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Adaptive features of innate immune cells and their relevance to graft rejection

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Abstract

Purpose of review—Allograft rejection involves both innate and adaptive immune cells, and the adaptive immune cells have dominated transplant studies for decades. Recent studies have identified surprising new features for the innate immune cells, including memory recall responses, which may have significant implications in further improvement of transplant outcomes.

Recent findings—Transplant survival is excellent in the short-term, but the long-term graft outcomes are not so, and most grafts are continuously lost to chronic rejection in the clinic. In both animal models and clinical settings, graft loss to chronic rejection is often dominated by innate immune cells, especially macrophages and natural killer (NK) cells in the grafts. Recent studies suggest that innate immune cells can acquire features of adaptive cells in that they either directly sense allogeneic nonself or become 'trained' in the allogeneic milieu, where they show features of memory recall responses. In certain models, targeting the adaptive features of such innate immune cells can promote long-term allograft survival. These findings may open new therapeutic opportunities in promoting transplant survival in the clinic.

Summary—The discovery of donor specificity and memory recall responses of certain innate immune cells, which are prominently featured in chronic allograft rejection, may open novel therapeutic opportunities in transplantation, as well as in treatment of cancers and autoimmune diseases.

Keywords

innate immune cells; macrophages; memory; natural killer cells; transplant rejection

INTRODUCTION

The ultimate goal in organ transplantation is to establish donor-specific tolerance, a tolerant state where patients would enjoy permanent graft survival without taking life-long immunosuppression drugs. Although this is readily achievable in experimental models, induction of transplant tolerance in the clinic remains a distant dream. Transplant patients

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Conflicts of interest

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still rely on global nonspecific immunosuppression to prolong graft survival [1]. Among all the issues associated with life-long immunosuppression, loss of transplants to chronic rejection, a slow and progressive deterioration of the grafts to diverse mechanisms, is particularly troubling. In fact, despite much improved immunosuppressive protocols and excellent short-term graft survival in the clinic, graft survival in the long-term has not changed much in the past few decades [2]. This apparent paradox prompts strong interests in identifying new alternative mechanisms in graft damage, mechanisms that are beyond the current 'T-cell centric' paradigm in the field.

The pervasive assumption is that graft rejection involves both innate and adaptive immune cells, in which the adaptive cells (primarily T cells) are mostly controlled by the current immunosuppressive drugs, leaving behind the innate immune cells to inflict graft damage over time. Indeed, in both animal models and clinical settings, the innate immune cells, especially macrophages and natural killer (NK) cells often predominatethecellularinfiltrates in chronicallyrejected organ transplants, whereas the adaptive T cells are few and far between [3]. In some observational clinical studies, early infiltration of the kidney transplants by macrophages is associated with poor graft outcomes [4], further supporting the role of innate immune cells in graft damage. Another hypothesis is that among the effector mechanisms that actually destroy the grafts, the innate mechanisms are just as important, regardless of the cell types that initiate the initial priming process after transplantation. For example, production of donor-specific antibodies (DSA) requires intense interactions between T cells (i.e. Tfh) and B cells in the germinal center, and the actual graft damage by DSA involves the activation of complement and/or recruitment of NK cells [5]. In fact, there is a growing awareness that the pathogenesis of DSA in organ transplantation may depend on the activation of innate pathways. Clearly, those revelations generate strong interests in the innate mechanisms and innate cell types in graft rejection, and such interests led to exciting new findings that greatly expanded the features of innate immune cells, as well as their roles in transplant rejection.

In this review article, we focused on the recently described adaptive features of innate immune cells, especially innate lymphoid cells, macrophages and NK cells, highlighting their memory attributes and memory recall responses, and in some cases, their target antigen specificities in selected models. We specifically emphasized the relevance of such adaptive features of innate cells in transplant models and whether they can be targeted to further improve transplant outcomes. We also discussed the heterogeneity and plasticity of innate cell types, as well as outstanding questions in the field, with the aim of provoking additional investigations in this area.

MYELOID CELL MEMORY AND 'TRAINED' IMMUNITY

Myeloid cells include monocytes, macrophages, and a subset of dendritic cells and neutrophils. The circulating monocytes further differentiate into macrophages and myeloid dendritic cells in the tissue. Thus, tissue resident macrophages, under either physiological or inflammatory conditions, have very different origins; they can be derived from circulating monocytes or from the yolk sac during embryonic development [6]. One of the striking features of myeloid cells is their heterogeneity, consisting of diverse subsets, and their

plasticity in that they are highly responsive to changes in the local environment. Those features are particularly relevant to transplant models, where myeloid cells affect transplant outcomes via a multiplicity of mechanisms.

