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NK Cells: Elusive Participants in Transplantation Immunity and Tolerance

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NK cells constitute an innate MHC class I-reactive lymphoid population that rapidly responds to infection, injury, or cell distress. In the transplant field, NK cells have most often been associated with pro-inflammatory immunity resulting in the exacerbation of allograft injury. Despite this general view of NK cell reactivity, it has been challenging to assign unambiguous obligate roles for NK cells in the allograft response. While recent reports continue to provide evidence supporting a role for NK cells in promoting both acute and chronic rejection, there are also a growing number of studies that illustrate an alternative role for NK cells in promoting allograft survival and tolerance. This review addresses the plasticity of NK responses in transplantation by suggesting specific ‘checkpoints’ whereby NK cells can either enhance or inhibit the allograft response in vivo.

Introduction

NK cells contribute a well-appreciated role in pro-inflammatory MHC class I-associated innate immunity. These cells are known to provide rapid reactivity to varied forms of injury including pathogen infection, cell transformation, and general cellular stress. NK cells interact with target cells through a complex integration of positive and negative signals, involving inhibitory classical MHC class I molecules and an array of activating ligands, many involving MHC class I-like molecules. Though an extensive description of this varied receptor and ligands is beyond the scope of the current discussion, there are a number of excellent and detailed recent reviews available that describe the structure and function of NK-associated receptors (1-3). Importantly, unlike antigen-specific CD8 T cells that recognize and are activated by peptide ligands presented by MHC class I molecules, NK cells utilize a sort of mirror image recognition system. That is, self MHC class I interactions delivery inhibitory signals to NK cells, forming the basis of the classical model of ‘missing self’ NK surveillance for unusual cells with reduced MHC expression (4). However, the lack of self MHC class I expression is not sufficient for the activation of NK cells. In addition, NK cells require the interaction with cell-surface activating ligands that are induced by a variety of stimuli including cell transformation, infection, and stress. Taken together, NK cells respond through a complex integration of these inhibitory and activating ligands expressed on host cells. The goal of this review is to highlight recent studies regarding the biology of NK cell contributions to allograft immunity and tolerance. Special emphasis will be placed on the increasingly appreciated and somewhat unexpectedly important role that NK cells can play in regulating the allograft response and in promoting tolerance induction.

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Situations whereby NK cells promote graft rejection

Much of our current understanding of NK cell biology is derived from basic cellular analyses and from studies of infectious disease and tumor immunology. The elusive aspect of NK cells in transplantation is that there are very few studies that provide definitive evidence for a required role for NK cells in most cases allograft rejection. For example, the inhibition or elimination of NK cells rarely results in significantly prolonged allograft survival. Given the emerging interest in the role of NK cells in allograft tolerance (see below) it might be tempting to underestimate the contribution of NK cells to graft injury. However, a number of studies over the past few years continue to highlight the ability of NK cells to promote several types of graft injury or rejection. In transplantation, NK cells are perhaps best known for their ability to directly reject MHC mismatched bone marrow allografts, as illustrated by recent studies (5,6). However, there are a few examples in which NK cells can play an essential role in organ or tissue allograft rejection. NK cells can be required for cardiac allograft rejection when the costimulatory molecule CD28 is either inhibited or genetically absent (7,8). In another model, IL-15-driven NK reactivity can result in skin allograft rejection independent of T and B cell adaptive immunity (9). NK cells can also enhance skin allograft rejection by promoting CD4 T cell-dependent 'indirect' (host APC-dependent) alloantigen presentation (10•,11•). This latter result may well be related to the ability of NK cells to kill MHC mismatched donor dendritic cells (DC) (12,13•) and so 'seed' antigen to self APCs. NK cells are also associated with chronic allograft injury. In a semi-allogeneic mouse model of 'hybrid resistance', NK cells were shown to be required for chronic cardiac allograft vascular injury (14). A recent clinical study strongly suggests that NK cells contribute to antibody-mediated rejection in kidney allograft recipients (15••). Though there are varied means by which NK cells could contribute to such injury, an obvious role for NK cells in antibody-dependent responses could be through antibody-dependent cellular cytotoxicity (ADCC) triggered by antibody Fc receptor binding and activation of host NK cells (16). Taken together, NK cells clearly have the capacity to exacerbate multiple forms of allograft injury.

