

The Role of Mast Cells After Solid Organ Transplantation

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Mast cells are best known as primary responders in allergic reactions, including anaphylaxis and asthma. However, recent studies have shown that mast cells are functionally diverse cells with immunoregulatory properties that influence both the innate and adaptive immunities. Mast cells are capable of producing an array of both proinflammatory and anti-inflammatory mediators, acting as antigen-presenting cells, and expressing a spectrum of costimulatory molecules. Moreover, mast cells seem to confer a certain degree of immune privilege to tissues in concert with T-regulatory cells and are essential players in fibrotic conditions. The following review of the literature serves to further define the role of mast cells in the immunologic reactions affecting transplanted solid organ grafts.

Keywords: Mast cells, Organ rejection, Allograft tolerance, Fibrosis.

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Recent evidence has shown that the function of mast cells reaches far beyond their historical role as primary responders in allergic reactions such as anaphylaxis and asthma (1). In fact, mast cells can be implicated in a number of pathologic clinical conditions and are responsible for a variety of diseases that may occur in every organ system.

Mast cells orchestrate important immune attacks against invading bacteria and viruses and have been shown to neutralize toxins from snakebites and bee stings (2–5). These cells usually reside at the host-environment interface (e.g., the skin, mucous membranes, so forth), where they are a part of the innate immune system with a critical role in fighting infections. Mast cells elicit the first and fastest immune response after antigen recognition through Toll-like receptors and rapidly release cytokines (presynthesized and stored tumor necrosis factor [TNF]- α , tryptase, histamine), which causes inflammation and chemotaxis of other immune cells (e.g., neutrophils) (2, 3). Along with their ability to ingest and kill opsonized pathogens, mast cells also facilitate early bacterial clearance and, therefore, are essential in the initiation of the innate immune response (6–10).

Results of recent studies have also shown that mast cells can modulate the adaptive immune system through rapid release of TNF- α , leading to subsequent T-cell sequestration in the lymph nodes (11) and promoting encounters between antigen-presenting cells (dendritic cells) and T cells (CD4⁺ T-helper cells) (11, 12). Moreover, mast cells process and present antigen to T cells through class I and class II major histocompatibility routes. Antigen processing is hereby comparable in efficiency to that seen with highly activated macrophages (13, 14).

Because mast cells are capable of initiating and regulating all aspects of the immune system, the question arises whether they also play a role during the immune responses that are elicited with transplanted allografts. Other investigators have noted the presence and increased number of mast cells after solid organ transplantation and have attempted to correlate these findings with episodes of acute and chronic rejection. However, not until Lu et al. (15) implicated mast cells in immunologic tolerance through amplification of regulatory T (Treg) cell function did a distinct role of mast cells after organ transplantation become clear.

This review summarizes what is in the medical literature about mast cells after organ transplantation and aims to further elucidate their role during acute and chronic allograft rejection.

Mast Cells and Their Mediators

Mast cells arise from CD34⁺CD13⁺c-kit⁺ hematopoietic progenitor cells and migrate into peripheral tissues, where they complete their maturation. Interestingly, they share an immunophenotypic homology with a population of monocytes that also originate from the same progenitors (16).

Mast cells are a heterogeneous group of cells, and their phenotypic characteristics can change in response to alter-

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ations in their microenvironment (17, 18). In humans, for example, there exist two populations of mast cells, which are defined by the presence of certain proteases in their secretory granules: those with protease tryptase (MC_T) constitute the mast cell population at large and those with tryptase and chymase (MC_{TC}), the subpopulation (19, 20).

Mast cells produce both proinflammatory and anti-inflammatory mediators, growth factors and express costimulatory molecules (17). The variety of cytokines and mediators include IL-1 to 6, IL-8, IL-10, IL-13, IL-16, interferon- γ , basic fibroblast growth factor (bFGF), TNF- α , transforming growth factor (TGF)- β , stem cell factor (SCF), nerve growth factor, platelet-derived growth factor, vascular endothelial growth factor, granulocyte-macrophage colony stimulating factor, P-selectin, serotonin, histamine, heparin, and prostaglandins. Tryptase, chymase, cathepsin G, and carboxypeptidase A represent the major proteases that are stored in mast cells (17, 21–26).