In experimental models where the heart allog-rafts are tolerized by donor-specific transfusion and anti-CD154 mAb in the mouse, Ochando and colleagues demonstrated that long-term graft survival critically depends on the $F4/80^{+}Ly6C^{low}$ macrophages [7▪]. They express DC-SIGN on the cell surface and produce copious IL-10 in the grafts, and promote graft survival by inducing $Foxp3^{+}$ Tregs [7▪]. Others showed that macrophages can become immune-suppressive cells (i.e. Mregs), where they upregulate the expression of PD-L1 and suppress graft rejection [8]. Interestingly, the heart graft itself contains a subset of tissue-resident macrophages that are marked by the expression of CD169 and Tim-4. These tissue-resident macrophages also express CD39 and CD73, which convert the inflammatory ATP to the immunosuppressive adenosine to suppress graft rejection [9]. However, such $Tim\text{-}4^{+}$ macrophages are extremely susceptible to apoptotic cell death and die in a Tim-4-dependent fashion [9]. We recently reported in a mouse model the induction of macrophages with an M2 phenotype in chronically rejected heart allografts, and their inhibition through targeted deletion of mTOR resulted in long-term graft survival following costimulatory blockade [10▪▪]. Thus, like in other settings, macrophages participate in the allograft responses in diverse phenotypes and distinct mechanisms.

Perhaps the most exciting finding is the recent discovery that monocytes and macrophages can respond to allogeneic nonself independent of adaptive immune cells, thus arguing for novel therapeutic approaches to specifically target such cells in transplant settings [11]. For example, in a heart transplant model in the mouse, in which graft rejection is confined to a single minor antigen mismatch, recognition of donor alloantigens by host monocytes resulted in the induction of monocyte-derived dendritic cells, which produce high levels of IL-12; they then mediate graft rejection by priming donor reactive T cells [12]. Mechanistically, sensing of donor allografts by the host monocytes is mediated by the CD47/Sirpa pathway, where the Sirpa polymorphism on donor cells activates the host monocytes via CD47, and subsequently, in the generation of dendritic cells to drive the rejection response [13▪▪]. We reported that macrophages can also become allospecific in that they reject allogeneic cells with a high degree of donor antigen specificity [14]. Interestingly, induction of allospecific macrophages in our model requires prior donor antigen priming and concurrent CD40 signaling. Importantly, such allospecific macrophages exhibit features of memory cells [14]. This is in line with the recent description of ‘trained immunity’ in infectious models, in which macrophages that are activated by certain pathogens subsequently show much enhanced responses upon a secondary challenge [15]. But such enhanced secondary responses do not exhibit features of antigen specificity, and are mostly because of open chromatin remodeling at certain gene loci, as well as to metabolic reprogramming in activated macrophages [15]. For example, earlier epidemiological and animal studies showed that myeloid cells from individuals who were vaccinated with Bacille Calm-ette–Guérin (BCG) strongly responded to other stimulus, such as *Candida albicans* [16,17], demonstrating a state of myeloid cell memory. Studies using the $Rag1^{-/-}$ mice showed that the BCG-vaccinated mice are protected against *C. albicans* re-infection, primarily through increased responsiveness of monocytes and macrophages [15]. In fact, in a

wide range of primary and secondary challenges, mostly involving BCG vaccine and fungal products (b-glucan) or *C. albicans*, macrophages clearly can be 'trained' to mount enhanced secondary responses. In addition, in models of parasitic and viral infections, macrophages also exhibit 'trained' immunity-like responses [18,19].

There are multiple pathways that potentially explain the phenomenon of 'trained' immunity, which include activation of the dectin 1-dependent signaling pathway, the NOD2-dependent pathway and the lipoprotein-CD36 pathway [20]. These pathways then activate the epigenetic mechanisms that mediate chromatin remodeling, producing an open chromatin structure that enable cells to respond in an accelerated fashion. Furthermore, activation of those pathways also results in metabolic rewiring, switching the cellular metabolic programs from glycolysis to lipid oxidation to meet the demand of long-lived 'memory' cells [20]. Importantly, a recent study demonstrated that macrophages infiltrating the allografts can be 'trained' by damage-associated molecular patterns (DAMPs) in the grafts and such 'trained' macrophages are directly involved in graft rejection [21▪▪]. Interestingly, targeting the graft infiltrating macrophages using nanoparticles that inhibit the TRAF6 and mTOR pathways prevents macrophage 'training', resulting in long-term graft survival in the mouse [21▪▪]. Clearly, these findings provide tremendous excitement that targeting certain adaptive features of 'trained' macrophages may be therapeutically important in prolonging graft survival.

