



Mast cell-mediated mechanistic pathways in organ transplantation

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ABSTRACT

Adaptive immunity has gained importance in transplant immunology for years, based on models in which T-cells orchestrate the immune responses during rejection. Most recently, researches revealed that innate immune cells, including mast cells (MCs) also play a pivotal role in allograft rejection. MC mediated immunoregulatory responses influence the innate and adaptive immune responses. Their capability to produce an array of both pro-inflammatory and anti-inflammatory mediators, expressing a wide range of costimulatory molecules in addition to acting as antigen-presenting cells (APCs), make them effective immune cells far beyond their classical role as primary orchestrator cells of allergy. Activated regulatory T cells (Treg) cells contribute to MC recruitment into grafts by releasing interleukin (IL)-9. Tregs are capable of stabilizing MCs and suppressing IgE mediated degranulation through interaction of Treg expressing OX40 with MCs expressing OX40L. MCs in turn release transforming growth factor (TGF)- β and IL-10 which possess suppressive properties. Thus, these cells can suppress the proliferation of T-cells and support the generation of Tregs. MCs in addition to orchestrating immune responses in grafts by cell-to-cell interactions with variety of immune cells, cause histologic changes, mainly fibrosis by releasing mediators such as histamine, fibroblast growth factor-2 (FGF-2), TGF- β , chymase, and cathepsin G. The role of MCs in transplant rejection remains controversial. The accumulation of MCs in rejected grafts suggests that they play a role in preventing graft tolerance, and contribute to the progression of chronic rejection of allografts. However, high expression of MC-related gene products in tolerant grafts and their known interaction with Tregs on the other hand, support the notion that they are an integral component in achieving peripheral tolerance.

1. Introduction

Mast cells (MCs), the granular immune cells develop from CD34⁺/CD117⁺ compatibility pluripotent progenitor cells (MCps) mobilized from the bone marrow (Elieh Ali Komi and Bjerner, 2019). Trafficking of MC progenitors to end organs is strictly controlled by chemokine network and a wide spectrum of adhesion molecules expressed by MCps and cells of residing tissues; for instance, $\alpha 4 \beta 7$ and $\alpha 4 \beta 1$ integrins expressed by MCps and vascular cell adhesion molecule-1 (VCAM-1) by endothelium mediate the trafficking of MCps into the lung tissues (Elieh-Ali-Komi and Cao, 2017; Komi et al., 2017; Summers et al., 2011). Various factors modulate MC growth and survival, including stem cell factor (SCF)-the main MC growth factor also known as C-KIT ligand, interleukin (IL)-3, IL-4, IL-9, IL-33, transforming growth factor beta (TGF β), and nerve growth factor (NGF) (Reber et al., 2015). (Fig. 1) IgE-dependent reactions, including exaggerated allergic responses to inhaled antigens are the hallmarks of these cells (Heib et al.,

2007). After MC activation, they release preformed and de novo synthesized mediators including histamine, leukotrienes (LTs), prostaglandins (PGs), proteases like tryptase, and numerous cytokines (Komi et al., 2017; McLachlan et al., 2003). MCs are capable of modulating and shaping the adaptive immune response, e.g. through tumor necrosis factor alpha (TNF- α)-mediated induction of T cell proliferation. Moreover, MCs with HLA-DR expression directly activate T cells through presenting native antigens to human CD4⁺ T cells (Jungraithmayr, 2015). MCs are also necessary in maintaining peripheral tolerance in case of skin and solid organ transplantation. Investigation of MCs kinetic during organ transplantation showed that early after establishment of tolerance, MCs migrate from the graft to the draining lymph nodes (LNs). After the efflux, MCs reenter the tolerant graft and accumulate in naïve tissues (Bond et al., 2015). The immune system of recipients during the allograft rejection is able to recognize the graft as foreign tissue and immune responses are triggered owing to a complicated network of immune cells (Libby and Pober, 2001).

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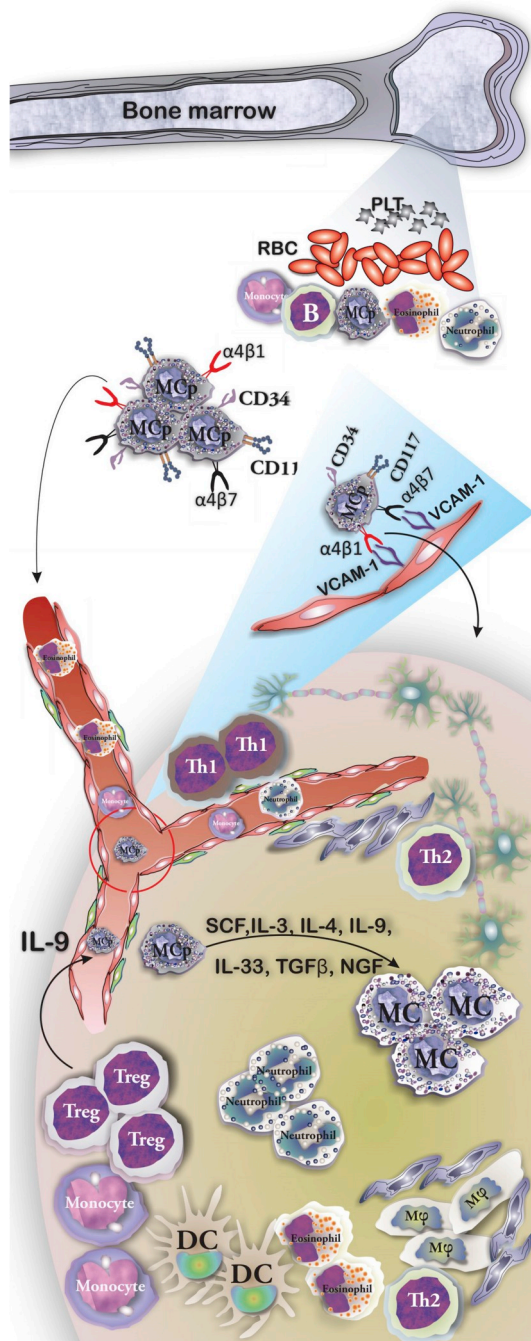


Fig. 1. MC development from CD34⁺/CD117⁺ progenitor cells and their controlled trafficking from bone marrow to tissues. MC progenitors (MCps) after being produced by bone marrow are released in blood circulation through which they reach to the target organs by the help of a controlled ligand-integrin based trafficking. MCps after reaching organs differentiate in MCs under influence of variety of cytokines, mainly SCF.

Allograft rejection depends on the ability of host T cells to react to the polymorphisms encoded within the major histocompatibility complex (MHC) and multiple minor histocompatibility loci (Walsh et al., 2004). In the absence of immunosuppression, a rejecting vascularized allograft is characterized by infiltration of host leukocytes, which finally leads to the necrosis of the graft cells and inducing of thrombosis in graft vessels. Such response in hosts with no previously exposure to graft alloantigens, is called acute rejection, which generally is observed within 1–2 weeks after transplantation (Libby and Pober, 2001). During acute allograft rejection, infiltration of variety of immune cells mainly

monocytes, T cells, B cells and natural killer (NK) cells to the graft is a common observation (van den Hoogen et al., 2017). In acute rejection, MCs support the survival of grafts by promoting the immunosuppressive properties of Treg cells and also by inhibition of the effector T cells; conversely, in chronic rejection, MCs have a damaging function especially by releasing profibrotic mediators (Kritas et al., 2013). The main effector mechanisms described in the rejection process involve antibodies, Th1 cells, and cytotoxic CD8⁺ T cells. Additionally, alternative mechanisms of rejection orchestrated by innate immune cells have been also reported. Moreover, Tregs and MCs play a role in local inflammation associated with rejection (Alegre et al., 2007; Wakabayashi et al., 1986). Activated Treg cells release high amounts of IL-9 that supports the MC growth and activation. IL-9 plays a key role in MC recruitment and activation in tolerant tissue (Lu et al., 2006; Sayed and Brown, 2007). In order to better understand the mechanisms of action of MCs, and their interactions with other components of the innate and adaptive immune system, we briefly summarize other important cell populations and their responses to organ allografts.

2. Innate response during allograft rejection

Despite the central role of adaptive immune responses for the mechanism of allograft rejection, early pro-inflammatory signals and innate cell responses, before the initiation of T-cells, are critical factors in initiation of allograft rejection (Land, 2007; Murphy et al., 2011).

2.1. Dendritic cells

Alloimmune response to a vascularized organ transplant requires trafficking of dendritic cells (DCs) to the secondary lymph nodes. When derived from the allograft, DCs act as potent inducers of an allor-response. Immature DCs express CXCR1, CCR1, CCR2, and CCR5 which are associated with inflammation. During maturation, expression of these receptors decreases. Conversely, the expression of chemokine receptors CCR4, CXCR4, and CCR7 that help the mature DCs to the lymphoid environments increases. They migrate to secondary lymphoid organs, including lymph nodes, spleen, and mucosal lymphoid tissues to present their MHC-associated antigens to activate naive T and B lymphocytes (Nelson and Krensky, 2001). Immature DCs can promote tolerance as they express insufficient levels of T cell costimulatory molecules including CD80/86 and CD40 and low level of MHC complex. Moreover, they release low levels of pro-inflammatory cytokines such as TNF α and IL-12. Lacking sufficient costimulation, these cells may induce T cell anergy or even apoptosis (Walsh et al., 2004).

2.2. NK and NKT cells

Infiltration of NK cells in cardiac and renal allografts occurs just after transplantation before T cell infiltration. NK cells released interferon gamma (IFN γ) promotes the expression of MHC class I and class II by allogeneic endothelial cells, and makes them more susceptible to attacks by alloantigen-specific T cells when recruited to the graft (Pratschke et al., 2009). In the presence of type I IFNs, NK cells support the maturation of DCs by producing IFN- γ and TNF- α . NK cells play a role in elimination of immature DCs but not the mature DCs, augmenting antigen presentation and activation of naive T cells. One possible mechanism by which NK cells contribute in rejection is their capability of killing Tregs (Murphy et al., 2011). Increase in T cells number and the decrease in NK and CD3⁺/CD56⁺ NKT cells has been observed following liver transplantation implying on a hepatic immunity shift from innate to adaptive responses (Werner et al., 2011). This reduction in cell counts may be associated to activation-induced cell death and loss of specific NKT cell surface markers (Wilson et al., 2003).

