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EUROPEAN JOURNAL OF INFLAMMATION Vol. 11, no. 3, 609-614 (2013)

EDITORIAL

IMPACT OF MAST CELLS IN REJECTION OF ALLOGRAFTS

S.K. KRITAS[1], A. SAGGINI[2], G. VARVARA[3], G. MURMURA[3], A. CARAFFA[4], P. ANTINOLFI[4], E. TONIATO[5], A. PANTALONE[6], G. NERI[7], S. FRYDAS[8], M. ROSATI[9], M. TEI[10], A. SPEZIALI[11], R. SAGGINI[7], F. PANDOLFI[11], G. CERULLI[10], T.C. THEOHARIDES[12] and P. CONTI[5]

[1]Department of Microbiology and Infectious Diseases, School of Veterinary Medicine, Aristotle University of Thessaloniki, Macedonia, Greece; [2]Department of Dermatology, University of Rome Tor Vergata, Rome, Italy; [3]Dental School, University of Chieti-Pescara, Italy; [4]Orthopedic Division, University of Perugia, Perugia, Italy; [5]Immunology Division, Medical School, University of Chieti-Pescara, Chieti, Italy; [6]Orthopedic Division, University of Chieti-Pescara, Chieti, Italy; [7]Department of Neurosciences and Imaging, Faculty of Medicine and Surgery, G. d'Annunzio University Chieti-Pescara, Chieti, Italy; [8]Department of Parasitology, School of Veterinary Medicine, University of Thessaloniki, Macedonia, Greece; [9]Gynecology Clinic, Pescara Hospital, Pescara, Italy; [10]Nicola's Foundation, Onlus, Arezzo, Italy; [11]Department of Internal Medicine, Catholic University of the Sacred Heart, Rome, Italy; [12]Department of Pharmacology and Experimental Therapeutics, Biochemistry and Internal Medicine Tufts University School of Medicine, Tufts-New England Medical Center, Boston, MA, USA

Received September 15, 2013 – Accepted November 5, 2013

Mast cells in the tissue are located close to nerves in and around the small vessels where they orchestrate important immune response after antigen recognition through Toll-like receptors. Mast cells can activate T and B lymphocytes and dendritic cells and have been postulated to act directly within tissue allografts and/or to induce indirect effects via inflammatory mediator release, therefore they have been shown to play an indispensable role in allograft tolerance. Major limitation in the success of transplantation is the immune response of the recipient to the donor tissue. The failure of tissue grafting is caused by an inflammatory reaction called rejection. Mast cells play a role during immune response and are elicited with transplanted allograft and also may exhibit their immune-regulatory effects directly through secretion of modulatory cytokines and activation of metabolic pathways. However, the role of mast cells in transplantation is poorly understood. The most severe rejection episodes have been found in patients with an increased number of mast cells. Mast cell mediators which can activate latent forms of TGF-β or increase angiotensin II levels are capable of inducing fibrosis through various mechanisms, activating fibroblasts and inducing collagen synthesis. Mast cells are also implicated in regulatory T-cell functions and are required to sustain peripheral tolerance via Treg, therefore there is an interaction between mast cells and Treg cells. Treg create IL-9 in enhancing mast cell growth and chemotaxis, suggesting that Treg and mast cells form a functional unit that mediates graft tolerance. In this study we concentrate our attention on the role of mast cells in rejection of allografts and try to understand the role of mast cell-related immune mechanisms in organ transplantation.

Key words: mast cells, rejection, allografts, inflammation, immunity

Mailing address:
Spyridon K. Kritas, DVM, PhD, Dipl. ECPHM,
Associate Professor,
Department of Microbiology and Infectious Diseases,
School of Veterinary Medicine,
Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece
Tel/Fax: +30 2310 999940
e-mail: skritas@vet.auth.gr

1721-727X (2013)
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The history of the mast cell (MC) goes back over 100 years to when Paul Ehrlich first described them. As Ehrlich depicted, mast cells are recognizable by their large granules that, after reaction with aniline dyes, exhibit metachromatic staining. Mast cells in the tissue are spatially located close to nerves and around the small vessels and orchestrate important immune attacks against invading bacteria and viruses (1-2).

Research on mast cell biology shows how they illicit positive or negative effects on tissue and organ function. Once released, mast cells undergo a maturation process that involves numerous factors including the specific cytokines and stem cell factor (SCF) (3). The SCF receptor, c-Kit, is abundantly expressed in mature mast cells and plays a critical role in the maturation, development and release. Several studies also reported that mast cells express other surface receptor binding sites such as β2-integrins, intercellular adhesion molecule-1 (ICAM-1), serotonin, vascular endothelial growth factors (VEGF A–D) and the receptors VEGFR1 and VEGFR2 , supporting the role of mast cells in angiogenic processes (4).

