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Innate immune cells in transplantation

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Abstract

Purpose of review—This review examines the recent literature on the role of innate cells in immunity to transplanted tissue. It specifically addresses the impact of monocytes/macrophages, neutrophils, NK cells, and platelets.

Recent findings—Current research indicates that innate immunity plays a dual role in response to transplanted tissue with the ability to either facilitate rejection or promote tolerance. Intriguingly, some of these cells are even capable of reacting to allogeneic cells, a feature usually only attributed to cells of the adaptive immune system.

Summary—This review highlights new therapeutic targets in the innate immune system that may be useful in the treatment of transplant recipients. It also emphasizes the need to use caution in exploring these new therapeutics.

Keywords

innate cells; transplantation; rejection; tolerance

Introduction

In 2012, more than 28,000 transplants were performed in the United States from living and deceased donors [1]. Five-year survival rates range from 38% (for intestinal and heart/lung transplants) to over 70% (for kidney and kidney/pancreas transplants). Much research has been dedicated to examining adaptive immune responses in transplant rejection. However, the innate immune system cannot be ignored and may hold within it targets to prolong graft survival. The innate immune system is a first line of defense against pathogens and in response to sterile injury. It consists of several cell types including monocytes, macrophages, neutrophils, NK cells, platelets, NKT cells and $\gamma\delta$ cells. Innate cells recognize broadly-expressed molecules derived from pathogens or apoptotic cells. They can have both pro- and anti-inflammatory effects on their own, but also play an important role in priming adaptive immune responses. We will discuss various ways in which monocytes, macrophages, neutrophils, NK cells and platelets influence organ transplantation.

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Monocytes and Macrophages

Monocytes are circulating phagocytic cells that give rise to tissue-resident dendritic cells (DCs) or macrophages. Macrophages can modulate the adaptive immune response with either pro- or anti-inflammatory effects [2].

Monocytes in graft function

In renal transplantation, graft survival has been shown to be associated with infiltration of monocytes. Increased presence of these cells or their macrophage counterparts within glomeruli, but not in peritubular capillaries or the interstitium is associated with decreased graft survival. One-year graft survival was 55.8% when higher numbers of monocytes were present in the glomerulus, but survival was as high as 90% with lower numbers of these cells [3]. Similar findings have been shown for pediatric patients following intestinal transplantation. In an attempt to find markers that could predict intestinal transplant rejection, Ashokkumar investigated sialoadhesin expression on infiltrating monocytes [4]. This immunoglobulin-like lectin is a marker of activation for these cells and is induced in response to IFN- α . More than 99% of monocytes in the blood of patients experiencing rejection expressed this molecule while only 12% expressed the same molecule in non-rejecting patients. To this end, it has been suggested that detection of sialoadhesin prior to transplantation and early after engraftment could be used to predict rejection [4].

In vitro studies have suggested that recruitment of monocytes into grafted tissue is dependent on recipient antibodies binding to endothelial-expressed donor HLA I molecules. This interaction caused increased expression of the adhesion molecule P-selectin. Recruitment of monocytes into the graft was further facilitated by monocyte Fc γ R binding to the HLA-antibody complex leading to enhanced expression of P-selectin. These two interactions facilitated monocyte firm adhesion to ICAM-1 [5]. These results were confirmed in vivo where transplantation of allogeneic hearts with anti-HLA-1 antibodies increased macrophage infiltration into the graft at 30 days. This effect was diminished if a P-selectin antagonist was administered [6].

Much effort has been put forth to determine mechanisms by which monocytes contribute to graft rejection. Co-culture experiments using peripheral blood mononuclear cells and human aortic endothelial cells have shown an increase in the chemoattractant molecule CXCL-10 in response to TNF- α stimulation. Expression of this molecule was minimal when either monocytes or endothelial cells were cultured alone, but increased dramatically when the two populations were cultured together [7]. These results provide a possible mechanism by which monocytes influence recruitment of T cells and other inflammatory cells to grafted tissue leading to rejection.

Detrimental effects of macrophages following transplant

Infiltration of monocyte-derived macrophages is associated with acute cellular rejection (ACR) in pediatric intestinal transplants. At time points immediately following reperfusion, early after transplant and late after transplant, patients who later undergo ACR had much higher infiltration of macrophages compared to patients, who did not experience rejection.