2.3. Macrophages and monocytes

Investigation of leukocyte accumulation in human grafts revealed that macrophages make up 38–60% of these cells (Liu et al., 2016). According to the heterogeneity of macrophage phenotypes or polarization, they are three groups of macrophages, naïve (M0), classically activated macrophages (M1) that possess pro-inflammatory properties and alternatively activated macrophages (M2) with anti-inflammatory activity (Elieh Ali Komi et al., 2018; Wang et al., 2019). While M1 subpopulation releases pro-inflammatory mediators, including TNF- α , M2 macrophages release anti-inflammatory mediators, mainly IL-10 (Knudsen and Lee, 2016). The population of graft infiltrating macrophages are provided either from donor that are transferred to the recipient upon surgery or from recruitment of recipient monocytes under influence of chemo-attractants, mainly monocyte chemoattractant protein-1 (MCP-1), CCL2, CX3CL1 and macrophage inflammatory protein-1 α (MIP-1 α). Moreover, monocytes are capable of infiltrating the graft parenchyma with the aid of the platelet endothelial cell adhesion molecule-1 (PECAM-1) and CD99 (Liu et al., 2016). The shift of macrophages to the M2 state occurs in the presence of MC and eosinophil derived IL-4. M2 macrophages release growth factors including TGF- β and platelet-derived growth factor (PDGF), which act as key mediators of fibrosis during wound healing (Liu et al., 2016; Loke et al., 2007). Macrophages and monocytes produce IL-1, IL-6, TNF- α which prevent the induction of Tregs, while promote differentiation of inflammatory Th17 cells (Li, 2010). Interestingly, platelets may involve in allograft rejection by expressing and shedding CD154 molecules. CD154 is expressed by activated T cells and acts as the ligand for CD40, a molecule promoting B cell and antigen presenting cell (APC) activation. Activated human platelets shed CD154 through which induce APC activation *in vitro* (Xu et al., 2006). (Fig. 2)

3. Adaptive response and allograft rejection

3.1. B cells

CD20⁺ B cells and plasma cells infiltration of allografts has been reported to correlate with irreversible acute rejection. B cells are capable of damaging grafts by releasing graft specific antibodies. Moreover, upon their infiltration they present graft-derived antigens to alloreactive T cells population via the process of allorecognition (Alegre et al., 2007; Ingulli, 2010). The efficiency of anti-CD20 monoclonal antibody (rituximab) in some forms of transplant rejection, suggests involvement of these cells in both acute and chronic allograft rejection in beyond their involvement in differentiation into the HLA antibody producing plasma cells. CD20⁺/CD69⁺ B lymphocytes invade 57% of endomyocardial biopsies from transplanted patients with grade 2R rejection (Sorrentino et al., 2006).

3.2. T CD4⁺ cells

Graft microenvironment and peripheral lymphoid organs participate in differentiation of CD4⁺ T cells to different effector cells involved in rejection. In presence of IL-12p70 cytokine, Th1 cells dominate and participate actively in delayed-type hypersensitivity (DTH) and also IFN- γ -dependent macrophage activation. Th2 cells play a role in IL-5-dependent eosinophilic rejection when exposed to IL-4. Interestingly, under influence of cytokines including, IL-6, IL-23 and TGF- β , Th-17 cells rise in number that may mediate neutrophilic rejection whereas in presence of TGF- β , the formation of Tregs is supported and these cells promote allograft acceptance mainly through IL-9-dependent MC recruitment. Th1 and Th2 cells are capable of inhibiting Th17 differentiation. Tregs might favor Th17 responses by production of TGF- β in presence of inflammatory signals such as IL-6 (Alegre et al., 2007). Both CD8⁺ and CD4⁺ T cells are able to recognize donor MHC class I and II respectively (Angaswamy et al., 2013). The

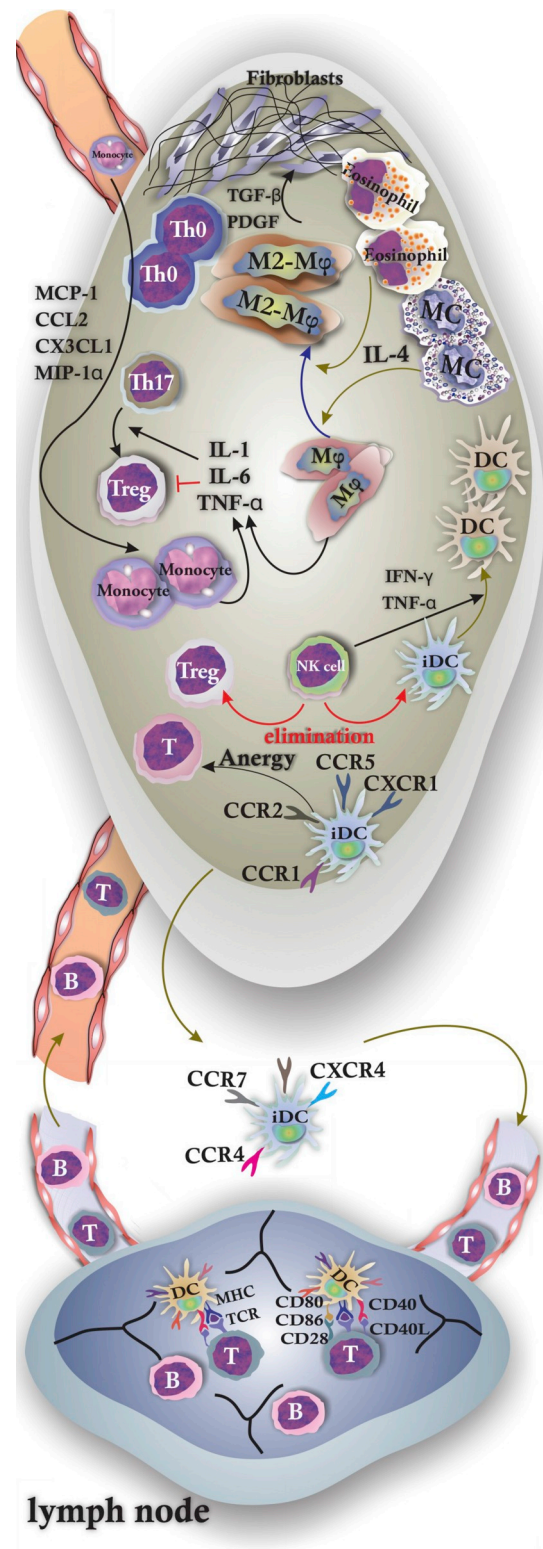


Fig. 2. Contribution of innate immune cells in rejection and acceptance of graft. iDCs migrate from graft to lymph nodes and activate B and T cells. Monocytes after being attracted to grafts by chemokines, mainly MCP-1, CCL2, CX3CL1, and MIP-1 α differentiate to macrophages. Monocytes and macrophages producing IL-1, IL-6, and TNF- α suppress Tregs, contribute to differentiation of Th0 cells to Th17 cells. Moreover, macrophages under influence of MC and eosinophil derived IL-4, differentiate to M2 phenotype, which contribute to fibrosis by producing TGF- β and PDGF.

allorecognition pathway is based on the ability of T cells to directly recognize intact non-self MHC molecules expressed by donor (Alegre et al., 2007). In contrast, the indirect pathway presentation of processed donor antigens occurs by the help of the recipient APCs to recipient T cells. Moreover, in recently described 'semi-direct' pathway recipient APCs acquire intact donor MHC molecules in a native configuration via cell-to-cell contact and activate host T cell responses involved in chronic rejection. The direct pathway is more active in early post-transplant events leading to acute allograft rejection, while the indirect pathway provides more sustainable source of allogeneic stimulation culminating in chronic rejection (Angaswamy et al., 2013). Memory $CD4^+$ T cells act as effector cells upon reactivation, and activate donor-reactive effector $CD8^+$ T cells (Benichou et al., 2017).

3.3. TCD8

$CD8^+$ T cells are an effective cytotoxic effector lymphocyte population during the process of graft rejection. They are capable of recognizing peptides displayed by MHC class I molecules. Moreover, their activation requires a costimulatory second signal, and an IL-2 signal. $CD8^+$ T cells proliferate and mature after activation into specific alloreactive effector cells that release perforin, granzyme, and toxic cytokines, mainly TNF- α (Buckley, 2003).

3.4. Tregs

$CD4^+CD25^+$ FOXP3 $^+$ regulatory T Cells (Tregs) suppress $CD4^+$ and $CD8^+$ T cell immune responses through variety of mechanisms including cytotoxicity, inhibition of cytokine production, e.g. IL-10 and TGF β , induction of apoptosis in effector T cells and inhibition of APCs (Whitehouse et al., 2017). In this context, not surprisingly therapies based on Tregs ability of inducing the tolerance have recently gained attention (Chandran et al., 2017; Whitehouse et al., 2017). Tregs benefit from various potential suppressive mechanisms to control immune responses. For instance, their expressed CD25 depletes IL-2 from T-cells surrounding microenvironment. Expressing CD39 and CD73 as ecto-enzymes, Tregs convert pro-inflammatory extracellular adenosine triphosphate (ATP) into adenosine monophosphate (AMP) by CD39 and then convert AMP into anti-inflammatory adenosine by CD73. Furthermore, they express CTLA-4, that binds to CD80/CD86 expressed by APCs. Such interaction blocks their binding to CD28 through which T-cell activation is limited (Romano et al., 2017). (Fig. 3)

4. Early evidence of MC association in transplant immunology

Moore et al. (1971) reported that increased levels of histamine in the urine of patients after renal transplantation were correlated with the rejection process. This finding suggested that the use of anti-histamine molecules may be of value, at least in the early post-transplant period (Moore et al., 1971). Further investigations showed a rise in producing intracellular histamine by histidine decarboxylase in rat skin allografts when compared with autografts (Dy et al., 1981). Table 1 summarizes primary evidence implying the role of MCs in transplantation immunology.