THE INNATE LYMPHOID CELLS

The innate lymphoid cells (ILCs) are an emerging family of immune cells. They develop from common lymphoid progenitors in the fetal liver and adult bone marrow but lack specific antigen receptors and lymphoid cell lineage markers [22,23]. ILCs represent a very small population of immune cells and are classified into three different groups: ILC1, ILC2 and ILC3, based on their expression of distinct transcription factors and diverse effector functions. ILC1 also include the cytolytic NK cells; they produce IFN-γ and TNF-α upon activation and express the transcription factor T-bet. ILC1 are primarily involved in type I immunity. ILC2 produce type 2 cytokines including IL-4, IL-5 and IL-13, and express the transcription factor GATA3; they mainly participate in allergic responses, as well as in parasitic immunity. ILC3 express the transcription factor RORγt and release IL-17 and IL-22 upon activation. ILC3 often provide protective immunity against bacterial and fungal infections at the mucosal surfaces [22].

From a functional standpoint, ILC1, ILC2 and ILC3 mirror their adaptive counterparts Th1, Th2 and Th17 cells, especially in their effector cytokine profiles. However, ILCs are innate cells and are poised to rapidly release inflammatory cytokines; their effector functions do not need further cellular differentiation, as seen in T-helper cells. Also, ILCs are mostly tissue-resident cells; they respond to changes in the tissue microenvironment and also significantly impact the nature, as well as the outcomes of local inflammatory responses [24]. The memory features of ILCs, especially that of ILC1 and ILC2, have been reviewed recently by others [25,26]. Evidence supporting the formation of memory ILCs mostly comes from mouse models involving hapten or cytokine stimulations [27]. Their features and potential roles in transplant models have not been explored so far. But this is an

interesting area where both donor and host ILCs may converge in the grafts and exert significant impact on transplant outcomes. Also, it remains completely unknown whether and how the commonly used immunosuppressive drugs affect ILCs in transplant recipients.

NATURAL KILLER CELL MEMORY

Evidence for NK cell memory existed as early as the 1960s, long before NK cells were first described in animal models of hybrid resistance studies [28]. The direct evidence of NK cell memory was reported in 2006 by von Andrian and colleagues in an animal model of contact hypersensitivity responses [29]. Since then, NK cell memory has been reported against a wide range of stimuli in mice, primates and humans [30–34,35,36▪]. As NK cells can respond to allografts through ‘missing self’ recognition [37], the clinical relevance of NK cell memory in transplant settings is currently under active investigation.

There are multiple situations where NK cells are known to acquire memory properties, and some of which have direct relevance to transplant rejection. Wayne Yokoyama and colleagues firstly described the cytokine-induced NK cell memory, where stimulation of mouse NK cells with IL-12, IL-15 and IL-18 in vitro produced NK cells with memory-like properties [31]. Such memory-like NK cells displayed enhanced IFN-γ production, but with no apparent increase in their cytolytic activities after re-challenge *ex vivo* [31]. Similar phenomenon was reported in human NK cells preactivated with IL-12, IL-15 and IL-18 [33]. Lanier and colleagues demonstrated that adoptive transfer of NK cells into syngeneic $Rag2^{-/-}$ IL-$2R\gamma^{-/-}$ mice that are deficient for T, B and NK cells resulted in long-lived NK cells, which were able to respond to viral infections vigorously, and capable of providing protections against viral re-challenge [38]. Recently, it has been shown that adoptive transfer of NK cells preactivated with IL-12, IL-15 and IL-18 into tumor-bearing mice produced potent antitumor effects [39], presumably by inducing memory-like NK cells [39]. Furthermore, a phase I study involving patients with relapsed or refractory acute myeloid leukemia showed that adoptive transfer of cytokine-induced memory NK cells induced sustained antileukemia responses [40]. In transplant settings, we reported that NK cells in $Rag^{-/-}$ mice (H-2b) readily reject the allogeneic DBA/2 cells (H-2d) via ‘missing self’ recognition, but the DBA/2 skin allograft survive long-term in the $Rag^{-/-}$ recipients [37]. However, pre-treatment of the $Rag^{-/-}$ recipients with an IL-15/IL-15Ra complex, which stimulates a marked expansion of NK cells *in vivo*, resulted in prompt rejection of the DBA/2 skin allografts. This rejection is solely mediated by NK cells, as the $Rag^{-/-}$ mice are deficient for T cells and B cells. Interestingly, NK cells activated by IL-15 also exhibited features of memory cells, as they expressed much higher levels of perforin, granzyme B, and IFN-g as compared with resting NK cells [41].