Importantly, these monocyte-derived macrophages also expressed high amounts of CCL-5, a T cell chemoattractant, [8]. Intravascular macrophages also correlate with antibody-mediated rejection in heart transplant recipients within the first year of surgery [9]. These two studies indicate a mechanism by which innate and adaptive immune responses interface in the rejection of allografts.

Evidence has recently emerged that monocytes and macrophages have the ability to generate an immune response to allogeneic cells on their own, a function generally attributed only to cells of the adaptive immune system. Zecher demonstrated that monocytes could mount immune responses to allogeneic splenocytes in RAG^{-/-} mice, which lack T and B cells, and were able to elicit recall responses four weeks later [10]. Adoptive transfer of monocytes from alloimmunized RAG^{-/-} was able to transfer immunity to naïve RAG^{-/-} mice. Alloimmunity was shown to be independent of MHC molecules, major determinants of T cell-mediated transplant rejection. Further proof of macrophages rejecting allogeneic cells was provided by Liu, who showed that macrophages require priming by encounter with antigen and interaction with CD4⁺ T cells to kill allogeneic cells during a second encounter [11]. CD40-CD40L interactions between CD4⁺ T cells and macrophages were required and the allogeneic cells were eliminated through phagocytosis. This study also showed that primed macrophages are a potential treatment for graft-versus-host disease (GVHD). Mice receiving allogeneic T cells with primed macrophages had improved survival compared to those only receiving allogeneic T cells indicating that macrophages were able to eliminate cells responsible for causing GVHD.

In the above studies, Zecher showed an MHC-independent role of monocytes/macrophages in alloimmunity while Liu demonstrated some specificity of macrophage alloimmunity based on which H-2 molecule was used in priming. Receptors have been found that are specific for H-2 molecules [12,13]. These macrophage MHC receptors (MMR) are important in the rejection of allogeneic skin grafts, but not lymphoma cells. Mice lacking MMR2 did not reject H-2K^d skin grafts, but were able to reject grafts from mice expressing H-2I^d. These results showed specificity of MMR2 for H-2K^d. Indeed, a separate receptor, MMR1 is specific for H-2D^d [14].

Lung recipients have a median 5-year survival of only 57.5%, which is in large part due to the development of bronchiolitis obliterans characterized by fibrosis of the small airways [15]. In this process, TGFβ is critical in inducing fibroblast proliferation and causing epithelial to mesenchymal transition [16]. Borthwick investigated the role that macrophages could play in this process. Alveolar macrophages from the bronchoalveolar lavage fluid of lung recipients were induced to become either classically activated (CAM) or alternatively activated macrophages (AAM) and then stimulated with *Pseudomonas aeruginosa*. CAM responded by producing more TNF-α and IL-8 than AAM. TNF-α, but not IL-8 or IL-1β enhanced the pro-fibrotic effects of TGF-β suggesting that CAM may exacerbate bronchiolitis obliterans. A small proof-of-concept study involving treatment of patients exhibiting progressive bronchiolitis obliterans syndrome with a monoclonal antibody targeting TNF-α was encouraging. Lung function improved in four out of five patients after four weeks of treatment [17].

Beneficial role of macrophages in transplantation

Macrophages can play a protective role in allograft survival as they can be induced to have a regulatory (M reg) phenotype in response to IFN- γ . These M regs can suppress allostimulation of T cells through the production of iNOS, which decreases IL-2 and IFN- γ production and inhibits proliferation. M regs also eliminate allogeneic T cells directly through phagocytosis and *ex vivo*-generated M regs can significantly extend the survival of cardiac allografts [18].

A separate subset of regulatory myeloid cells also functions through production of iNOS. These cells termed myeloid-derived suppressor cells (MDSC) are distinct from the above-mentioned M regs and are identified as CD11b⁺Gr1⁺ cells. Wu showed that TGF- β was important in the regulation of MDSC suppressive effects. Surprisingly, the presence of TGF- β and the downstream signaling molecule Smad3 (normally associated with anti-inflammatory effects) decreased the production of iNOS and therefore counteracted the suppressive effects of MDSC on alloreactive T cells. Following skin transplantation, Smad3-deficient mice had a survival advantage compared to wildtype mice [19].