Mast cells elicit the first and fastest immune response after antigen recognition through Toll-like receptors and synthesize over 50 biologically potent molecules that include most of the known pro-inflammatory cytokines [e.g., interleukin (IL)-1, IL-8, IL-10, IL-13, interferon-[gamma], basic fibroblast growth factor (bFGF), TNF-α, IL-16, IL-18 and IL-33], tryptase, histamine and other compounds which causes inflammation and chemotaxis of other immune cells (5). Active compounds of mast cell granules in addition to histamine and heparin include: serine proteases, prostaglandin D2, leukotriene C4, and cytokines (6). Mast cells can activate T and B lymphocytes and dendritic cells. Mast cells have been postulated to act directly within tissue allografts and/or to induce indirect effects via inflammatory mediator release into the circulation (such as from regional lymph nodes) (7).

Moreover, mast cells process and present antigen to T cells through class I and class II major histocompatibility complexes (8). Therefore, they are essential in the initiation of the innate immune response and recently they have been shown to play an indispensable role in allograft tolerance. Alloantigens are usually products of polymorphic genes and are cells or tissue antigens that are present in some members of a species and not in others and are recognized as foreign on an allograft. Transplantation is the process of taking cells, tissues or organs, called a graft, from one individual and placing into a different individual. A major limitation in the success of transplantation is the immune response of the recipient to the donor tissue. The failure of tissue grafting is caused by an inflammatory reaction called rejection. Mast cell activation in inflammatory response, like host allograft rejection, may cause tissue mast cells to release unwanted mediators into the environment adding a detrimental effect during transplantation (9).

Mast cells, have proinflammatory activity, and they are unexpectedly involved in the induction of transplant tolerance (10). Many studies have done much to clarify our understanding about mast cells and graft rejection (11) and recent evidences suggest that mast cells play a role during the immune responses that are elicited with transplanted allograft. Mast cells also may exhibit their immunoregulatory effects directly through secretion of modulatory cytokines and activation of metabolic pathways (12).

However, the role of mast cells in transplantation is poorly understood. In several studies the authors reported a great increase in the number of mast cells after transplantation (1974 by Colvin and Dvorak) (13). Therefore, mast cells are abundant in the tissue of transplanted patients and their infiltration has been observed from the first week after transplantation. Patients with increased numbers of mast cells also had the most severe rejection episodes. This high number of mast cells it is often associate with the severity of fibrosis and edema (14). In addition, genes related to mast cells such as alpha-chymase, carboxypeptidase, high affinity IgE receptor, etc. are over expressed in tolerant allograft. Mast cell mediators such as histamine, bFGF, and TGF-β and proteases such as chymase and cathepsin G, which can activate latent forms of TGF-β or increase angiotensin II levels, are capable of inducing fibrosis through various mechanisms, activating fibroblasts and inducing collagen synthesis (15). 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 (16).

The activation of mast cells in graft rejection can be revealed by toluidine blue staining which shows that they are partially degranulated. Mast cell-derived TGF- β provoke an increase of extracellular matrix in mast cell competent animals, an effect absent in experimental model animal (17). In addition, TGF-β generated from mast cell may inhibit immune alloreactivity directly through suppression of effector T-cell function and inhibition of Th1 and Th2 lymphocytes (18).

These recent findings have implicated mast cells in

Table I. *Some recent findings.*

- Mast cells suppress murine GVHD in a mechanism independent of CD4+CD25+ regulatory T cells.

- Mast cell activation contributes to sickle cell pathobiology and pain in mice.

- Mast cell quantitation in renal transplant biopsy specimens as a potential marker for the cumulative burden of tissue injury.

- Mast cell-deficient Kit(W-sh) "Sash" mutant mice display aberrant myelopoiesis leading to the accumulation of splenocytes that act as myeloid-derived suppressor cells.

- Mast cells: multitalented facilitators of protection against bacterial pathogens.

- SHP-1 regulation of mast cell function in allergic inflammation and anaphylaxis.

- Mast cells rescue implantation defects caused by c-kit deficiency.

- Complement factor C5a as mast cell activator mediates vascular remodelling in vein graft disease.

- Chemokine (C-C motif) receptor 2 mediates mast cell migration to abdominal aortic aneurysm lesions in mice.

- Mast cell activation and degranulation promotes renal fibrosis in experimental unilateral ureteric obstruction.

- Mast cells promote the growth of Hodgkin's lymphoma cell tumor by modifying the tumor microenvironment that can be perturbed by bortezomib.

- p85β regulatory subunit of class IA PI3 kinase negatively regulates mast cell growth, maturation, and leukemogenesis.

- Mast cells mediate allograft tolerance.

- IL-9 contributes to immunosuppression mediated by regulatory T cells and mast cells in B-cell non-hodgkin's lymphoma.