Mast cells are distributed throughout the connective tissues, adjacent to blood or lymphatic vessels, and near or within peripheral nerves. Mast cell-fibroblast interactions are known to be important in the structure and function of these connective tissues; in fact, fibroblasts have been shown to take up mast cell granules, thereby altering the fibroblast metabolism (27, 28). Different mast cell-derived mediators, including histamine, chymase, cathepsin G, and TGF- β , have been implicated in the activation of fibroblasts and collagen production. We believe this mechanism of mast cell-mediated fibroblast activation may also contribute to an increased incidence of allograft fibrosis and chronic allograft failure.

Acute Rejection

Others have investigated the involvement of mast cells during acute allograft rejection in various organ systems. One of the first studies, in 1974 by Colvin and Dvorak (29), histologically examined 26 biopsy specimens obtained at various intervals from the renal allografts of 23 patients. Although an association between mast cells and acute rejection was not found, the authors did note a 10-fold increase in the number of mast cells 5 months to 5 years after transplantation. The mast cells were present in the cortical interstitium and renal tubules, external to their basement membrane, and around the small vessels. Results of another report from 1989 showed an increased density of mast cell aggregation in edematous regions of the submucosa of ureters from irreversibly rejected kidney allografts (30). The mast cells were especially abundant in the perivascular region, and toluidine blue staining showed that they were partly degranulated.

In a study of 96 endomyocardial biopsies from 11 patients after orthotopic heart transplantation, Li et al. (31) observed an infiltration of mast cells during the first week after transplantation. Patients with increased numbers of mast cells also had the most severe rejection episodes. Based on these results, the authors suggested that mast cells play an important role in promoting and sustaining the inflammatory response during episodes of acute rejection.

In a study by Lajoie et al. (32), 28 kidney biopsy specimens were stained with tryptase antibody. Positive correlations were found between the number of mast cells and the time after kidney transplantation and the number of mast cells and the severity of interstitial fibrosis and edema (32).

TABLE 1. Correlative studies evaluating the implication of MCs in allograft rejection

	Acute rejection	Chronic rejection
Heart		
Li et al. (31<)	↑	↑
Koskinen et al. (36<)	↔	↑
Zweifel et al. (49<)	↑	∅
Lung		
Minami et al. (35<)	↓	∅
Yousem (33<)	↑	↑
Liver		
O'Keefe et al. (37<)	↔	↑
El-Refaie et al. (34<)	↑	↑
Kidney		
Greenstein et al. (30<)	↑	∅
Lajoie et al. (32<)	↑	∅
Pardo et al. (42<)	∅	↑
Roberts and Brenchley (43<)	∅	↑
Yamada et al. (50<)	∅	↑
Ishida et al. (51<)	∅	↑
Intestine		
Walgenbach et al. (41<)	∅	↑

↑, increase of MCs; ↔, no change; ↓, decrease of MCs; ∅, not investigated.

The density of mast cells was increased in patients with moderate or severe acute rejection compared with patients who had only mild or no rejection. The authors concluded that mast cells may play a role in acute rejection of renal allografts and in the development of interstitial fibrosis.

Yousem (33) investigated whether mast cells are involved in acute rejection of human lung allografts. The transbronchial biopsy specimens of 29 patients with acute rejection were stained using tryptase antibody. It was found that higher grades of acute rejection were also accompanied by an increased number of mast cells, particularly around the airways and small vessels. Moreover, there was a statistically significant difference in the average number of mast cells noted in patients with mild, moderate, or severe acute rejection. In liver transplant recipients, El-Refaie and Burt (34) also noted a significant increase in mast cell density during episodes of acute moderate and acute severe cellular rejection.

Although the results of these studies showed a positive correlation between the number of mast cells and the severity of acute rejection, other studies have provided different results (Table 1). Minami et al. (35) studied histamine release from pulmonary mast cells after orthotopic lung transplantation in rats and found no significant increase in mast cells and no significant correlation with rejection. Although histamine levels correlated with the number of mast cells, there was a decrease in the number of mast cells in the lung allografts of rats during acute rejection when compared with syngeneic grafts or to control grafts (the left lung of control animals that did not undergo operation). Two other studies investigating the possible involvement of mast cells during episodes of acute rejection—one in the cardiac allografts of rats and the other after liver trans-

plantation in humans—also did not find a significant, positive correlation (36, 37).