Kupffer cells, liver-resident macrophages, have been suggested to contribute to tolerance induction. In the rat, distinct combinations of donor-recipient strains result in either tolerance or rejection of liver allografts. Luan has shown that Kupffer cells from tolerant combinations have increased expression of indoleamine 2,3-dioxygenase (IDO) compared to cells isolated from rejecting combinations [20]. IDO is important in the degradation of tryptophan leading to the depletion of a key molecule necessary for efficient T cell proliferation [21]. Kupffer cell production of IDO may therefore regulate allogeneic T cell responsiveness.

Macrophages are also important in wound healing and this holds true in the case of transplantation as well. Following corneal transplantation, clodronate depletion of macrophages reduces neovascularization and leads to irregular extracellular matrix alignment and detachment of donor corneas [22]. This study highlights the negative impact of eliminating all macrophages following transplantation and points to the need to target specific subsets or molecules involved in rejection.

Neutrophils

Neutrophils are bone marrow-derived cells, which mediate early immune responses to infection. These cells also play a role in transplant-mediated ischemia-reperfusion injury (IRI). Intravital two-photon microscopy has shown that neutrophils accumulate in large numbers in cardiac and pulmonary grafts within a few hours of reperfusion [23,24]. Notably, monocytes regulate transendothelial migration of neutrophils into lung grafts and may provide chemotactic cues to them in the graft tissue following extravasation. Zhu has recently provided some insight how neutrophils are recruited into cardiac grafts. High-mobility group box 1 (presumably released from apoptotic cardiomyocytes) stimulated macrophages in a TLR4-dependent manner to produce IL-23. This cytokine stimulated $\gamma\delta$ T cells to produce IL-17, leading to the production of the neutrophil chemoattractants KC,

MIP-2 and LIX. Each component of this pathway was required for efficient recruitment of neutrophils and maximal tissue damage [25].

Most studies have shown that neutrophilic infiltration has a deleterious effect on graft survival. Heart allografts survive longer when recipients lack expression of CXCR2, a receptor for neutrophil chemokines. The decrease in neutrophil recruitment to the graft delayed T cell infiltration potentially due to decreased expression of pro-inflammatory chemokines and cytokines including TNF- α , IL-6, and IFN- γ . Furthermore, neutrophil depletion or inhibition of neutrophil chemotactic pathways synergizes with costimulatory blockade in prolonging the survival of cardiac allografts [26]. One group, after finding that CXCR2-deficient mice reach euglycemia following pancreatic islet transplant more rapidly and consistently compared to wildtype mice, endeavored to treat human islet transplant recipients with the CXCR1/2 inhibitor reparixin. In contrast to untreated controls, patients receiving this drug had improved transplant outcomes with glycemic control and decreased insulin requirement [27]. Using two-photon microscopy our group observed that neutrophils interact with donor DC's within lung allografts shortly after transplantation. TNF- α production by neutrophils stimulated DCs to produce IL-12, which skewed T cell differentiation towards T_H1 and triggered graft rejection [28]. Neutrophils recruited to murine pulmonary allografts in response to respiratory infection with *Pseudomonas aeruginosa* express B7 and provide costimulation in trans to alloreactive CD4⁺ T cells thereby enhancing alloimmune responses [29]. In a study of lung transplant recipients, increased neutrophilia was associated with the presence of donor-specific antibodies which correlated inversely with allograft survival [30].

While neutrophils are generally associated with poor outcomes following transplantation, Christoffersson has characterized an important role of a subset of these cells in the vascularization of transplanted hypoxic tissue. CD11b⁺Gr-1⁺CXCR4^{hi} cells were recruited to transplanted pancreatic islets in response to VEGF-A. These cells had a phenotype distinct from neutrophils recruited by the inflammatory chemokine MIP-2, expressing far higher levels of MMP-9, a matrix metalloproteinase responsible for degrading components of the extracellular matrix. This unique neutrophil subset through expression of MMP-9 was required for optimal revascularization of transplanted islets [31].

