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The enigmatic role of mast cells in dominant tolerance

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Abstract

Purpose of review—The role of regulatory T cells (T^{reg}) in peripheral tolerance has been studied extensively in transplantation research. Recently, mast cells have been shown to play an indispensable role in allograft tolerance. The purpose of this review is to inform the reader on the current standings of the role of mast cells in dominant tolerance with an emphasis on the interaction of mast cells with T^{reg}.

Recent findings—Mast cells are required to sustain peripheral tolerance via T^{reg}. T^{reg} can stabilize mast cells degranulation by contact-dependent mechanisms through the interaction of OX40 and its ligand OX40L, and by production of soluble factors, such as interleukin-10 and transforming growth factor-β. Conversely, the activation and subsequent degranulation of mast cells break peripheral tolerance.

Summary—Both mast cells and T^{reg} are needed to create a local immunosuppressive environment in the transplant. T^{reg} are not only necessary to suppress effector T-cell responses but also to stabilize mast cells. Mast cells in return could contribute to the immunosuppressive state by release of transforming growth factor-β, interleukin-10 and specific proteases. However, the molecular basis for mast cells control of T^{reg} suppression in organ transplantation is still unresolved.

Keywords

dominant tolerance; mast cells; regulatory T cells

Introduction

Peripheral tolerance, subdivided in linked suppression and infectious tolerance, is explained by the generation of regulatory T cells (T^{reg}) in the periphery called adaptive T^{reg} (aT^{reg}) [1]. The importance of aT^{reg} in organ transplantation has been reported in clinical and animal studies [2,3]. Additionally, mast cells are necessary in the establishment of peripheral tolerance [4,5], and multiple studies [6,7,8••,9,10,11•,12] have addressed the impact of T^{reg} on the stabilization of mast cells by several mechanisms. Conversely, how mast cells influence T^{reg} or contribute to suppression of alloreactive immune responses needs yet to be elucidated. On the basis of current knowledge of mast cells, we will discuss some of the possible modes of interaction.

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Background

The establishment of an adaptive immune system is dependent on a complex series of events to avoid self-reactivity. With regard to T-cell development, progenitors migrate from bone marrow to the thymus in which rigorous selection steps take place known as 'central tolerance'. During this process, a small proportion of thymocytes upregulates the forkhead transcription factor forkhead box P3 (FoxP3) [13–15]. These T cells, called natural T^{reg} (nT^{reg}), have profound suppressive capacity in the development and function of effector T cells (T^{eff}) [16]. They are able to silence self-reactive T^{eff} that have escaped thymics election as shown in autoimmunity studies [17,18]. Furthermore, during antigen presentation by dendritic cells in the absence of costimulation, nT^{reg} are able to induce a suppressor phenotype in naive T cells (called adaptive T^{reg}, aT^{reg}). This active process is known as infectious tolerance.

In allogeneic organ transplantation, the introduction of foreign proteins leads to the rapid expansion of T^{eff} and subsequent rejection. Both experimental and clinical studies [2,3] have shown the importance of T^{reg} in organ transplantation. Many experimental approaches have been designed to induce a population of T^{reg} with specificity for these alloantigens to allow the allogeneic tissue to be accepted. Indeed, when looking at cellular composition in accepted grafts large numbers of T^{reg} are present. Curiously, another cell type is also abundantly present: the mast cell.

Mast cells are members of the innate immune system and can be found at locations that are in close contact with the outside world such as skin, lung and intestinal mucosa. They are characterized by staining of granules with basic dyes [19], such as toluidine blue, and can also be detected by antibody staining for the highly expressed stem cell factor receptor, c-kit, in combination with the high affinity immunoglobulin E (IgE) receptor, FcεRI [20]. Until recently, they have been considered proinflammatory in both protection against parasitic infections and allergies. This side of the mast cells is based on the activation and subsequent degranulation mediated by cross-linking of FcεRI by IgE [20,21]. The immediate response leads to the release of a wide array of proinflammatory mediators, chemotactic factors and proteolytic enzymes, inducing a rapid inflammation and tissue remodeling [21]. Further, mast cells aid in wound healing by releasing factors that promote fibrogenic activities, platelet activation and recruitment of leukocytes to fight off possible infection [22–26]. Thus, although detrimental in allergies, the role of mast cells in mounting an immune response to defend against parasites and in maintaining the physical barrier is indispensable.

Mast cells are not known for their immune suppressive capacities, and many correlative studies [27] show an increased number of mast cells in rejecting grafts, suggesting that mast cells play a role in preventing graft tolerance. However, the initial work by Zelenika *et al.* [28] showed a high expression of mast cells-related gene products in tolerant grafts, emphasizing the beneficial role for mast cells in maintaining peripheral tolerance. Additionally, our laboratory showed, in a skin graft model, the functional need for mast cells during the initiation phase of tolerance [5]. This finding was later confirmed in a heterotopic heart transplant model [4]. The duality of mast cells as positive and negative regulators of the immune response is only beginning to be resolved.

Dominant tolerance

As mentioned above, tolerance can be defined depending on the mechanism involved in its establishment. In this regard, recessive tolerance is accomplished by deletion of alloreactive T cells. On the contrary, dominant tolerance is explained by the generation of aT^{reg} and

manifested as linked suppression and infectious tolerance, which will be discussed below [1].