While NK cells can promote allograft rejection, probably the more unexpected findings over the past few years have focused on the roles that NK cells play in regulating the immune response, including a pronounced role in allograft tolerance in some cases. In a more general sense, it has become apparent that NK cells are not merely mono-thematic but rather demonstrate considerable functional plasticity in immunity. Below is outlined a proposed series of major 'checkpoints' whereby NK can either enhance or regulate the allograft response.

NK 'checkpoints' 1 and 2: Consequence of NK interactions with donor and host antigen-presenting cells, respectively

NK cells are well known for their reciprocal interactions with antigen-presenting cells, especially DCs (17,18). NK cells demonstrate contact-dependent activation or inhibition of DCs (19) depending on the nature of the DC and the microenvironment. DCs in turn can rapidly induce IFN-g production and cytotoxic activity in NK cells (20), in part due to the production DC-derived IL-15 (21). NK cells are an early source of IFN-γ and can rapidly 'license' DCs resulting in DC maturation and the subsequent promotion of T cell activation (17). Such NK cell interactions with donor DC generally promote a Th1-like alloresponse (22); without such donor NK:DC encounters, the response can default to a more Th2-like response (23). However, while NK cells can sometimes drive the activation of immature DCs (24), there is an alternative outcome whereby DCs can directly kill immature or uninfected DC (17,19,25). It will continue to be important to clarify those signals that trigger positive (DC activation) versus negative (DC killing) outcomes of NK:DC interactions in the setting of allograft immunity.

Most of the studies mentioned above involve NK interactions with self APCs, largely using infectious disease models. Over the past few years, the capacity of NK cells to kill *donor*-derived APCs has surfaced as a major pathway whereby NK cells can modify allograft reactivity and actually promote allograft tolerance rather than rejection. We had found that NK cells and perforin were surprisingly necessary for some forms of induced allograft tolerance (26). Soon thereafter, Yu *et al* made the important observation that host NK cells rapidly killed MHC-disparate allogeneic DCs (12). This DC killing appeared to be the direct result of a 'missing self' event since donor DCs expressing self MHC class I (i.e. host x donor F1 cells) were protected from such elimination. A more recent report connected these two studies by demonstrating the NK cells could mediate perforin-dependent killing of donor APC (13•). Thus, this initial NK:donor DC interaction represents a key primary 'checkpoint' in how NK cells can impact the allograft response (Figure 1). Importantly, rapid elimination of donor-type DCs would be expected to blunt the 'direct' (donor APC-dependent) allogeneic response that accounts for the dramatically high frequency of alloreactive T cells. Indeed, inhibition of NK cell responses can prevent donor DC elimination and actually enhance CD4 T cell alloreactivity (23).

A secondary consequence of rapid killing of donor DC would be the enhanced availability of donor antigens to host-type APC. Recent studies illustrate this phenomenon by showing enhanced 'indirect' (host APC-dependent) reactivity as a result of a host NK response (10,11). Although the alloreactive repertoire is numerically dominated by 'direct' allospecific T cells, NK cells responding to donor DC would serve to impact the qualitative nature of the allograft response by inhibiting the magnitude of the 'direct' response and diverting reactivity to promote 'indirect' reactivity (Figure 1). This leads to a second and potentially pivotal 'checkpoint' in allograft immunity whereby NK cells interact with host DC presenting donor-derived antigens. The fact that NK cells augment such 'indirect' donor reactive CD4 T cell responses implies that NK cells interact with host DC to promote this form of alloreactivity (10,11•). Thus, NK cells interfacing with host DC presenting donor-derived antigens is likely to enhance graft-destructive T cell reactivity in a manner analogous with host reactivity to pathogens (17). If donor-derived DCs are eventually eliminated, then it is likely that host APC-dependent 'indirect' reactivity is likely to form the key branch point that dictates eventual allograft outcome. While indirect antigen presentation may certainly promote destructive allograft reactivity, this same pathway also appears to be essential for allograft tolerance induction (27,28•,29•). Furthermore, while regulation of alloreactivity by NK cells has largely focused on the ability of NK cells to either activate or kill DC and potentially reactive T cells, it will be important to determine if NK cells can exert other types of regulatory functions. A very intriguing recent study indicates that IL-10 producing NK cells can promote regulatory activity, suppressing host resistance to parasitic infection (30••). It will be interesting to determine if alternatively activated NK cells producing IL-10 can provide a cytokine-dependent route for regulating alloimmunity. Going forward, it will be important to clarify our understanding of the potential roles that NK cells play in modifying indirect donor antigen presentation.