Although the results of the aforementioned studies clearly identify the presence of mast cells in organ grafts after transplantation, the exact role of mast cells during episodes of acute rejection was still unclear. Recent evidence, however, has done much to clarify our understanding about mast cells and graft rejection (15). These novel findings have implicated mast cells in regulatory T cell function. In brief, specialized T cells (Treg cells) regulate immune cells and prevent them from attacking healthy tissues. This mechanism of peripheral tolerance can be exploited to induce immune tolerance and prevent the rejection of transplanted organs. Lu et al. (15) groundbreaking findings of mast cell dependent Treg function built on the observation that mast cell-related genes (e.g., mouse alpha-chymase, carboxypeptidase A3, tryptophan hydroxylase, and high affinity IgE receptor) were overexpressed in tolerant allografts and that tolerant grafts were always infiltrated with Treg and mast cells (38). Moreover, IL-9 is secreted by Treg cells, enhancing mast cell growth and chemotaxis and suggesting that Treg and mast cells form a functional unit that mediates graft tolerance (39). Lu et al. (15) also demonstrated that immune tolerance to allogeneic skin transplants could not be achieved in genetically engineered mast cell-deficient mice. However, after injection of mast cell-enriched cell cultures (adoptive transfer), immune tolerance did ensue. In addition, it was noted that neutralization of IL-9 prevented the regulation of graft rejection by Treg cells, emphasizing the importance of the interaction among Treg cells, IL-9, and mast cells.

Another recent study supports the findings of Lu et al. In a heterotopic heart transplant model of mast cell-deficient and mast cell-competent rats with cyclosporine immunosuppression, Boerma et al. (40) demonstrated that donor heart survival was significantly reduced in the mast cell-deficient rats. Acute rejection was more severe in the mast cell-deficient rats, and, interestingly, more T-lymphocytes were found in the transplanted hearts of mast cell-competent rats than in the hearts of mast cell-deficient rats. This observation was associated with a significantly increased extracellular matrix associated TGF- β immunoreactivity in the mast cell-competent rats. Based on these results, the authors concluded that mast cells play a protective role, both after cardiac transplantation and during episodes of acute rejection.

The two latter-mentioned investigations were the first functional studies to assess the role of mast cells during solid-organ rejection. The results of both studies demonstrate the protective role of mast cells during acute organ rejection, thereby contradicting the results of previous studies that seemed to implicate mast cells in rejection episodes simply because of their presence in the rejected tissue. Although the exact mechanisms of this protective mast cell-related effect and of the mast cell-assisted Treg function remain obscure, it has now become quite evident that mast cells are crucial for achieving a state of decreased immune alloreactivity or even peripheral immune tolerance.

Chronic Rejection and Allograft Fibrosis

Despite the seemingly protective effects of mast cells during acute allograft rejection, their long-term effects and contributions to the progression of chronic allograft failure

seem to be detrimental. Previous studies have shown that different mast cell mediators are capable of inducing fibrosis through various mechanisms and pathways. These mediators range from histamine, bFGF, and TGF- β to proteases such as chymase and cathepsin G, which can activate latent forms of TGF- β or increase angiotensin II levels through tissue conversion of angiotensin I. Therefore, all the pathways are profibrotic, because of their ability to activate fibroblasts and induce collagen synthesis. Thus, the studies that have evaluated the relationship between mast cells and chronic rejection consistently provide evidence of the cells' adverse effects on allograft fibrosis and long-term graft function.

Li et al. (31) have assessed the involvement of mast cells in chronic rejection and noted that the presence of larger numbers of mast cells was associated with an increased incidence of allograft fibrosis. Activated mast cells and their mediators (heparin and histamine) seemed to lead to tissue fibrosis through the stimulation of fibroblasts and the increased synthesis of collagen. The investigators noted that fibrosis developed quickly in the tissue samples with increased mast cell activity.

In another study, the presence of mast cells and chronic rejection were evaluated in the intestinal (small bowel) allografts of rats, wherein the structure and function of the muscularis and enteric nervous system are altered (41). Chronic rejection resulted in significant up-regulation of the number of mast cells in the serosa, muscularis, and mucosa. In addition to the increase in the number of mast cells, there was also an increase in IL-4 mRNA positive cells. Because IL-4 is produced by mast cells, the authors hypothesized that this is a possible mechanism for IL-4 and histamine-related fibroblast activation, which may, in turn, lead to fibrosis of the intestinal wall during chronic rejection.

Yousem (33) investigated the involvement of mast cells in chronic lung rejection and found that chronic rejection was accompanied by a far greater number of mast cells than were present in acute rejection. Mast cell hyperplasia occurred more often in the walls of the large and small airways and at sites of mural and luminal fibrosis. The authors therefore hypothesized that mast cells play an important role in the development of bronchiolitis obliterans because of their location and their release of bFGF and histamine (a fibroblast mitogen).