Natural Killer Cells

Natural Killer (NK) cells, known for their capacity to kill virally-infected cells and tumor cells, are able to both downregulate alloimmune responses and promote graft rejection [32]. Tolerance to islet allografts, mediated through treatment with either anti-CD154 or anti-LFA-1, was found to be dependent on the presence of NK cells [33]. NK cells mediated the tolerogenic effects in these models in perforin-dependent fashion. Yu demonstrated that NK cells promote immunosuppression-mediated long term survival of skin allografts through elimination of donor passenger leukocytes [34]. Jungraithmayr recently extended these findings and observed that IL-15-stimulated NK cells eliminate donor DCs through perforin-dependent mechanisms in a lung transplant model. Killing these DCs abrogated the downstream activation of allogeneic T cells and therefore attenuated allograft rejection [35]. In lymphopenic hosts NK cells attenuate homeostatic proliferation of memory CD8⁺ T cells

by competing for IL-15 [36]. Under these circumstances NK cell depletion can result in accelerated allograft rejection. IL-15, however, was shown in earlier studies to be responsible for activating NK cells, which mediated rejection of skin allografts. Of note, this observation was made in a RAG^{-/-} host, in which T and B cells were not present [37].

In a model where allogeneic splenocytes were injected into naive hosts, NK cells killed transplanted cells in a perforin-dependent manner presumably due to “missing self” recognition [11]. There also exists evidence that different NK cell subsets are important in rejection of bone marrow allografts. Those expressing Ly49 bind self-MHC and if those MHC molecules are not present, NK cells will eliminate them [38]. This provides evidence for functional education of NK cells whereby they are “licensed” during development to be tolerant to cells with specific MHC I molecules. In the absence of these MHC molecules, cells are considered foreign and therefore are eliminated. Transplanting parental hearts into F1 mice results in development of chronic allograft vasculopathy, which is dependent on NK cells and recipient IFN- γ [39]. Donor-specific antibodies lead to chronic allograft vasculopathy in a NK cell-dependent manner. This mechanism of rejection is dependent on the Fc portion of antibodies, but is independent of complement [40].

Platelets

Platelets are cells small in size, but large in number that are efficient at binding to the endothelium. Their location along the vasculature allows for platelet interaction with various cell types recruited to transplanted organs. In a skin transplant model, Swaim and colleagues recently demonstrated that these cells are able to exacerbate tissue rejection through amplification of T cell recruitment and release of inflammatory mediators. Depletion of these cells resulted in prolongation of graft survival and was associated with decreased plasma levels of TNF- α and IFN- γ . T cell recruitment was thought to be amplified due to glutamate receptor signaling on platelets stimulating the production of thromboxane [41].

Interactions between platelets and T cells have been observed in bone marrow transplant models as well where transfusion of platelets increases the risk of rejection of allogeneic bone marrow inoculums [42]. Platelet transfusion primed alloimmunity in a CD4⁺- and CD8⁺-dependent manner although only CD8⁺ T cells were responsible for rejection. Minor histocompatibility mismatches on the platelets were necessary for priming the rejection event.

Conclusions

This review has highlighted the complex role of innate cells in transplant rejection. Macrophages, neutrophils, and NK cells are all capable of both prolonging allograft survival and hindering it (Table 1). Often, unique subsets of these cells or the microenvironment in which they are activated are the determining factors in their impact on transplant outcomes. Therefore, attempts at targeting innate immune cells will need to have specificity for uniquely pro-inflammatory molecules or cell subsets. An exciting alternative in the treatment of transplant recipients might also be in stimulating innate cell subsets capable of promoting allograft tolerance.

Acknowledgments

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Key Points

- The role of innate cells in transplantation is underappreciated.
- Monocytes/macrophages, neutrophils, and NK cells all have the ability to promote tolerance or facilitate rejection.
- Innate immune cells are capable of influencing the adaptive immune system.

Table 1

Effects of Innate Immune Cells on Transplant Outcome

Cell Type	Mechanisms promoting tolerance or protection	Mechanisms facilitating rejection
Monocytes/ Macrophages	Kill allogeneic T cells by phagocytosis ¹⁸ Regulate allogeneic T cells through IDO ²⁰ Promote wound healing after transplant ²²	Kill transplanted cells by phagocytosis ¹¹ Enhance adaptive immunity ^{8,9} MHC receptor mediated rejection ^{12,13,14} Enhance fibrosis ¹⁷
Neutrophils	CXCR4 ^{hi} subset necessary for revascularization ³¹	Enhance adaptive immunity ^{25, 25} Decrease recovery of smooth muscle cells ²⁷ Presence associated with donor-specific antibodies ²⁸
NK Cells	Kill DCs to prevent downstream activation of allogeneic T cells ^{34,35}	Kill transplanted cells with perforin due to missing self ^{11,36,37}
Platelets		Enhance adaptive immunity through recruitment ³⁹ and priming ⁴⁰ of T cells