NK 'checkpoint' 3: NK cell interactions with T cells

While NK:DC interactions have been a major focus of how NK cells mold the adaptive immune response, the ability of NK cells to directly interact with T cells is arguably an under-appreciated facet of NK cell biology. Thus, direct NK:T cell interactions form a third 'checkpoint' whereby NK cells can either enhance or regulate T cell alloreactivity (Figure 1). On one hand, NK cells may directly enhance T cell alloreactivity, such as by producing IFN-γ that promotes Th1-like T cell responses in a paracrine fashion (31,32) and by direct contact via OX40-O40L interactions (33). However, there is an alternative outcome of NK-T cell interactions that can inhibit or eliminate activated T cells. T cells themselves can

express activating or inhibitory NK ligands, rendering them amendable for direct NK cell recognition. On this point, it essential to emphasize that because NK cells do integrate activating and inhibitory signals on target cells, it is possible for NK cells to kill 'stressed' self target cells despite the expression of inhibitory self MHC class I molecules (34). A recent study showed that in persistent LCMV virus infection, reduction in T cell expression of the NK inhibitory ligand CD244 (2B4) can result in direct killing of CD8+ T cells by NK cells through a perforin-dependent process (35••). Interestingly, the direct NK cell-mediated killing of 'stressed' activated T cells was shown to be perforin-dependent (34,35), consistent with our own results in vivo (26). Two more recent studies using mouse models of graft-versus-host-disease (GVHD) each suggest a role for NK cells in the direct inhibition of GVHD-inducing T cells (36,37). In one case, results indicate that chronically activated CD4 T cells express ligands for the NK activating receptor NKG2D and that anti-NKG2D antibodies inhibited T cell elimination (36). It is intriguing to speculate that in the presence of some tolerance-inducing agents, alloreactive T cells may be inappropriately activated and express NK activating ligands, making them vulnerable to terminal 'pruning' by cytotoxic NK cells. Finally, in addition to a direct inhibition though cell killing, NK cells may also exert a more indirect role in controlling T cell reactivity. In an interesting recent study, NK cells were found to restrain CD8 T cell homeostatic expansion in the setting of lymphopenia, providing an additional non-antigen-specific means of NK cell-dependent T cell regulation (38•). Thus, NK cells have may have multiple routes of directly augmenting or inhibiting T cell immunity.

Checkpoint 4: Cross-regulation between NK cells and Tregs

The interaction between NK cells and regulatory T cells forms another 'checkpoint' of NK cell influence on allograft immunity and tolerance (Figure 1). Because NK cell activity has surprisingly been associated with some forms of allograft tolerance, it is at least plausible that NK cells might promote active regulatory T cell (Treg) activity. However, with rare exceptions (39,40) this is not observed. Rather, there appears to be largely a cross-regulation between NK and Treg activities (at least Tregs defined by a CD4+CD25+Foxp3+ phenotype). Tregs can directly inhibit NK activity (41,42) and a recent study found that depletion of regulatory cells resulted in pronounced pathogenic NK activity resulting in autoimmune pathology (43••). Conversely, activated NK cells can inhibit Treg induction (44) and, under some conditions of pathogen infection, NK cells can directly lyse regulatory T cells (45•), thus promoting protective effector T cell activity. Thus, this interplay between NK cells and Tregs can play a role in maintaining the balance between excessive regulation of immunity and over-exuberant immune reactivity. If such antagonistic interactions between NK cells and Tregs are generally the case, then how can NK cells promote allograft tolerance, a process that often relies on Treg function? At present, we would propose that NK cells do not primarily promote allograft tolerance through the direct induction of Tregs. Rather, by blunting APC and effector T cell activity as described above, other regulatory mechanisms may contribute to tolerance. That is, NK cells may not so much 'induce' tolerance, but rather simply inhibit destructive allograft immunity and so provide a more tolerance-permissive environment for other regulatory pathways to occur.