The potential relationship between mast cells and fibrosis in chronic renal rejection in humans was investigated in another study (42). Thirty kidneys from patients with chronic rejection were compared with 10 normally functioning kidneys from control patients. The number of mast cells was significantly higher in the cortex and medulla of the kidneys of patients with chronic rejection, and there was a positive correlation between the number of mast cells and the extent of fibrosis and tubular atrophy. Roberts and Brenchley (43) suggest that an increased number of mast cells is a consistent feature of renal fibrosis, whatever the underlying pathology, and that the number of mast cells correlates with the extent of the interstitial fibrosis.

Although Koskinen et al. (36) did not find a correlation between acute cardiac rejection in rats and an increase in mast cell numbers, the localization pattern of the cells during acute rejection changed from an interstitial to a predominantly perivascular accumulation. This observation is important because changes in the heart, which lead to a form of chronic

rejection, manifest mainly in and around the vessels (allograft vasculopathy). Therefore, episodes of acute rejection may promote the progression of chronic rejection as previously described in other organs (44). During the progressive process of chronic rejection, cardiac allografts with severe intimal thickening also had higher numbers of mast cells at perivascular and interstitial sites around the occluded intramyocardial vessels. Thus, there was a significant correlation between mast cells and the extent of intimal thickening. Most of these mast cells also expressed fibroblast growth factors, which has been previously shown to correlate with the development of allograft vasculopathy after cardiac transplantation (45).

Because of the resemblance between cholestatic liver disease and chronic liver allograft rejection and the known adverse effects of mast cells in cholestatic liver disease, hepatic fibrogenesis, and primary biliary cirrhosis, others have investigated possible mast cell involvement in the evolution of chronic liver rejection (34, 37, 46, 47). In chronic rejection, mast cells frequently surrounded damaged bile ducts and inflamed portal tracts, with their density being greatest around the bile ducts and in the portal tracts that were manifesting the early signs of biliary damage.

Although the aforementioned evidence seems to implicate mast cells as a cause of chronic graft rejection (Table 1), these data must be cautiously considered because they are observational, and the process of chronic graft rejection is still poorly understood. However, the results of the studies cited earlier do seem to support the notion that mast cells have some possible role in the progression of chronic allograft failure.

Mast Cell Distribution and Phenotype

The examination of phenotypic and quantitative changes in mast cells 1 month after syngeneic unilateral lung transplantation in rats showed an increase in mast cell proteases (RMCP-I and RMCP-II) and in histamine levels in the left transplanted versus the contralateral recipient lung. There was also a significant difference between the transplanted left lung of rats in the transplant group and those of the controls (48). These results demonstrate that the effects of lung transplantation on mast cell populations are localized to the transplanted lung and are not part of a more generalized systemic response.

Zweifel et al. (49) describe an increase in mast cell numbers with a change in mast cell phenotype during ongoing acute rejection after heterotopic heart transplantation in rats. The change in phenotype was associated with increased expression of SCF and IL-3, both of which are known to be responsible for mast cell chemotaxis, growth, and differentiation. Resident cardiac donor mast cells significantly decreased in number during acute rejection, and recipient mast cells invaded the cardiac allograft. The investigators also noted a phenotypic switch of the recipient mast cells at the transcriptional and translational levels (49).

Changes in mast cell phenotype after organ transplantation have been confirmed by the results of two other studies (50, 51). Yamada et al. (50) evaluated the different mast cell phenotypes involved in the progression of renal allograft rejection in 18 allografts to see if they correlated with the severity of interstitial fibrosis. All of the rejected kidneys contained abundant mast cells scattered throughout the thickened interstitium, and there was massive infiltration of macrophages

and T-lymphocytes. The investigators also noted a significant increase in the expression of IL-4 in the mast cells and T-lymphocytes during rejection, especially in tryptase- and chymase-positive mast cells (MC_{TC}). The increased mast cell population in the rejected kidneys closely correlated with the severity of interstitial fibrosis.

Ishida et al. (51) evaluated whether mast cell phenotypes could be predictive of long-term renal graft function in humans. They found that tryptase-positive chymase-negative mast cells (MC_T) were the predominant phenotype in normally functioning kidneys and organ grafts before transplantation. After transplantation, however, MC_{TC} were the predominant subtype in grafts at 100 days. In addition, the number of mast cells present correlated with decreased creatinine clearance, increased fibrosis, and worsened graft function.