5. Role of MCs in transplant biology

MCs play a key role in Treg dependent peripheral tolerance. Activated Tregs produce IL-9, that acts as a MC growth and activation factor. The cytokine is also involved in MC activation and recruitment to tolerant tissues (Elieh Ali Komi and Grauwet, 2018). Interestingly, Tregs contribute to stabilize MCs and suppress IgE mediated degranulation through interaction of OX40 and OX40L (de Vries et al., 2009b). MCs in turn contribute to the immunosuppressive state through release of TGF- β , IL-10 and specific proteases. Tregs increase cAMP and inhibit calcium flux in MC degranulation through OX40–OX40L

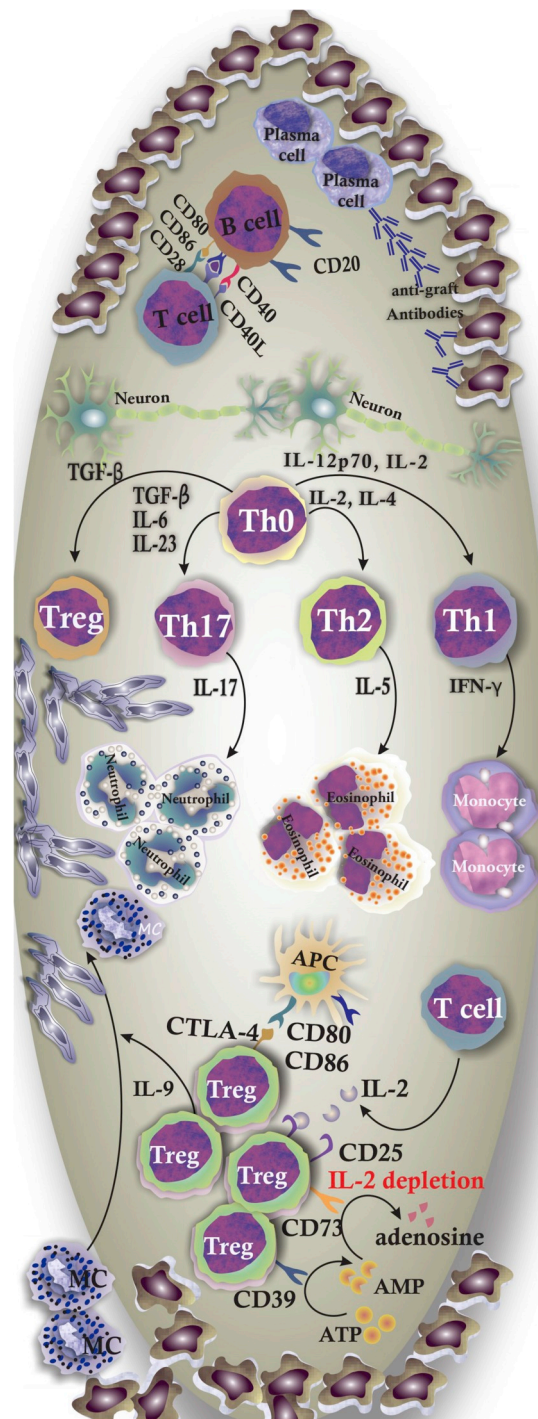


Fig. 3. Contribution of specific immunity in rejection and acceptance of graft. Tregs contribute to establish a suppressive microenvironment in grafts by applying a variety of cell-to-cell interactions and expressing surface receptors including CD25, CD39, and CD73. Th0 cells differentiation to other subsets is determined by the presence of cytokines and the cytokine profile of differentiated cells determines the type of cells involved in rejections.

interaction both *in vitro* and *in vivo*. MCs produce IL-10 and TGF- β which can suppress T-cell proliferation and generate Treg (de Vries et al., 2009a). MCs not only produce TGF- β but also regulate its level and activity through releasing chymase from the extracellular matrix (ECM). TGF- β possesses pro-fibrogenic and immunosuppressive properties (Boerma et al., 2007). Indeed, mediators including histamine, FGF-2, TGF- β , chymase, and cathepsin G, (two latter mediators activate

Table 1
Primary evidence implying the role of MCs in transplantation biology.

Biopsy type	Results	Reference
Renal allografts necropsy specimen	In all patients treated with azathioprine and prednisone MCs were increased in number (more than tenfold above normal) in the cortical interstitium and occasionally invaded renal tubules.	Colvin and Dvorak (1974)
Post-transplant endomyocardial	Infiltration of MCs during the first week after transplantation was observed and increased number of MCs and granules were correlated with fibrosis.	Li et al. (1992)
Renal allografts from patients with acute interstitial rejection	A positive correlation was found between the number of MCs and the time since transplantation, the severity of interstitial fibrosis, and interstitial edema.	Lajoie et al. (1996)
Transbronchial biopsies of patients with acute rejection and patients with bronchiolitis obliterans	Increasing grades of acute rejection were associated with the number of MCs.	Yousem (1997)
Transplanted livers with end-stage chronic rejection and livers with acute cellular rejection	In patients with chronic rejection MCs were hyperplastic especially surrounding inflamed and damaged bile ducts within portal tracts.	O'Keeffe et al. (2002)
Renal allograft biopsies from patients with acute renal transplant rejection (ARTR)	MCs are one of the constitutive cell types in the interstitium in ARTR. Interstitial expression of α -SMA showed that MCs have a role in the development of early interstitial fibrosis in renal allografts.	Danilewicz and Wagrowska-Danilewicz (2004)
Transplanted livers with different grades of acute rejection, and with end stage chronic rejection	Tryptase ⁺ /c-Kit ⁺ MCs were strongly correlated with acute liver allograft rejection grades and chronic liver allograft rejection.	El-Refaie and Burt (2005)
Kidney allografts	Strong correlation was found between the number of MCs and the graft interstitial fibrosis and time post-transplantation.	Papadimitriou et al. (2013)

latent TGF- β or increase angiotensin II levels by converting angiotensin I in tissues) are capable of inducing fibrosis. These mediators activate fibroblasts by which they induce collagen synthesis (Jahanyar et al., 2008). Upregulation of CPA, MCP1, MCP5, and MCP6 have been reported frequently in accepted allografts. MCP6 is involved in tolerance and inflammation reducing the local IL-6 concentration (de Vries and Noelle, 2010). IL-6 and TNF- α synergistically act in favor of allograft rejection (Shen and Goldstein, 2009). MC-derived TNF α is involved in the recruitment of DCs to sites of inflammation (de Vries and Noelle, 2010). This mediator is associated with overexpression of VCAM-1, ICAM-1, and P-selectin in human bronchial xenografts, activation of bronchial microvasculature and thereby recruiting leukocytes to the airway (Koskinen et al., 2001; Pilewski et al., 1994). IL-10 supports peripheral T cell tolerance and histamine via acting on histamine 2 receptor (H2R) induces the secretion of IL-10 in DCs (Takagaki et al., 2009). MCs express the serotonin-specific transporter (SERT) by which they take up serotonin and store it. Additionally, serotonin acts as a 'third' signal for T-cell proliferation. MCs contribute to establishment of tolerant conditions by depleting the serotonin from the environment (de Vries et al., 2009a). MCs have cell-to-cell interactions with T-cells, for instance their capability of expressing MHC-II molecules enables them to directly present antigens to T-cells. MCs are involved in naive T cells to Th2 phenotype skewness, inducing the production of Th2 cytokines including IL-4, IL-10 and IL-13 and suppressing the production of IFN- γ . Considering that the graft environment has a Th2 skewed phenotype, it is thought to be associated with MC ability of antigen presenting to T cells under tolerant conditions, which could act in favor of the graft acceptance (de Vries et al., 2009a). (Fig. 4) In another study on the role of MCs in transplantation immunology, cromolyn, a widely used MC stabilizer was used to prevent MC degranulation in pulmonary allotransplantation. The researchers concluded that cromolyn without interfering the MC recruitment can ameliorates the development of obliterative bronchiolitis and parenchymal fibrosis in pulmonary allografts, (Chang et al., 2014). Cromolyn sodium or ketotifen have been reported to inhibit MC activation and decrease the pro-inflammatory cytokine levels in serum and lung. It also significantly decreases NF-kappaB p65 subunit translocation to the nucleus in lung after orthotopic autologous liver transplantation (Zhang et al., 2013).

6. MCs and skin graft rejection

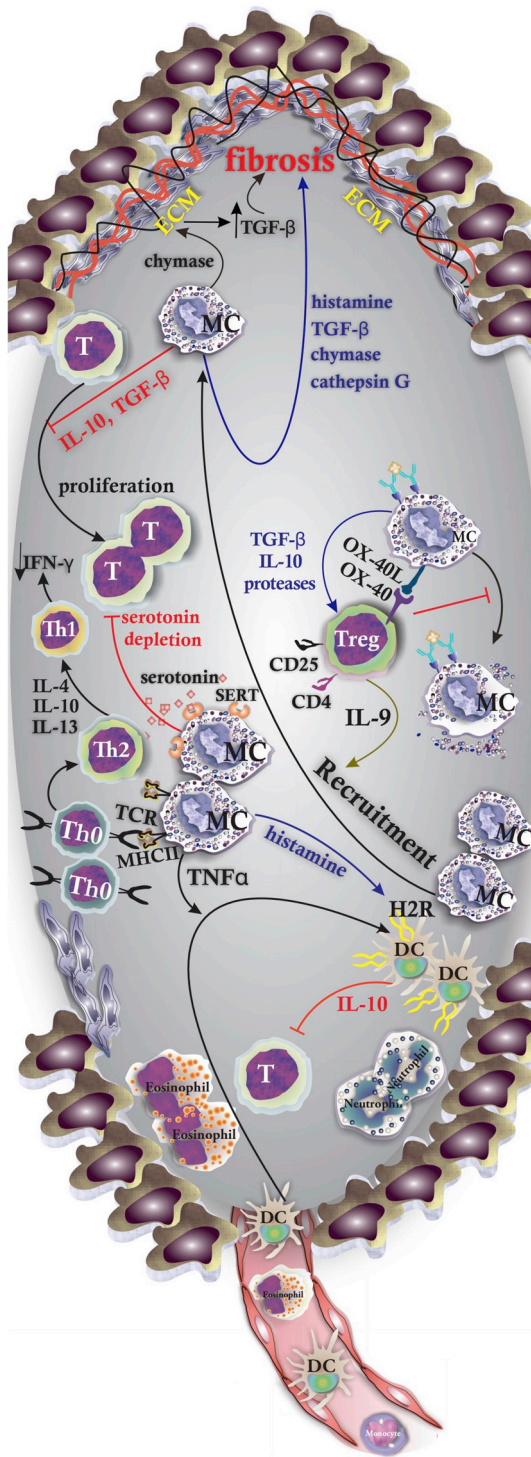
Lu et al. studied the role of MCs in allograft survival, by inducing allospecific tolerance in W^{sh} mice by administration of anti-CD154 and intravenous infusion of allogeneic cells (also known as donor-specific transfusion, DST). Mice were then grafted with allogeneic skin. Anti

