has become clear that this type of response is neither always necessary nor sufficient to induce chronic rejection. Indeed, our group has reported that chronic vascular lesions can develop in animals rendered tolerant to donor antigens. Specifically, it was observed that cardiac allograft vasculopathy (CAV) was regularly observed in a parental to F1 heart transplant murine model i.e., C57BL/6 hearts placed in (C57BL/6 × BALB/c)F1 recipients (H-2^b to H-2^{d/b}). In this system, which eliminated conventional alloreactive response by T and B cells, no acute rejection was observed, but recipient mice developed clear signs of CAV around 50 days post-transplantation [66–68]. No CAV was observed in F1 mice transplanted with syngeneic F1 grafts, showing that absence of H-2^d molecules on parental transplants was involved in this process. Similar findings were obtained in several other parental to F1 donor/recipient combinations indicating that this represents a general phenomenon. Strikingly, immunohistological examination of the CAV lesions revealed the presence of NK cells displaying Ly49G2 activation marker in the intima and adventia [66–68]. These observations suggested that recipient NK cells from (C57BL/6 × BALB/c) F1 mice were intimately involved in the chronic rejection process, presumably due to lack of BALB/c-derived self-MHC class I H-2^d expression on donor endothelial cells. Surprisingly, no CAV was observed when RAG1 KO mice devoid of T and B cells but not of NK cells were used as recipients. However, CAV was restored in RAG1 KO adoptively transferred with syngeneic CD4⁺ T cells [67,68]. This demonstrated that NK cells alone were not sufficient to ensure CAV but that they mediated their effect indirectly by activating some CD4⁺ T cells. This conclusion was confirmed by experiments showing abrogation of CAV only when both CD4⁺ T cells and NK cells were depleted [67,68]. Therefore, similar to what has been described in the case of acute rejection, it is likely that NK cells play an accessory role in chronic rejection by providing help to Th1 cells. The mechanisms by which NK cells promote the activation of CD4⁺ T cells in this model are not yet understood. This may involve cognate interactions between NK and T cells or bystander T cell activation via cytokines or other soluble mediators. Likewise, in the absence of alloantigens on the graft, the nature of the antigen(s) recognized by CD4⁺ T cells is unknown. It is possible that initial tissue injury caused by NK cells results in the release of normally sequestered autoantigens and subsequent activation of some autoreactive T cells. In support of this view, recent studies from our laboratories have shown that autoimmune T cells directed to a heart tissue antigen cardiac myosin are regularly induced after transplantation and can result in CAV [69–72]. Alternatively, it is possible that NK cell activation triggers changes in antigen processing by local APCs such as cardiac dendritic cells thus allowing for the presentation of formerly cryptic determinants on heart autoantigens. Recent evidence shows that exposure of APCs to γ IFN is sufficient to alter self-antigen processing and trigger the presentation of initially cryptic self-peptides and activate autoreactive T cells [73]. It is therefore plausible that release of γ IFN by activated NK cells may cause the presentation of cryptic self-determinants [74–76] and initiate an autoimmune cascade eventuating in chronic rejection of parental heart transplants in F1 recipients. Current experiments in our laboratory are underway to address these hypotheses.

Role of NK cells in regulation of alloimmunity and tolerance to allogeneic organ transplants

Although the literature regarding the role of NK cells in acquired tolerance is sparse, there is accumulating evidence showing that NK cells can contribute to the suppression of proinflammatory T cell-mediated alloimmunity and facilitate tolerance induction to allografts in recipients treated with donor specific transfusion and certain immunosuppressive regimens [77–79]. In support of this view are experiments showing that NK cells can prolong skin graft survival by killing donor dendritic cells and preventing direct allorecognition and subsequent direct alloresponses by T cells secreting type 1 cytokines [27,28]. This phenomenon has been associated with immune deviation of the adaptive alloresponse towards type 2 immunity (Th2/CT2) and graft infiltration by eosinophils presumably owing to antigen presentation by other APCs and/or lack of γ IFN and IL-12 cytokines [79]. Likewise, NK cells have been shown to promote tolerance to kidney allografts in rats induced with anti-CD28 monoclonal antibodies by suppressing proinflammatory immunity [79]. In another study, it was reported that tolerance to islet allografts in recipients treated with anti-CD40L or anti-LFA-1 antibodies could be abrogated following depletion of NK cells [77]. The mechanisms by which NK cells can promote tolerance in these models are not clear. While, NK cells need to be activated to exert their tolerogenic functions, this process does not seem to rely on their ability to sense the absence of self-MHC class I molecules on allogeneic cells. In turn, perforin expression by NK cells was apparently required, a result suggesting that tolerogenic properties of NK cells in this model is associated with their cytotoxic functions [77]. This suggests that elimination of donor APCs is either not always involved in this process or that it occurs via a mechanism, which do not necessarily rely on the missing self-MHC class I paradigm.