The findings of Ishida et al. demonstrate that the mast cell phenotype in kidney allografts is composed of mainly mast cells with profibrotic mediators (e.g., chymase and cathepsin G) and that mast cell numbers correlate with allograft fibrosis and impaired kidney function. These findings provide further evidence of the possible adverse role of mast cells during chronic allograft rejection and allograft fibrosis.

Immunosuppressive Therapy

In studying the role of mast cells during allograft rejection, two separate groups noted that mast cell numbers decreased as immunosuppressive therapy was modified or strengthened (36, 41). Walgenbach et al. found (41) that mast cell numbers were significantly decreased after rescue treatment with tacrolimus. Moreover, Koskinen et al. (36) found that along with increased immunosuppressive therapy and decreased intra-graft mast cell numbers, the production of mast cell mediators such as bFGF and TNF- α also gradually decreased.

The exact mechanism for this immune-pharmacologic inhibition of mast cells is unknown, but there are two possibilities: (1) that immunosuppressive therapy directly inhibits mast cell maturation and function or (2) that it indirectly inhibits regulatory signals. It is also possible that a combination of both mechanisms is responsible for the inhibition of mast cells with immunosuppressive therapy.

One possible indirect mechanism for decreased mast cell activation may be related to the inhibition of Treg cells associated with the use of immunosuppressive therapy (e.g., calcineurin inhibitors), subsequently resulting in a decrease of stimulatory mediators that are important for mast cell activation and chemotaxis. Further studies are needed to elucidate the exact underlying mechanisms.

Indirect Immunoregulatory Effects

Findings by Lu et al. (15) have provided substantial evidence for the role of mast cells in Treg-mediated immunoregulatory activities. These investigators were also able to identify IL-9 as a potential important mediator. IL-9 is produced by Treg cells and seems to be responsible for mast cell recruitment and function. Accordingly, anti-IL-9 treatment decreases intra-graft mast cell numbers and facilitates graft rejection.

However, Lu et al. did not identify the possible mast cell-derived mediators that may be responsible for the activation of Treg cells and the decreased immune alloreactivity.

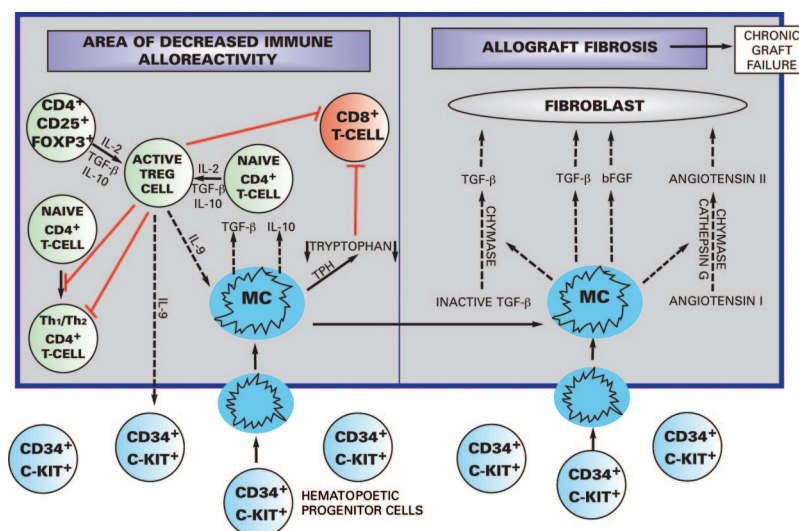


FIGURE 1. Hypothetical model based on current knowledge. Treg suppressive activity is IL-2 dependent; increased amounts of IL-2 result from immune activation, which fuels the initial expansion of natural Treg cells ($CD4^+CD25^+Foxp3^+$). Activated natural Treg cells produce IL-9, which locally recruits mast cells (MC) through chemotaxis of their hematopoietic progenitors ($CD34^+CD13^+c-kit^+$ stem cells) and subsequent IL-9-driven mast cell migration, growth, and activation. Activated mast cells secrete TGF- β and IL-10, further amplifying activation of natural Treg cells and inducing de novo differentiation and activation of inducible Treg cells from naïve $CD4^+CD25^-$ T-cells. Activated Treg cells inhibit $CD8^+$ effector T-cell function and differentiation of Th1 and Th2 $CD4^+$ T-helper cells from their naïve progenitors and suppresses Th1 and Th2 cells directly. Increased catabolism of tryptophan and subsequent decreased tissue tryptophan levels, through mast cell-derived tryptophan hydroxylase (TPH), directly suppress $CD8^+$ effector T-cell function. Mast cell-derived bFGF and TGF- β activate fibroblasts. Secretion of mast cell-derived chymase and cathepsin G locally converts angiotensin I to angiotensin II and activates latent forms of TGF- β , thereby promoting collagen synthesis by fibroblasts and subsequent allograft fibrosis and long-term graft failure.