CD154 co-administration with DST resulted in long-term survival of skin allografts in wild-type (WT) mice with median survival time (MST) of 70 days, in comparison to the W^{sh} mice (MST = 17 days). Indeed, W^{sh} mice with co-administration of anti-CD154/DST did not accept the graft and rejected allografts as rapidly as control mice (MST = 13 days). This group of researchers at the next step reconstituted MC population of Wsh by bone-marrow-derived mast cells (BMMCs). After 8 weeks the mice were grafted with skin transplants after anti-CD154/DST co-administration and the fate of grafts was studied. Local reconstitution of MCs could improve graft survival on W^{sh} mice (MST = 44 days) (Lu et al., 2006). (Fig. 5) Expression of the CD200 in skin grafts is associated to graft survival by suppressing CD200R⁺ MCs, enhancing IL-9 production, the attraction/expansion of Treg, and attenuating T cell effector activation. Following overexpression of CD200 on the surface of skin DCs, overexpression of genes associated with Treg cells mainly PD-1, Foxp3, CTLA4, and also MC chymase occur. Inhibition of CD200-CD200R interactions, using CD200tr resulted in rapid rejection in CD200tg mice, MC degranulation, and hampering Treg infiltration. Application of sodium cromoglycate could suppress these effects (Gorczynski et al., 2011). Establishing tolerance in allogeneic skin graft requires IL-6 degradation by MC protease 6 (MCP6). High expression of MCP6 correlates with low levels of IL-6 in accepted allografts. Not surprisingly, establishment of tolerance in allogeneic graft cannot be completely achieved in MCP6^{-/-} mice (de Vries et al., 2010).

7. Role of MCs in internal organ transplantation

7.1. Kidney transplantation

Immunohistochemistry (IHC) method with an anti-tryptase antibody was conducted and it was shown that the number of MCs increases in acute rejection of renal allografts, showing that MCs increase in number in the renal interstitium of renal diseases including IgA nephropathy (Ehara and Shigematsu, 2003). Chronic allograft nephropathy (CAN) is known as the main cause of declining long-term graft function and graft failure in human kidney transplantation. Ishida et al. studied the accumulation of MCs, their subtypes in samples obtained from normal control kidney, pre-transplanted kidney, and allografted kidney 100 days after living-related renal grafting using specific antibodies against neutrophil cathepsin G and human tryptase. In this study, cells immunoreactive for tryptase were considered total MC while cells immunoreactive for both tryptase and cathepsin G were considered MCTC. They reported that the ratio of MCTC to total MC was significantly increased in allografts at 100 days and was correlated significantly with creatinine clearance and fibrosis index (FI) (Ishida



et al., 2005). Yamada et al. investigated the role of chymase in human renal rejection. According to chymase positivity, rejected kidneys were classified as chymase positive and chymase negative. They reported that the interstitial fibrotic area in the chymase positive group was

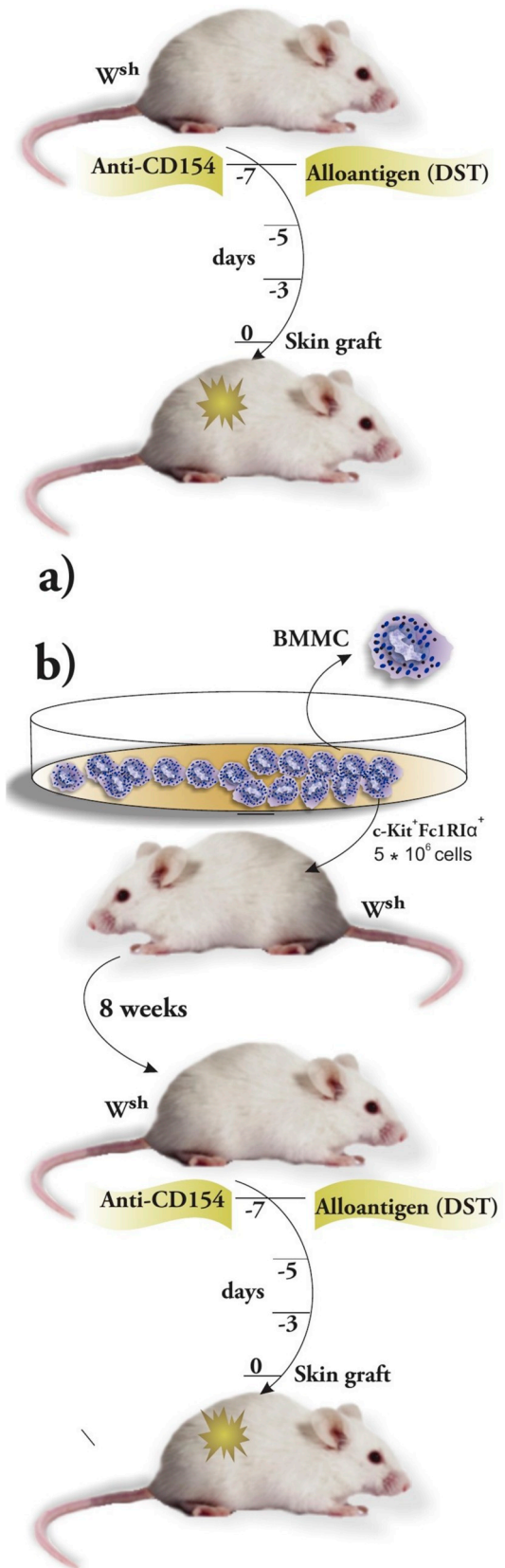


Fig. 5. a) W^{sh} mice co-administered with anti-CD154 and DST to induce allospecific tolerance were grafted with allogeneic skin. Treating with anti-CD154/DST promoted long-term acceptance of allografts in WT mice but not in the W^{sh} mice. b) BMMCs reconstructed W^{sh} mice after eight weeks from reconstitution had comparable MC density in skin to that observed in C57BL/6 WT mice. Local MC reconstitution could extend graft survival in W^{sh} mice.

remarkably extended than that in the chymase negative kidneys, and concluded that elevated expression of chymase in MCs correlates with the severity of interstitial fibrosis in rejected kidneys (Yamada et al., 2001). Chymase has been reported to act as monocyte chemoattractant and tryptase acts not only as a chemoattractant for fibroblasts in kidney but even a mitogenic factor as well (Eddy, 2001). Kidney resident fibroblasts express both ANG II and the histamine1 receptor subtypes. Release of MC mediators including histamine and renin links MC

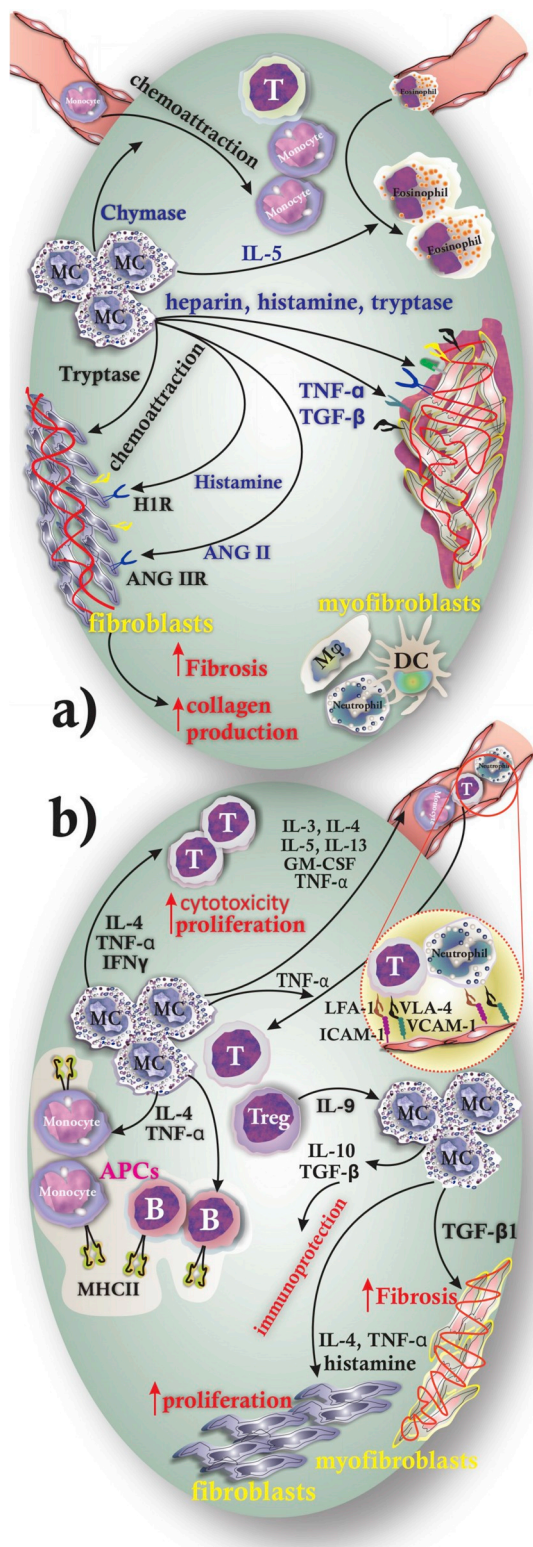


Fig. 6. Role of MC mediators in recruiting immune cells and interactions with ECM and other immune cells in kidney and lung transplantation. a) In kidney transplantation MC derived chymase and IL-5 mediate the chemoattraction of monocytes and eosinophils respectively to kidney. MCs release tryptase, which acts as chemoattractant and mitogen for fibroblasts. Kidney fibroblasts express the ANG II receptor and HR1, which activate fibroblast, induce their proliferation, collagen production, and fibrosis upon MC degranulation. MC mediators stimulate the proliferation of myofibroblasts and fibrosis in renal allografts. b) MC- derived mediators including IL-4, TNF- α and histamine promote fibroblast proliferation of fibroblast in lung tissue. MC release FGF-2 and TGF- β 1 induce the fibrosis via myofibroblasts. IL-4 and TNF- α upregulate the expression of MHCII molecules on APCs. Additionally, MCs support the flux of immune cells mainly neutrophils and T cells in transplanted organ by releasing IL-3, IL-4, IL-5, IL-13, GM-CSF and TNF- α which promote the expression of adhesion molecules on endothelial cells.