It is possible that the mechanisms by which NK cells promote tolerance differ depending upon the nature of the transplant and/or the immunosuppressive regimen. In addition, it is likely that different subsets of NK cells can exhibit some tolerogenic effects via distinct mechanisms including leukocyte cytotoxicity and cytokine secretion. For instance, under appropriate circumstances such as chronic inflammation or infection, activated NK cells are known to secrete IL-10, a process enhanced upon exposure to IL-12 typically produced by dendritic cells [29]. IL-10 cytokine production by NK cells has been implicated in the maintenance of immune privilege in the uterine decidua thus protecting the fetus from rejection by maternal allospecific T cells [80] and in the prevention of inflammatory reactions in the central nervous system and the eye [81–84]. Likewise, NK cells have been shown to be critical to the activation of regulatory T cells in anterior chamber acquired immune deviation (ACAID), a phenomenon in which donor-specific tolerance is induced through injection of alloantigens in the anterior chamber of the eye [81–84]. Finally, a recent study from Lakkis's group showed that NK cells can delay allograft rejection by reducing the homeostatic proliferation of CD8⁺ effector memory T cells (TEMs) which represents a major barrier to transplant tolerance induction in lymphopenic hosts. In this study, it was observed that regulation of homeostatic CD8⁺ TEM expansion by NK cells was perforin-independent but presumably mediated via competition for IL-15 cytokine [30]. Altogether, these different studies demonstrate that NK cells represent an essential element of the immune response involved in tolerance to allogeneic transplants. It is clear that NK cells can mediate their tolerogenic effects via multiple mechanisms relying on their cytotoxic functions, their cytokine secretion or their ability to compete for activation with alloaggressive cells. It is likely that different NK cell subsets and different mechanisms are involved in tolerance induction depending upon the nature of the transplant and the alloimmune response it evokes in the host.

Conclusion

It has become increasingly clear that, in contrast to conventional wisdom, NK cells play an important role in alloimmunity and rejection of solid organ allografts. NK cells become activated by stressed ligands expressed on graft tissue and via a type of allorecognition relying on their ability to sense the absence of self-MHC class I on allogeneic or semi-allogeneic target cells. Early NK cell activation can skew the downstream alloimmune response by lymphocytes toward tolerance or rejection.

On one hand, NK cells can contribute to both acute and chronic allograft rejection by killing directly allogeneic target cells thereby amplifying the inflammatory process and presumably the presentation of allodeterminants to T cells activated in an indirect fashion. In addition, NK cells can contribute to the rejection process by secreting chemokines necessary for graft infiltration by other and by producing γ IFN thus enhancing direct Th1 cell alloreactivity while antagonizing regulatory type immunity. Finally, it is possible that chronic inflammation and NK cell activation at the graft site associated with pro-inflammatory cytokine release and donor cell cytotoxicity can lead to the presentation of formerly sequestered tissue specific antigens and the processing of cryptic self-determinants. This process may result in chronic allograft rejection mediated essentially by CD4⁺ autoreactive Th1 cells. Interestingly, recent studies demonstrated that some NK cells exposed to virally infected targets behave as long-lived memory cells [26]. If NK alloreactive memory cells were generated during life via exposure to alloantigens or microorganisms, these cells could induce anamnestic alloresponses after transplantation and contribute to accelerated rejection of solid organ allografts.

On the other hand, several studies show that NK cells can contribute to allograft acceptance by promoting some tolerance pathways. This phenomenon has been shown to involve IL-10 secretion by activated NK cells and subsequent type 2 cytokine immune deviation as well as stimulation of regulatory T cell responses. In addition, NK cells can suppress adaptive alloimmunity directly by eliminating donor APCs. The nature of the factors controlling the immunogenicity vs. tolerogenicity of the NK response after transplantation is still unclear. Hence, these studies suggest that manipulating early NK cell response may be used to influence the overall adaptive alloimmune response and the fate of an organ allograft. This may be achieved by suppressing selected NK cell subsets involved in acute and/or chronic rejection or via activation or adoptive transfer of potentially tolerogenic NK cells. A better characterization of the receptors, their ligands and cytokines involved in NK functions as well as a better understanding of the mechanisms by which NK cells mediate their effects on other leukocytes will be necessary to successfully manipulate these cells in transplanted patients.

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Abbreviations

NK cells	Natural killer cells
ADCC	Antibody dependent cell-mediated cytotoxicity
MHC	Major histocompatibility complex
γ IFN	Interferon gamma

TNFα	Tumor necrosis factor alpha
MICA/MICB	MHC class I chain-related genes (A and B)
APCs	Antigen presenting cells
TCR	T cell receptor
DCs	Dendritic cells
CAV	Cardiac allograft vasculopathy
DST	Donor specific transfusion
ACAID	Anterior chamber acquired immune deviation

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