Certain viruses are powerful activators of NK cells and capable of inducing the formation of memory NK cells in both animal models and humans. In murine cytomegalovirus (MCMV)-infected mice, a subset of NK cells that express the Ly49H receptor, which recognizes the MCMV-encoded glycoprotein m157, has been shown to undergo activation and proliferation, followed by the generation of memory NK cells [30]. Upon re-infection with MCMV, the memory NK cells readily undergo a robust secondary expansion and rapidly releasing cytokines, thus providing potent protective immunity in the mouse [30]. Similar

features were observed in NK cells in response to other viruses, including herpes simplex virus 2 (HSV-2), vaccinia virus, influenza, vesicular stomatitis virus (VSV) [42–44]. In most cases, adoptive transfer of virus-sensitized NK cells into naive mice protected the mice from lethal challenges with the sensitizing virus, but not from challenges with a different virus [42].

Studies in primates and humans also showed the existence of memory NK cells. NK cells are shown to prevent disease progression in monkeys infected with simian immunodeficiency virus (SIV) [45,46]. Moreover, NK cells from Ad26-vaccinated monkeys efficiently lysed target cells 5 years after vaccination [34], suggesting that durable memory NK cells can be induced in primates. Similarly, in human studies, several labs reported that NK cells expressing the CD94/NKGC2 receptor vigorously expanded following human CMV (HCMV) infection and persisted for years [47,48]. The memory features of NK cells are also observed in the setting of hepatitis B virus (HBV), hepatitis C virus (HCV), chikungunya virus infections in patients [49,50]. Recently, Paust *et al.* reported using humanized mice and human volunteers that NK cells displayed vaccination-dependent, antigen-specific recall responses in vitro, and a large number of NK cells were recruited to sites of varicellazoster virus (VZV) challenge only in VZV-experienced human volunteers [36▪]. These NK-mediated recall responses in humans were long-lived and occurred decades after initial VZV exposure.

It should be noted that in both animal models and humans, memory T cells and memory B cells are potent barriers to the induction of allograft tolerance [51]. To what extent the memory NK cells promote graft rejection and prevent tolerance induction remains largely unknown, especially in humans, and certainly deserves some attention. In the clinic, viral infections are very common in transplant patients, mostly because of broad and prolonged immunosuppression [52], and it is conceivable that those patients must have an expanded pool of memory NK cells. Whether memory NK cells developed to viral infections exhibit features of heterologous immunity in transplant settings, where virus-induced memory NK cells could cross-react with transplant antigens, requires further investigation.

CONCLUSION

The adaptive feature of innate cells, especially those of NK cells and macrophages, are well documented in animal models, including models of transplant rejection, and the molecular basis for such adaptive features is also rapidly emerging. Moving forward, however, there remain significant challenges in the field. First, innate memory is very different from the classic adaptive memory, in that the innate memory is often transient, lacks definitive antigen specificity and mainly involves epigenetic and metabolic rewiring of cellular programs. To what extent those innate features contribute to the overall immune memory remains to be clarified. Whether innate memory represents a stable phenotype or a temporary state of cellular responses also warrants further studies. Second, despite compelling data from animal studies, features of innate memory in transplant patients in the clinic are understudied and clearly deserved more attentions. Finally, translational studies aimed at developing novel therapeutics targeting aspects of innate memory without

compromising the host protective immunity are critically important in moving the field forward, as well as in further improving transplant outcomes in the clinic.

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KEY POINTS

- Innate immune cells can acquire features of memory such that they respond more vigorously to secondary challenges.
- NK cells, monocytes and macrophages are known to respond and reject allografts via different mechanisms.
- Targeting aspects of myeloid cell memory can promote long-term graft survival in animal models.
- There are similarities and marked differences between innate and adaptive memory cells, and their relative contributions to tolerant resistance remain to be studied.
- The innate memory cells in transplant patients and their relevance to graft loss are largely unknown.