degranulation to fibroblast activation, proliferation, collagen production, and fibrosis (Silver, 2013). MC-derived heparin, histamine, tryptase, FGF-2, TNF- α and TGF- β , induce the proliferation of myofibroblasts and fibrosis in renal allografts (Levi-Schaffer and Weg, 1997; Pardo et al., 2000). Moreover, MCs secretion of IL-5, may induce an eosinophilic infiltrate in acute and chronic renal rejection (Pardo et al., 2000). (Fig. 6A)

7.2. Lung transplantation

In addition to populations of macrophages and neutrophils, MCs are found after syngeneic lung transplantation during ischemia reperfusion injury around vessels (Jungraithmayr, 2015). Once ischemia-reperfusion injury occurs, recruitment of alloimmune T effectors and Treg cells into the graft is promoted by expression of pro-inflammatory and pro-angiogenic growth factors including vascular endothelial growth factor (VEGF) (Wedel et al., 2015). Release of MC derived mediators alters innate and adaptive immune responses and their release influences the allogeneity between organ donor and recipient. IL-4 and TNF- α released from MCs promote the expression of MHC class II on APCs including monocytes, B cells, and in presence of IFN- γ , increase the cytotoxicity and proliferation of T cells. GM-CSF, TNF- α , IL-3, IL-4, IL-5, and IL-13 accelerate the adhesion and transendothelial migration of variety of immune cells, i.e neutrophils and T cells by upregulation of VCAM-1 and ICAM-1 on endothelial cells (Jungraithmayr, 2015). TGF- β 1, and FGF-2 act as profibrotic factors in pathology of interstitial lung diseases through promoting fibrosis by α SMA expressing myofibroblasts. Interestingly, IL-4, TNF- α and histamine play a role in promoting the fibroblast proliferation. MC-released TNF- α plays a dual role in either organ rejection or establishing tolerance. It acts as a T cell recruitment mediator and also supports the interaction between DCs and T cells leading to the proliferation of organ damaging allospecific T cells. TNF- α supports the induction of tolerogenic DCs through GM-CSF-mediated mechanism which finally results in establishing tolerance by suppressing of T cell proliferation. Tregs produce IL-9 when activated and induce MC growth and activation. In turn, activated MCs release IL-10 and TGF- β , which possess immunoprotective properties. Decreased levels of MC-derived TGF- β and IL-10 supports the development of acute rejection (Jungraithmayr, 2015). In chronic lung allograft rejection, MCs promote fibrosis by releasing profibrotic mediators i.e histamine, FGF-2, TGF- β , heparin, cathepsin G, and chymase to activate fibroblasts and promote collagen synthesis (Jungraithmayr, 2015). One aspect of MC presence in transplanted kidneys is phenotype changing with time. MCTC population increases post renal transplantation and correlates with severity of interstitial fibrosis. MCT are the predominant subtype of MCs residing in normally functioning kidney allograft, and gradually MCTC become dominant at 100 days (Banga et al., 2016). (Fig. 6B)

7.3. Liver transplantation

Hepatic MC involvement in chronic rejection, fibrogenesis, and cholestatic liver diseases has been investigated in recent years. MCs normally reside in liver surrounding the vessels, the bile ducts in the portal tracts, and the hepatic parenchyma. It has been reported that hepatic MC infiltration of portal tracts and surrounding can damage bile ducts, and has a role in the pathogenesis of chronic rejection (Nakano et al., 2012). O'Keefe et al., in order to study the involvement of hepatic MCs in liver rejection, compared biopsy specimen from normal, transplanted end-stage chronic rejection and transplanted livers with acute rejection after staining MCs with human anti-tryptase antibody. Since chronic rejection after liver transplantation is predominantly a cholestatic process characterized by bile duct damage and loss, they decided to study the hepatic MCs involvement in its pathogenesis. They reported a marked accumulation of MCs in the chronic-rejection group compared with controls. Furthermore, portal tracts containing MCs were frequently found in the chronic-rejection group. In chronic rejection, hepatic MCs frequently were seen surrounding damaged bile ducts in inflamed portal tracts. These results suggest that hepatic MCs may be involved in chronic liver rejection (O'Keefe et al., 2002; Walls et al., 1990). Yang et al. studied the role of MCs in acute rejection differently. Considering the fact that cromolyn (CRM), acts as a MC stabilizer, and compound 48/80 (CMP 48/80), as MC degranulator, they preconditioned inbred male Dark Agouti donor rats with CRM and CMP 48/80 and used female Lewis rats as recipients of liver grafts. Three days after transplantation, they collected blood samples and liver specimen to perform histology analysis and to assess the cytokine mRNA expression. Since Th1/Th2 cytokine expression is closely connected to transplantation rejection and tolerance and Th-1 cytokine (IFN- γ) is known to increase the chance of rejection, (while Th-2 cytokine (IL-10) is associated to allograft survival), they measured both cytokines at serum and mRNA levels. They concluded that the expression of IFN- γ mRNA was reduced while IL-10 mRNA levels were higher in allografts in the CRM and CMP 48/80 groups, when compared to PBS group. Furthermore, they reported that rejection activity indexes (RAIs) and liver functions were all alleviated through CRM or CMP 48/80 preconditioning (Yang et al., 2014). Other studies revealed some interesting aspects of MCs, Foxp3⁺ Tregs, and $\gamma\delta$ T cells interactions during liver allograft rejection. Hematopoietic stem/progenitor cells are believed under influence of SCF/c-Kit signaling to enter the liver allografts to promote tolerance and simultaneously induce liver regeneration for the replacement of donor with recipient hepatic cells. Foxp3⁺ Tregs are capable of producing IL-9 and SCF, which effectively activate hepatic MCs; in turn, activating MCs release histamine, IL-2, and TGF- β 1. TGF- β supports the generation of IL-17 producing $\gamma\delta$ T cells. Released IL-17 attracts Foxp3⁺ Tregs, enhances their immunosuppressing properties, and induces IL-9 and SCF production by Foxp3⁺ Tregs. Indeed, hepatic levels of SCF and IL-9 correlate to Foxp3/IL-10 expression and MC activation in tolerogenic liver allografts (Nakano et al., 2012).

7.4. Heart transplantation

Cardiac MC activation has been documented in the presence of reactive oxygen species (ROS), C5a, endothelin-1(ET-1), IL-33, and several neuropeptides (Levick et al., 2011). MC density increases notably in heart post myocardial infarction (MI) and during the healing phase post-MI. The maximum accumulation of cardiac MCs is observed in areas where collagen has deposited (Levick et al., 2011). The participation of MCs in cardiac transplant rejection is poorly understood. Monitoring the results of heterotopic cardiac allografts in out-bred genetically MC-deficient or corresponding WT rats show that MC accumulation and function contribute to a long survival of cardiac transplantation. However, some studies suggest that the presence of MCs is associated to development of fibrosis and chronic rejection of cardiac

allografts (Itoh et al., 2010). Itoh et al. investigated the role of MCs in acute/chronic rejection by transplanting either FVB or C-H-2^{bm12}/KhEg murine hearts into MC-deficient Kit^{W-sh/W-sh} or littermate control Kit^{+/+} C57BL/6J recipient mice for acute rejection (total allo-mismatch) or chronic rejection (MHC class II-mismatch), respectively. Donor hearts were then harvested at 5 (acute) and 52 days (chronic) post-transplant and the pattern of cell infiltration were studied by immunohistochemistry. Moreover, they studied cytokine membrane arrays in donor hearts for IFN- γ , VCAM-1, ICAM-1, TNF- α , MCP-1, IL-2, IL-4, IL-6, IL-10, and IL-17, and found no significance in overall graft survival, inflammatory cell recruitment, or cytokine expression between studied groups (Itoh et al., 2010). CCL11 (Eotaxin) was originally shown to act as an eosinophil chemotactic factor which can induce their activation. CCL11 exerts its chemotactic effects by acting on CCR3, also expressed on MCs. CCL11 induces MC differentiation by the expression of specific proteases and is associated with fibrogenesis. It has been reported that cardiac macrophages produced eotaxin during heart transplant rejection, which attract MCs into myocardial. MC mediated myocardial fibrosis correlates remarkably with CCL11 concentrations and the density of myocardial MC in heart tissue (Zweifel et al., 2010).

8. Role of MCs in vein graft disease

Repopulation of vein grafts with infiltrating MCs occurs rapidly after grafting. An accumulation of both activated or resting MCs could be found in the perivascular region of these grafts (de Vries and Quax, 2018). The outcomes of MC presence in vein grafts include neointima thickening, unstable lesions and features of plaque rupture (due to the function of MC released tryptase and chymase in degradation of collagen) (de Vries and Quax, 2018; Wezel et al., 2016; Wu et al., 2015). MC derived chymase supports the generation of Ang II and TGF- β 1 through which it contributes to occurrence of stenosis and the neointimal formation after the implantation of polytetrafluoroethylene graft (Jin et al., 2007). C5a-C5aR signaling activates MCs. De Vries et al. studied the role of MCs and C5a-C5aR axis in vein graft disease. They reported the accumulation of MCs and upregulation of C5aR (CD88) during vein graft disease in mice with apolipoprotein-E deficiency, and showed that application of C5a enhances vein graft lesion formation. Additionally, treatment with C5a-receptor antagonists was reported to decrease vein graft disease (de Vries et al., 2013). Wu et al. inserted a vein graft into the right carotid artery in WT and Kit^{W-sh/W-sh} (mice with MC deficiency) mice. The formation of vein graft neointimal lesions was significantly reduced in MC deficient mice. L-selectin, CCL2, M-CSF and MIP-3 α expression in the vein grafts was also reduced. They isolated bone marrow cells from C57BL/6 mice and to obtain BMMCs, and cultured the cells in the presence of SCF and IL-3. After confirming the phenotype of cells obtained from culture by flow cytometric investigation of expressing c-Kit and Fc ϵ RI they locally injected the BMMCs to deficient mice. Locally reconstitution of MCs in Kit^{W-sh/W-sh} mice could successfully restore the reduced neointimal formation (Wu et al., 2015).