Because mast cells host a variety of cytokines with diverse regulatory functions, they are also an important source of TGF- β , with its potent immunosuppressive properties. It has been shown that along with IL-2, TGF- β is required for the activation of natural Treg cells ($CD4^+CD25^+FOXP3^+$) and for the activation and differentiation of naïve $CD4^+$ cells ($CD4^+CD25^-$) into Treg cells (Fig. 1) (52–56).

Another recent study has provided evidence for the presence of mast cell-derived IL-10 and its important anti-inflammatory functions (25). IL-10 has been implicated in the suppression of inflammatory bowel disease through Treg cell activation (55, 57–60). Therefore, mast cell-derived TGF- β and IL-10 may also serve as important mediators for Treg activation in allografts (Fig. 1). A potential indicator of the presence of mast cell-derived TGF- β after transplantation is the increased extracellular matrix-associated TGF- β immunoreactivity in mast cell competent animals versus their mast cell deficient counterparts (40).

Direct Immunoregulatory Effects

Mast cells also may exhibit their immunoregulatory effects directly through secretion of modulatory cytokines and activation of metabolic pathways. The aforementioned indirect mast cell-related effects through Treg cell activation may be enhanced with additional suppressive effects that may directly interfere with the activation and function of effector T cells ($CD8^+$ and $CD4^+$). Therefore, mast cell-derived TGF- β may also inhibit immune alloreactivity directly through suppression of effector T-cell function and inhibition of Th1 and

Th2 $CD4^+$ T cells, as well as through differentiation of the latter from naïve $CD4^+$ T cells (52, 53, 61).

Aside from its function in promoting the expression of Treg cells, IL-10 also interferes with T-cell activation by selectively inhibiting the CD28 costimulatory pathway, which, after inhibition, renders T cells tolerant or anergic (55, 62). It has also been reported that IL-10 modulates dendritic cells in favor of promoting tolerance (63).

Another possible direct inhibitory impact on effector T-cell function may be related to tryptophan metabolism. Dendritic cells metabolize tryptophan through activation of the enzyme indoleamine 2,3-dioxygenase (64). It is through decreased tryptophan levels that the indoleamine 2,3-dioxygenase-dependent suppression of T-cell responses inhibits maternal T-cell immunity to fetal tissues during mammalian gestation (65). Similarly, mast cells express tryptophan hydroxylase, a specific serotonin-synthesizing enzyme that also decreases tryptophan levels in tissues (66). Therefore, this mechanism of mast cell-mediated tryptophan catabolism may also be directly involved in the suppression of effector T-cell function (Fig. 1). Further studies are needed to confirm these possible connections.

DISCUSSION

Strong evidence supports the notion that mast cells may actually play a dual role in the context of organ transplantation. With regard to acute alloreactive responses, mast cells seem to have a protective role by the activation and am-

plification of Treg cell function and through the potential direct effects attenuating effector T-cell responses. Conversely, various correlative studies also have disclosed a possible adverse role for mast cells in the progression of chronic organ rejection through release of different profibrotic mediators and increased collagen deposition. Although these observations require validation by both functional and mechanistic studies, current evidence strongly and consistently supports this interrelationship. For future studies, mast cell-deficient and mast cell-competent animal models may be used to further elucidate this pathomechanism.

Finally, some interest has been shown in the use of statins for the prevention of chronic allograft rejection. It is well known that statins inhibit T cells and repress major histocompatibility-II molecules (67, 68). However, a recent study has shown that statins also inhibit mast cell function through inhibition of SCF-induced differentiation of mast cells from their hematopoietic progenitors (69). Therefore, it may be possible that statins not only exert their beneficial effects on chronic allograft rejection through previously known mechanisms but also through mast cell inhibition. Moreover, if statins suppress mast cell activity it may be necessary to avoid statin therapy in the early posttransplant period, because it may potentially interfere with the early tolerogenic and advantageous effects of mast cells. Further studies are therefore needed to fully understand the role of mast cell-related immune mechanisms in organ transplantation.

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