Conclusions

Clearly, the transplant field is experiencing an increasingly complex view of how NK cells impact the allograft response. A key point from this discussion is that NK cells exert a greater degree of plasticity that most previous views of allograft immunity would indicate. Specifically, NK cells are not simply innate cells that trigger a defined, programmed response leading to pro-inflammatory immunity. Rather, NK cells likely act at several checkpoints to influence graft outcome. It is highly possible that there are other key

checkpoints of NK activity that were not outlined in Figure 1. For example, how NK cells directly interact over time with nonhematopoietic cells in the graft –such as with vascular endothelium and tissue parenchymal cells – may also prove to be important for dictating graft outcome. Also, finding more unexpected features of NK cells, such as their ability to produce regulatory cytokines such as IL-10 (30) and the capacity to demonstrate 'adaptive' properties (46•) continue to expand our view of NK cell function in vivo. Thus, rather than simply inhibit NK cells to promote allograft survival, it may be essential to consider how we can attenuate graft-destructive features of NK reactivity while preserving other regulatory properties of these cells.

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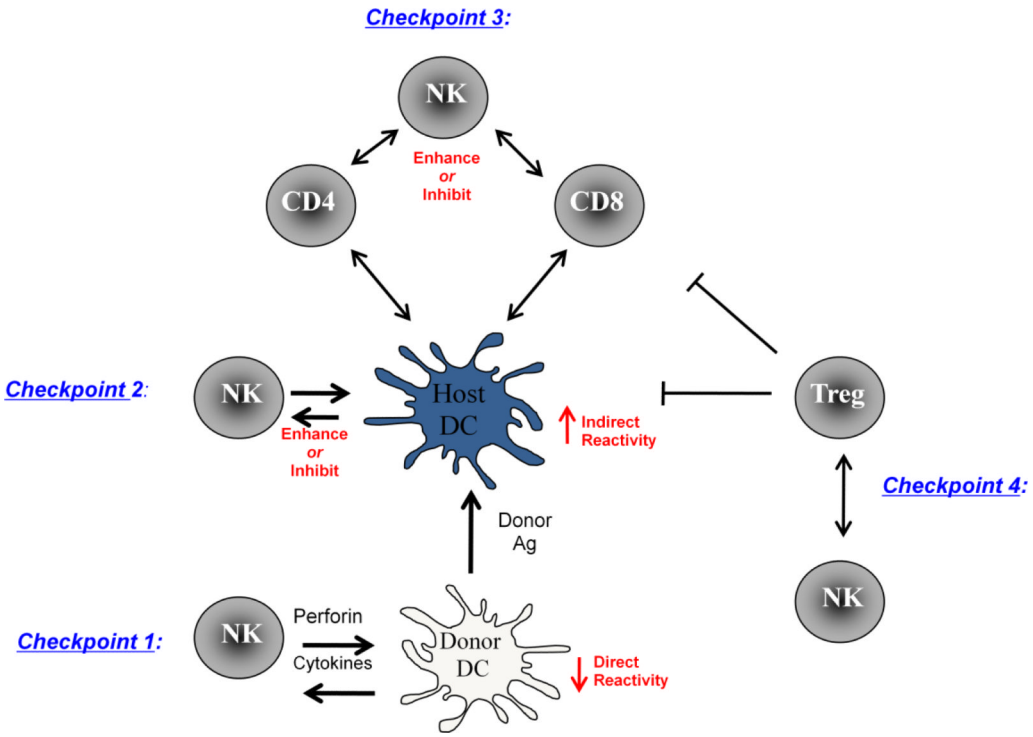

Figure 1.

Major proposed checkpoints in NK cell-mediated impact on allograft immunity. As described in the text, we propose three key areas, or 'checkpoints' whereby NK cells positively or negatively impact T cell-dependent allograft immunity. (1) Checkpoint 1: NK cells can directly lyse donor DC resulting in blunted direct antigen (donor APC-dependent) presentation to host T cells and enhanced release of donor antigens acquired by host APC (indirect, or host-APC dependent presentation). (2) Checkpoint 2: NK cells can either augment or inhibit the capacity of host APC to direct donor-derived antigens to reactive T cell. (3) Checkpoint 3: NK cells can enhance or inhibit T cell reactivity through a direct interaction with activated T cells. (4) Checkpoint 4: NK cells and regulatory T cells (Treg) tend to cross-regulate one another to either promote or inhibit regulatory activity.