9. Application of MC/MC mediator targeted therapies in transplantation immunology

Pharmaceutically targeting of MCs in organ transplantation requires more investigations to clarify how pharmaceutically could induce MC activation (specially using tyrosine kinase inhibitors) or degranulation (using modern stabilizers) favouring the allograft survival. Pharmaceutically targeting of MCs includes:

9.1. Targeting MC recruitment to organ

During acute rejection myocardial fibrosis in rat heart allografts correlates with CCL11 concentrations.

It is suggested that targeting CCL11 with monoclonal antibodies

including bertilimumab may hamper MC infiltration and myocardial fibrosis after heart transplantation (Zweifel et al., 2010).

9.2. Prevention of MC degranulation by stabilizers

Yang et al. (2014) to reduce acute rejection, preconditioned donor rat livers with cromolyn (CRM), a widely used MC stabilizer (Komi et al., 2019), or compound 48/80 (CMP 48/80), a MC degranulator. They concluded that preconditioning the donor livers with CRM or CMP 48/80 reduce acute rejection and contribute to prolong survival of recipients after orthotopic liver transplantation (Yang et al., 2014). Cromolyn was reported promising in rat lung transplantation too. Cromolyn is capable of prevention of acute graft failure associated with prolonged ischemic time. Application of Iodoxamide tromethamine, a derivative of cromolyn sodium in lung preservation solutions lead to better post-ischemic function in cold stored rat lungs after reperfusion (Barr et al., 1998). Local intragraft injection of CRM prevents the collapsing of tolerance (de Vries et al., 2009b). Application of disodium chromoglycate, has been reported promising in attenuation of renal fibrosis (Summers et al., 2012). Cyclosporine and FK506 inhibit the antigen-induced release of histamine and also the production of arachidonate products in MCs and basophils. Since these autacoids possess proinflammatory properties, preventing their release from MCs could be considered as a potential therapeutic benefit of these drugs (Harrison et al., 2007). The benefits of using topical cyclosporine in BALB/c mice with allergic rhinitis (AR) has been reported (Joo et al., 2016). Additionally, tranilast, which possesses anti-allergic properties is capable of inhibiting the release of chemokines and mediators from MCs through blocking the process of exocytosis (Darakhshan and Pour, 2015; Baba et al., 2016). Tranilast by targeting SCF/c-kit signaling pathway prevents renal interstitial fibrosis, and inhibition of MC infiltration prevents renal interstitial fibrosis (Yin et al., 2018). Tranilast was used in graft versus host disease (GVHD) (Mukai and Ogawa, 2018) and cardiac allograft vasculopathy (Izawa et al., 2001).

9.3. Targeting MC- immune cells crosstalk

Blockade of CD40 (expressed by DCs, endothelial cells, macrophages, and B cells)-CD40L (expressed by MCs) interactions by the use of antiCD40L monoclonal antibody supports the survival of allografts in mice models of vascularized organs (Guillot et al., 2002).

9.4. Application of antagonists of MC mediator receptors

In skin allografts, treating mice with Ketotifen, an H1R antagonist with an MC stabilizing effect, delays graft rejection (Ngo Nyekel et al., 2018).

10. Concluding remarks

Collaboration between innate and adaptive immune cells in exerting immune responses in transplantation immunology determines the fate of allotransplants. Thus, we need to look far beyond just T cells as the main effector cells in the allograft response. In fact, other cells of immune system mainly NK cells, macrophages, B cells, and MCs, are able to influence the fate of allograft and maintenance of immune tolerance. Shifting from cellular to molecular level will provide us with a better insight into the detailed mechanism of allograft rejection. In this regard, investigating the potential role of serum acute phase chemokines, cytokines such as IFN- γ , TNF- α , IL-6, IL-1 β , and chemokine receptors in organ transplantation and tissue survival, could be a novel aspect of transplantation biology (He et al., 2003). MCs, although known for their pro-inflammatory properties, surprisingly play a key role in maintenance of tolerance toward an allogeneic transplant. MCs may have harmful effects on graft survival, during the maintenance phase of dominant tolerance through slow non-IgE-mediated degranulation that

causes fibrosis and intima hyperplasia. The mechanisms of interaction between Tregs and MCs that contribute to maintaining a favorable MC-Treg axis in dominant tolerance remain unclear (de Vries et al., 2009a). Owing to ability of MCs in expressing a wide array of chemokine and chemokine receptors, they are capable of effectively recruiting alloreactive leukocytes to the allograft, thus possibly playing a role in transplantation biology (Tan and Zhou, 2005). MCs are also known for expressing a broad range of TLRs. Activation of surface expressed TLRs of APCs, especially DCs upregulates co-stimulatory and MHC molecules, and triggers further adaptive immune response. In this regard, TLR 2 and 4 during ischemia-reperfusion injury activate DCs. However, possible role of MC expressed TLRs, their ligands and signaling in transplantation biology needs to be further investigated (Goldstein, 2006; Goldstein and Palmer, 2005; Land, 2006, 2007). Moreover, migration kinetics of MCs to donor grafts and secondary lymphoid organs during tolerance induction and rejection, is poorly understood and warrants further investigation (Bond et al., 2015).

Conflicts of interest

Daniel Elieh Ali Komi, and Domenico Ribatti declare that they have no conflict of interest.

Author contributions

Daniel Elieh Ali Komi and Domenico Ribatti have prepared the manuscript. Domenico Ribatti has revised and added inputs. Daniel Elieh Ali Komi has designed and generated the figures.

References

- Alegre, M.L., Florquin, S., Goldman, M., 2007. Cellular mechanisms underlying acute graft rejection: time for reassessment. *Curr. Opin. Immunol.* 19, 563–568.
- Angaswamy, N., Tiriveedhi, V., Sarma, N.J., Subramanian, V., Klein, C., Wellen, J., Shenoy, S., Chapman, W.C., Mohanakumar, T., 2013. Interplay between immune responses to HLA and non-HLA self-antigens in allograft rejection. *Hum. Immunol.* 74, 1478–1485.
- Baba, A., Tachi, M., Ejima, Y., Endo, Y., Toyama, H., Matsubara, M., Saito, K., Yamauchi, M., Miura, C., Kazama, I., 2016. Anti-allergic drugs tranilast and ketotifen dose-dependently exert mast cell-stabilizing properties. *Cell. Physiol. Biochem. : Int. J. Exp. Cell. Physiol. Biochem. Pharmacol.* 38, 15–27.
- Banga, A., Han, Y., Wang, X., Hsieh, F.H., 2016. Mast cell phenotypes in the allograft after lung transplantation. *Clin. Transplant.* 30, 845–851.
- Barr, M.L., Carey, J.N., Nishanian, G.P., Roberts, R.F., Sakamaki, Y., Darbinian, S.H., Starnes, V.A., 1998. Addition of a mast cell stabilizing compound to organ preservation solutions decreases lung reperfusion injury. *J. Thorac. Cardiovasc. Surg.* 115, 631–636 discussion 636–637.
- Benichou, G., Gonzalez, B., Marino, J., Ayasoufi, K., Valujskikh, A., 2017. Role of memory T cells in allograft rejection and tolerance. *Front. Immunol.* 8, 170.
- Boerma, M., Fiser, W.P., Hoyt, G., Berry, G.J., Joseph, L., Joseph, J., Wang, J., Crew, M.D., Robbins, R.C., Hauer-Jensen, M., 2007. Influence of mast cells on outcome after heterotopic cardiac transplantation in rats. *Transpl. Int. : Off. J. Europ. Soc. Organ Transplant.* 20, 256–265.
- Bond, G., Nowocin, A., Sacks, S.H., Wong, W., 2015. Kinetics of mast cell migration during transplantation tolerance. *Transpl. Immunol.* 32, 40–45.
- Buckley, R.H., 2003. 27. Transplantation immunology: organ and bone marrow. *J. Allergy Clin. Immunol.* 111, S733–S744.
- Chandran, S., Tang, Q., Sarwal, M., Laszik, Z.G., Putnam, A.L., Lee, K., Leung, J., Nguyen, V., Sigdel, T., Tavares, E.C., Yang, J.Y.C., Hellerstein, M., Fitch, M., Bluestone, J.A., Vincenti, F., 2017. Polyclonal regulatory T cell therapy for control of inflammation in kidney transplants. *Am. J. Transplant. : Off. J. Am. Soc. Trans. Am. Soc. Trans. Surg.* 17, 2945–2954.
- Chang, J.C., Leung, J., Tang, T., Holzknecht, Z.E., Hartwig, M.G., Duane Davis, R., Parker, W., Abraham, S.N., Lin, S.S., 2014. Cromolyn ameliorates acute and chronic injury in a rat lung transplant model. *J. Heart Lung Transplant. : Off. Pub. Int. Soc. Heart Transplant.* 33, 749–757.
- Colvin, R.B., Dvorak, H.F., 1974. Letter: basophils and mast cells in renal allograft rejection. *Lancet* 1, 212–214.
- Danilewicz, M., Wagrowska-Danilewicz, M., 2004. Immunohistochemical analysis of the interstitial mast cells in acute rejection of human renal allografts. *Med. Sci. Monit. : Int. Med. J. Exp. Clin. Res.* 10, Br151–156.
- Darakhshan, S., Pour, A.B., 2015. Tranilast: a review of its therapeutic applications. *Pharmacol. Res.* 91, 15–28.
- de Vries, V.C., Noelle, R.J., 2010. Mast cell mediators in tolerance. *Curr. Opin. Immunol.* 22, 643–648.
- de Vries, M.R., Quax, P.H.A., 2018. Inflammation in vein graft disease. *Front. Cardiovasc.*