- Graft-infiltrating cells expressing a CD200 transgene prolong allogeneic skin graft survival in association with local increases in Foxp3(+)Treg and mast cells.

regulatory T-cell function. Mast cells are required to sustain peripheral tolerance via Treg, therefore, there is an interaction (cross-talk) between mast cells and Treg cells (19). Both mast cells and Treg are needed to create a local immunosuppressive environment in the transplant. Li-Fan Lu et al. (10, 16) demonstrated the existence of this novel T_{Reg}–IL-9–mast cell relationship within tolerant allografts. Important evidence has been demonstrated (10) for the role of mast cells in Treg-mediated immunoregulatory activities which produce IL-9 responsible for mast cell recruitment and function.

Activated mast cells secrete TGF-β and IL-10 for further amplification and activation of natural Treg cells which inhibit $CD8^+$ effector cells (20). Therefore, Treg secrete IL-9, enhancing mast cell growth and chemotaxis and suggesting that Treg and mast cells form a functional unit that mediates graft tolerance (10). We believe that the interactions among Treg cells, IL-9, and mast cells are very important and neutralization of IL-9 prevents the regulation of graft rejection by Treg cells, (10). A recent study has shown that statins inhibit mast cell function through inhibition of SCF-induced differentiation of mast cells from their hematopoetic progenitors (21).

It has been also reported that mast cells can be recruited to the graft by Foxp3+ Treg cells through the production of IL-9 to maintain tolerance (22). In these events mast cell degranulation often induces prompt rejection of the graft (23).

In addition, tissue survival is significantly reduced in the mast cell-deficient individual and acute rejection is more severe in mast cell-deficient experimental animals. Mast cells also influence the presence of T cells in those individuals where more T-lymphocytes are found in the transplanted tissue. These observations lead to the conclusion that mast cells may play a protective role after tissue transplantation and acute rejection. Recently, it was reported that mast cells suppress murine GVHD in a mechanism independent of $CD4^+CD25^+$ regulatory T cells (24).

In spite of their protective effects during acute allograft rejection, mast cell long-term effects and contributions to the progression of chronic allograft failure seem to be detrimental. However, the exact mechanisms of this protective mast cell-related effect and of the mast cell-assisted Treg function remain to be clarified.

Increased numbers of mast cells have been reported in explanted human tissues and they have a major role in the pathophysiology of diseases where there is an elevation in mast cell density, associated with a concomitant increase in matrix metalloproteinase activity and extracellular matrix degradation (25). In addition, *in vitro* studies have verified that mast cell proteases are capable of activating collagenase, gelatinase and stromelysin. These adverse events do not occur in W/W^v mast cell-deficient mice or when mast cells are pharmacologically inactivated (26). Therefore, mast cells cause activating matrix metalloproteinases and causing collagen degradation and fibrosis in the stressed, injured or diseased tissue. However, the factors responsible for initiating mast cell activation are poorly understood, in fact, our understanding of the effects of secretagogues on tissue mast cells is very limited (11).

Autoimmune disease is recognized as a disorder driven by T cells, in particular $CD4^+$ T cells. Mast cells have also been observed in fibrotic areas in experimental animals with dilated hypersensitivity following experimentally-induced autoimmune diseases (27). These effects can be reduced by using interleukin-10 and TGF-β (produced by Treg), which has been shown to inhibit histamine levels, mast cell density and mast cell size (28); while interferon gamma protects against chronic inflammation by preventing mast cell degranulation and fibrosis.

Endothelin 1 (ET 1), also known as preproendothelin-1, is a protein that in humans is encoded by the *EDN1* gene (29). The protein encoded by this gene is proteolytically processed to release a secreted peptide termed endothelin 1. This peptide is a potent vasoconstrictor and is produced by vascular endothelial cells. ET 1 is one of three isoforms of human ET 1. Since administration of ET 1 in animal model causes mast cell degranulation, MMP-2 activation and collagen degradation, it has been reported that blocking ET 1 receptor prevent MMP activation and attenuates inflammation in transplanted animal models (16).

The complexity of non-T cells in transplant models is very important, and will be the topic of future research regarding the complex interactions among diverse subsets of non-T cells *in vivo* in transplant rejection and tolerance induction. Many points still

remain to be elucidated, for example the innate immune response to allograft, or how mast cells interact with Treg cells in allograft rejections.

Mast cells are also involved in chronic rejection where they are associated with an increased incidence of allograft fibrosis, Li et al. (16). These effects stimulate fibroblasts, increase collagen synthesis and lead to tissue fibrosis. Therefore, chronic rejection is associated with an up-regulation of mast cells in the tissue and their generation of IL-4 transcription and translation which may activate fibroblasts and lead to fibrosis (30). The number of mast cells is significantly higher in patients with chronic rejection, and there is a potential relationship between mast cells and fibrosis.

In acute rejection, mast cells seem to have a protective role by the activation and amplification of Treg cell function and through the inhibition of the effector T lymphocytes; while in chronic rejection, they have adverse function through the production of several different profibrotic mediators. Understanding how mast cells are involved in transplantation, may shed light on potential new therapies useful for improving preventing rejection. However, further studies are needed to fully understand the role of mast cell-related immune mechanisms in organ transplantation.

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