- Med. 5, 3.
- de Vries, V.C., Pino-Lagos, K., Elgueta, R., Noelle, R.J., 2009a. The enigmatic role of mast cells in dominant tolerance. *Curr. Opin. Organ Transplant.* 14, 332–337.
- de Vries, V.C., Wasiuk, A., Bennett, K.A., Benson, M.J., Elgueta, R., Waldschmidt, T.J., Noelle, R.J., 2009b. Mast cell degranulation breaks peripheral tolerance. *Am. J. Transplant.* : Off. J. Am. Soc. Trans. Am. Soc. Trans. Surg. 9, 2270–2280.
- de Vries, V.C., Elgueta, R., Lee, D.M., Noelle, R.J., 2010. Mast cell protease 6 is required for allograft tolerance. *Transplant. Proc.* 42, 2759–2762.
- de Vries, M.R., Wezel, A., Schepers, A., van Santbrink, P.J., Woodruff, T.M., Niessen, H.W., Hamming, J.F., Kuiper, J., Bot, I., Quax, P.H., 2013. Complement factor C5a as mast cell activator mediates vascular remodelling in vein graft disease. *Cardiovasc. Res.* 97, 311–320.
- Dy, M., Lebel, B., Kamoun, P., Hamburger, J., 1981. Histamine production during the anti-allograft response. Demonstration of a new lymphokine enhancing histamine synthesis. *J. Exp. Med.* 153, 293–309.
- Eddy, A.A., 2001. Mast cells find their way to the kidney. *Kidney Int.* 60, 375–377.
- Ehara, T., Shigematsu, H., 2003. Mast cells in the kidney. *Nephrology* 8, 130–138.
- El-Refaie, A.M., Burt, A.D., 2005. Mast cells and c-Kit expression in liver allograft rejection. *Histopathology* 47, 375–381.
- Elieh Ali Komi, D., Bjerner, L., 2019. Mast cell-mediated orchestration of the immune responses in human allergic asthma: current insights. *Clin. Rev. Allergy Immunol.* 56, 234–247.
- Elieh Ali Komi, D., Grauwet, K., 2018. Role of mast cells in regulation of T cell responses in experimental and clinical settings. *Clin. Rev. Allergy Immunol.* 54, 432–445.
- Elieh Ali Komi, D., Sharma, L., Dela Cruz, C.S., 2018. Chitin and its effects on inflammatory and immune responses. *Clin. Rev. Allergy Immunol.* 54, 213–223.
- Elieh-Ali-Komi, D., Cao, Y., 2017. Role of mast cells in the pathogenesis of multiple sclerosis and experimental autoimmune Encephalomyelitis. *Clin. Rev. Allergy Immunol.* 52, 436–445.
- Goldstein, D.R., 2006. Toll like receptors and acute allograft rejection. *Transpl. Immunol.* 17, 11–15.
- Goldstein, D.R., Palmer, S.M., 2005. Role of Toll-like receptor-driven innate immunity in thoracic organ transplantation. *J. Heart Lung Transplant.* : Off. Pub. Int. Soc. Heart Transplant. 24, 1721–1729.
- Gorczyński, R.M., Chen, Z., Khatri, I., Yu, K., 2011. Graft-infiltrating cells expressing a CD200 transgene prolong allogeneic skin graft survival in association with local increases in Foxp3(+) Treg and mast cells. *Transpl. Immunol.* 25, 187–193.
- Guillot, C., Guillonnet, C., Mathieu, P., Gerdes, C.A., Menoret, S., Braudeau, C., Tesson, L., Renaudin, K., Castro, M.G., Lowenstein, P.R., Anegón, I., 2002. Prolonged blockade of CD40-CD40 ligand interactions by gene transfer of CD40lg results in long-term heart allograft survival and donor-specific hyporesponsiveness, but does not prevent chronic rejection. *J. Immunol.* 168, 1600–1609 Baltimore, Md. : 1950.
- Harrison, C.A., Bastan, R., Peirce, M.J., Munday, M.R., Peachell, P.T., 2007. Role of calcineurin in the regulation of human lung mast cell and basophil function by cyclosporine and FK506. *Br. J. Pharmacol.* 150, 509–518.
- He, H., Stone, J.R., Perkins, D.L., 2003. Analysis of differential immune responses induced by innate and adaptive immunity following transplantation. *Immunology* 109, 185–196.
- Heib, V., Becker, M., Warger, T., Rechtsteiner, G., Tertilt, C., Klein, M., Bopp, T., Taube, C., Schild, H., Schmitt, E., Stassen, M., 2007. Mast cells are crucial for early inflammation, migration of Langerhans cells, and CTL responses following topical application of TLR7 ligand in mice. *Blood* 110, 946–953.
- Ingulli, E., 2010. Mechanism of cellular rejection in transplantation. *Pediatr. Nephrol.* 25, 61–74.
- Ishida, T., Hyodo, Y., Ishimura, T., Takeda, M., Hara, I., Fujisawa, M., 2005. Mast cell numbers and protease expression patterns in biopsy specimens following renal transplantation from living-related donors predict long-term graft function. *Clin. Transplant.* 19, 817–824.
- Itoh, S., Nakae, S., Velotta, J.B., Kosuge, H., Connolly, A., Tsai, M., Adachi, H., Galli, S.J., Robbins, R.C., Fischbein, M.P., 2010. The role of recipient mast cells in acute and chronic cardiac allograft rejection in C57BL/6-Kit^{W-sh}/W-sh mice. *J. Heart Lung Transplant.* : Off. Pub. Int. Soc. Heart Transplant. 29, 401–409.
- Izawa, A., Suzuki, J., Takahashi, W., Amano, J., Isobe, M., 2001. Tranilast inhibits cardiac allograft vasculopathy in association with p21(Waf1/Cip1) expression on neointimal cells in murine cardiac transplantation model. *Arterioscler. Thromb. Vasc. Biol.* 21, 1172–1178.
- Jahanyar, J., Koerner, M.M., Loebe, M., Youker, K.A., Torre-Amione, G., Noon, G.P., 2008. The role of mast cells after solid organ transplantation. *Transplantation* 85, 1365–1371.
- Jin, D., Ueda, H., Takai, S., Muramatsu, M., Furubayashi, K., Ibaraki, T., Kishi, K., Katsuoka, Y., Miyazaki, M., 2007. Roles of chymase in stenosis occurring after polytetrafluoroethylene graft implantations. *Life Sci.* 81, 1291–1300.
- Joo, Y.H., Chang, D.Y., Kim, J.H., Jung, M.H., Lee, J., Cho, H.J., Jeon, S.Y., Kim, S.J., Kim, S.W., 2016. Anti-inflammatory effects of intranasal cyclosporine for allergic rhinitis in a mouse model. *Int. Forum Allergy Rhinol.* 6, 1139–1144.
- Jungraithmayr, W., 2015. The putative role of mast cells in lung transplantation. *Am. J. Transplant.* : Off. J. Am. Soc. Trans. Am. Soc. Trans. Surg. 15, 594–600.
- Knudsen, N.H., Lee, C.H., 2016. Identity crisis: CD301b(+) mononuclear phagocytes blur the M1-M2 macrophage line. *Immunology* 45, 461–463.
- Komi, D.E.A., Rambasek, T., Wohrl, S., 2017. Mastocytosis: from a Molecular Point of View.
- Komi, D.E.A., Khomtchouk, K., Santa Maria, P.L., 2019. A review of the contribution of mast cells in wound healing: involved molecular and cellular mechanisms. *Clin. Rev. Allergy Immunol.* [Epub ahead of print].
- Koskinen, P.K., Kovanen, P.T., Lindstedt, K.A., Lemstrom, K.B., 2001. Mast cells in acute and chronic rejection of rat cardiac allografts—a major source of basic fibroblast growth factor. *Transplantation* 71, 1741–1747.
- Kritas, S.K., A.S. Varvara, G., Murmura, G., Caraffa, A., Antinolfi, P., Toniato, E., A.P., Nerf, G., Frydas, S., Rosati, M., Tepa, M., Speziali, A., R.S. Pandolfi, F., Cerulli, G., Theoharides, T.C., Conti, P., 2013. Impact of mast cells in rejection of allografts. *Eur. J. Inflamm.* 11, 609–614.
- Lajoie, G., Nadasdy, T., Laszik, Z., Blick, K.E., Silva, F.G., 1996. Mast cells in acute cellular rejection of human renal allografts. *Mod. Pathol.* : Off. J. United States Can. Acad. Pathol. 9, 1118–1125.
- Land, W.G., 2006. Immunosuppressive strategies in organ transplantation in the light of innate immunity. *Exp. Clin. Transplant. Off. J. Middle East Soc. Organ Transplant.* 4, 406–415.
- Land, W.G., 2007. Innate immunity-mediated allograft rejection and strategies to prevent it. *Transplant. Proc.* 39, 667–672.
- Levi-Schaffer, F., Weg, V.B., 1997. Mast cells, eosinophils and fibrosis. *Clin. Exp. Allergy : J. Br. Soc. Allerg. Clin. Immunol.* 27 (Suppl. 1), 64–70.
- Levick, S.P., Melendez, G.C., Plante, E., McLarty, J.L., Brower, G.L., Janicki, J.S., 2011. Cardiac mast cells: the centrepiece in adverse myocardial remodelling. *Cardiovasc. Res.* 89, 12–19.
- Li, X.C., 2010. The significance of non-T-cell pathways in graft rejection: implications for transplant tolerance. *Transplantation* 90, 1043–1047.
- Li, Q.Y., Raza-Ahmad, A., MacAulay, M.A., Lalonde, L.D., Rowden, G., Trethewey, E., Dean, S., 1992. The relationship of mast cells and their secreted products to the volume of fibrosis in posttransplant hearts. *Transplantation* 53, 1047–1051.
- Libby, P., Pober, J.S., 2001. Chronic rejection. *Immunity* 14, 387–397.
- Liu, Y., Kloc, M., Li, X.C., 2016. Macrophages as effectors of acute and chronic allograft injury. *Curr. Transplant. Rep.* 3, 303–312.
- Loke, P., Gallagher, I., Nair, M.G., Zang, X., Brombacher, F., Mohrs, M., Allison, J.P., Allen, J.E., 2007. Alternative activation is an innate response to injury that requires CD4+ T cells to be sustained during chronic infection. *J. Immunol.* 179, 3926–3936 Baltimore, Md. : 1950.
- Lu, L.F., Lind, E.F., Gondek, D.C., Bennett, K.A., Gleeson, M.W., Pino-Lagos, K., Scott, Z.A., Coyle, A.J., Reed, J.L., Van Snick, J., Strom, T.B., Zheng, X.X., Noelle, R.J., 2006. Mast cells are essential intermediaries in regulatory T-cell tolerance. *Nature* 442, 997–1002.
- McLachlan, J.B., Hart, J.P., Pizzo, S.V., Shelburne, C.P., Staats, H.F., Gunn, M.D., Abraham, S.N., 2003. Mast cell-derived tumor necrosis factor induces hypertrophy of draining lymph nodes during infection. *Nat. Immunol.* 4, 1199–1205.
- Moore, T.C., Thompson, D.P., Glasscock, R.J., 1971. Elevation in urinary and blood histamine following clinical renal transplantation. *Ann. Surg.* 173, 381–388.
- Mukai, S., Ogawa, Y., 2018. Therapeutic potential of tranilast for the treatment of chronic graft-versus-host disease in mice. *PLoS One* 13, e0203742.
- Murphy, S.P., Porrett, P.M., Turka, L.A., 2011. Innate immunity in transplant tolerance and rejection. *Immunol. Rev.* 241, 39–48.
- Nakano, T., Lai, C.Y., Goto, S., Hsu, L.W., Kawamoto, S., Ono, K., Chen, K.D., Lin, C.C., Chiu, K.W., Wang, C.C., Cheng, Y.F., Chen, C.L., 2012. Immunological and regenerative aspects of hepatic mast cells in liver allograft rejection and tolerance. *PLoS One* 7, e37202.
- Nelson, P.J., Krensky, A.M., 2001. Chemokines, chemokine receptors, and allograft rejection. *Immunity* 14, 377–386.
- Ngo Nyekel, F., Pacreau, E., Benadda, S., Msallam, R., Abrink, M., Pejler, G., Davoust, J., Benhamou, M., Charles, N., Launay, P., Blank, U., Gautier, G., 2018. Mast cell degranulation Exacerbates skin rejection by enhancing neutrophil recruitment. *Front. Immunol.* 9, 2690.
- O’Keeffe, C., Baird, A.W., Nolan, N., McCormick, P.A., 2002. Mast cell hyperplasia in chronic rejection after liver transplantation. *Liver Transplant.* : Off. Pub. Am. Ass. Stud. Liver Dis. Int. Liver Transplant. Soc. 8, 50–57.
- Papadimitriou, J.C., Drachenberg, C.B., Ramos, E., Ugarte, R., Haririan, A., 2013. Mast cell quantitation in renal transplant biopsy specimens as a potential marker for the cumulative burden of tissue injury. *Transplant. Proc.* 45, 1469–1471.
- Pardo, J., Diaz, L., Errasti, P., Idoate, M., de Alava, E., Sola, I., Lozano, L., Panizo, A., 2000. Mast cells in chronic rejection of human renal allografts. *Virchows Arch. : Int. J. Pathol.* 437, 167–172.
- Pilewski, J.M., Panettieri Jr., R.A., Kaiser, L.R., Albelda, S.M., 1994. Expression of endothelial cell adhesion molecules in human bronchial xenografts. *Am. J. Respir. Crit. Care Med.* 150, 795–801.
- Pratschke, J., Stauch, D., Kotsch, K., 2009. Role of NK and NKT cells in solid organ transplantation. *Transpl. Int. : Off. J. Europ. Soc. Organ Transplant.* 22, 859–868.
- Reber, L.L., Sibilano, R., Mukai, K., Galli, S.J., 2015. Potential effector and immunoregulatory functions of mast cells in mucosal immunity. *Mucosal Immunol.* 8, 444–463.
- Romano, M., Tung, S.L., Smyth, L.A., Lombardi, G., 2017. Treg therapy in transplantation: a general overview. *Transpl. Int. : Off. J. Europ. Soc. Organ Transplant.* 30, 745–753.
- Sayed, B.A., Brown, M.A., 2007. Mast cells as modulators of T-cell responses. *Immunol. Rev.* 217, 53–64.
- Shen, H., Goldstein, D.R., 2009. IL-6 and TNF-alpha synergistically inhibit allograft acceptance. *J. Am. Soc. Nephrol. : JASN (J. Am. Soc. Nephrol.)* 20, 1032–1040.
- Silver, R.B., 2013. Role of mast cells in renal fibrosis. *Kidney Int.* 84, 214.
- Sorrentino, C., Scarinci, A., D’Antuono, T., Piccirilli, M., Di Nicola, M., Pasquale, M., Di Iorio, C., Di Carlo, E., 2006. Endomyocardial infiltration by B and NK cells foreshadows the recurrence of cardiac allograft rejection. *J. Pathol.* 209, 400–410.
- Summers, S.A., Chan, J., Gan, P.Y., Dewage, L., Nozaki, Y., Steinmetz, O.M., Nikolic-Paterson, D.J., Kitching, A.R., Holdsworth, S.R., 2011. Mast cells mediate acute kidney injury through the production of TNF. *J. Am. Soc. Nephrol. : JASN (J. Am. Soc. Nephrol.)* 22, 2226–2236.
- Summers, S.A., Gan, P.Y., Dewage, L., Ma, F.T., Ooi, J.D., O’Sullivan, K.M., Nikolic-Paterson, D.J., Kitching, A.R., Holdsworth, S.R., 2012. Mast cell activation and

- degranulation promotes renal fibrosis in experimental unilateral ureteric obstruction. *Kidney Int.* 82, 676–685.
- Takagaki, K., Osawa, S., Horio, Y., Yamada, T., Hamaya, Y., Takayanagi, Y., Furuta, T., Hishida, A., Ikuma, M., 2009. Cytokine responses of intraepithelial lymphocytes are regulated by histamine H(2) receptor. *J. Gastroenterol.* 44, 285–296.
- Tan, J., Zhou, G., 2005. Chemokine receptors and transplantation. *Cell. Mol. Immunol.* 2, 343–349.
- van den Hoogen, M.W., Steenbergen, E.J., Baas, M.C., Florquin, S., Hilbrands, L.B., 2017. Absence of intragraft B cells in rejection biopsies after rituximab induction therapy: consequences for clinical outcome. *Transplant. Direct.* 3, e143.
- Wakabayashi, T., Mori, S., Degawa, H., Takeda, Y., Tomikawa, S., Sugimoto, H., Yamauchi, J., Ohtsubo, O., Akiyama, N., 1986. Identification of inflammatory cells infiltrating renal allografts. *Acta Pathol. Jpn.* 36, 953–962.
- Walls, A.F., Jones, D.B., Williams, J.H., Church, M.K., Holgate, S.T., 1990. Immunohistochemical identification of mast cells in formaldehyde-fixed tissue using monoclonal antibodies specific for tryptase. *J. Pathol.* 162, 119–126.
- Walsh, P.T., Strom, T.B., Turka, L.A., 2004. Routes to transplant tolerance versus rejection; the role of cytokines. *Immunity* 20, 121–131.
- Wang, Y., Smith, W., Hao, D., He, B., Kong, L., 2019. M1 and M2 macrophage polarization and potentially therapeutic naturally occurring compounds. *Int. Immunopharmacol.* 70, 459–466.
- Wedel, J., Bruneau, S., Kochupurakkal, N., Boneschanski, L., Briscoe, D.M., 2015. Chronic allograft rejection: a fresh look. *Curr. Opin. Organ Transplant.* 20, 13–20.
- Werner, J.M., Lang, C., Scherer, M.N., Farkas, S.A., Geissler, E.K., Schlitt, H.J., Hornung, M., 2011. Distribution of intrahepatic T, NK and CD3(+)CD56(+)NKT cells alters after liver transplantation: shift from innate to adaptive immunity? *Transpl. Immunol.* 25, 27–33.
- Wezel, A., de Vries, M.R., Maassen, J.M., Kip, P., Peters, E.A., Karper, J.C., Kuiper, J., Bot, I., Quax, P.H., 2016. Deficiency of the TLR4 analogue RP105 aggravates vein graft disease by inducing a pro-inflammatory response. *Sci. Rep.* 6, 24248.
- Whitehouse, G.P., Hope, A., Sanchez-Fueyo, A., 2017. Regulatory T-cell therapy in liver transplantation. *Transpl. Int. : Off. J. Europ. Soc. Organ Transplant.* 30, 776–784.
- Wilson, M.T., Johansson, C., Olivares-Villagomez, D., Singh, A.K., Stanic, A.K., Wang, C.R., Joyce, S., Wick, M.J., Van Kaer, L., 2003. The response of natural killer T cells to glycolipid antigens is characterized by surface receptor down-modulation and expansion. *Proc. Natl. Acad. Sci. U.S.A.* 100, 10913–10918.
- Wu, J., Grassia, G., Cambrook, H., Ialenti, A., MacRitchie, N., Carberry, J., Wadsworth, R.M., Lawrence, C., Kennedy, S., Maffia, P., 2015. Perivascular mast cells regulate vein graft neointimal formation and remodeling. *PeerJ* 3, e1192.
- Xu, H., Zhang, X., Mannon, R.B., Kirk, A.D., 2006. Platelet-derived or soluble CD154 induces vascularized allograft rejection independent of cell-bound CD154. *J. Clin. Invest.* 116, 769–774.
- Yamada, M., Ueda, M., Naruko, T., Tanabe, S., Han, Y.S., Ikura, Y., Ogami, M., Takai, S., Miyazaki, M., 2001. Mast cell chymase expression and mast cell phenotypes in human rejected kidneys. *Kidney Int.* 59, 1374–1381.
- Yang, M., Ma, Y., Ding, J., Rao, L., Li, J., 2014. Preconditioning donor livers with cromolyn or compound 48/80 prolongs recipient survival in a rat orthotopic liver transplantation model. *Transplant. Proc.* 46, 1554–1559.
- Yin, D.D., Luo, J.H., Zhao, Z.Y., Liao, Y.J., Li, Y., 2018. Tranilast prevents renal interstitial fibrosis by blocking mast cell infiltration in a rat model of diabetic kidney disease. *Mol. Med. Rep.* 17, 7356–7364.
- Yousem, S.A., 1997. The potential role of mast cells in lung allograft rejection. *Hum. Pathol.* 28, 179–182.
- Zhang, A., Chi, X., Luo, G., Hei, Z., Xia, H., Luo, C., Wang, Y., Mao, X., Xia, Z., 2013. Mast cell stabilization alleviates acute lung injury after orthotopic autologous liver transplantation in rats by downregulating inflammation. *PLoS One* 8, e75262.
- Zweifel, M., Matozan, K., Dahinden, C., Schaffner, T., Mohacsi, P., 2010. Eotaxin/CCL11 levels correlate with myocardial fibrosis and mast cell density in native and transplanted rat hearts. *Transplant. Proc.* 42, 2763–2766.