Regulatory T cells

Early observations suggested that a specific population of $CD4^+$ T cells is responsible for the prevention of autoimmune diseases. Elimination of these cells through genetic mutation in the *Foxp3* gene, in the mutant mouse strain scurfy [29] and the human X-linked recessive syndrome immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) [30], resulted in profound systemic autoimmunity. FoxP3 is expressed in regulatory $CD25^+CD4^+$ T cells, and retroviral transduction of FoxP3 in naive $CD4^+CD25^-$ T cells engendered suppressive properties among these cells [14]. In addition, transfer of this subset of CD4 T cells was able to protect against the development of autoimmunity [31]. Therefore, FoxP3 is regarded as a key marker that defines T^{reg}.

It was shown that T^{reg} suppresses the proliferation of the effector population by inhibition of interleukin (IL)-2 secretion on the target cells. This can either be contact dependent by activation of its T-cell receptor [32] through the expression of granzyme A [33] or B [34] or in a contact-independent manner via IL-10 [35], IL-35 or transforming growth factor beta (TGF-β) [36]. Further research demonstrated that more than one population of T^{reg} can be found, which can be divided in two main groups. As described above, nT^{reg} and aT^{reg}, the latter including several distinct populations: regulatory type 1 T cell (Tr1) (IL-10-producing T cells) [35], T helper cell type 3 (Th3) (TGF-β-producing T cells) [36] and a recently described subset of reversion-resistant T^{reg} derived in the presence of the vitamin A metabolite retinoic acid [37].

Linked suppression and infectious tolerance

Davies *et al.* [38] showed that copresentation of tolerated self-antigen with nontolerated alloantigen on the same antigen-presenting cell led to tolerance to both self-antigens, now known as linked suppression. This process is independent of $CD8^+$ T cells, showing that the newly induced T^{reg} are sufficient for this effect [39].

Another mechanism was revealed when naive T cells from untreated mice were transferred into tolerated mice in which all T cells were deleted by thymectomy and CD4 antibody treatment. These naive T cells were able to break the established tolerance [40]. Surprisingly, when the infused naive lymphocytes are allowed to coexist for 2 weeks with the tolerated T-cell repertoire before deleting this endogenous pool of lymphocytes, tolerance to skin grafts was maintained [41]. These elegant experiments clearly demonstrate that naive T cells can become suppressive by the coexistence with tolerant cells and was named ‘infectious tolerance’. Years later, the same observations were confirmed using a cardiac allograft transplantation model [42].

The mast cells–regulatory T cell axis in dominant tolerance

Although the role of T^{reg} in the maintenance of peripheral tolerance is quite established, other cells of the immune system contribute significantly. As mentioned previously, mast cells are known for their proinflammatory properties, and it was surprising that mast cells were absolutely required for the establishment of tolerance toward an allogeneic transplant [4,5]. Still unclear are the mechanisms of interaction between the T^{reg} and the mast cells that help maintain a favorable mast cell–T^{reg} axis in dominant tolerance.

Proinflammatory and immune suppressive mast cells

It is known that during the maintenance phase of dominant tolerance, mast cells have a detrimental effect on graft survival, especially in highly vascularized tissues such as kidney, heart and lung. This effect has been attributed to the slow non-IgE-mediated degranulation causing fibrosis and intima hyperplasia [4,43,44]. In favor of this notion, a retrospective study [45] among allergic rhinitis patients who received a kidney transplant showed more severe episodes of rejection compared with non-atopic transplanted patients, suggesting that the release of proinflammatory mediators caused by IgE-mediated degranulation of mast cells induces the overt inflammation. We confirmed this finding in a skin graft model with ovalbumin-sensitized mice. Subsequent local challenge led to acute rejection of the graft, showing that mast cell degranulation breaks established acquired tolerance (unpublished observation).

However, we and others [4,5] have shown that for the establishment of tolerance, mast cells are essential. Further, in the murine skin graft model, increased levels of IL-9 were found. IL-9 is a cytokine abundantly secreted by T^{reg} and is known to enhance mast cells growth and chemotaxis. The observation that IL-9 neutralization leads to graft loss confirms that IL-9 is an important molecular link between T^{reg} and mast cells [5].

Regulatory T cell dampens the proinflammatory properties of mast cells

Recently, it was reported that T^{reg} can directly stabilize mast cells by desensitizing mast cells against FcεRI-mediated degranulation. It has been shown in an in-vitro system with bone marrow-cultured mast cells that T^{reg} can downregulate FcεRI in a contact-dependent manner [11•]. Additionally, Gri *et al.* [8••] showed that T^{reg} can increase cyclic AMP (cAMP) and inhibit intracellular calcium flux in mast cells degranulation by OX40–OX40 ligand (OX40L) interaction *in vitro* and *in vivo*. This mechanism of mast cells desensitization was independent of IL-10 and TGF-β [11•].

However, IL-10, TGF-β and also IL-4 have been shown to have an impact on mast cells development, survival and FcεRI expression by different mechanism [6,7,10,12,46]. It was observed in signal transducer and activator of transcription 6 $(STAT6)^{-/-}$ mice that STAT6 signaling was absolutely required for IL-4-mediated FcεRI down-regulation [46], and the synergistic effect of IL-10 was not impaired [6]. In the presence of IL-4, the expression of the FcεRI-β-subunit was decreased, with minimal impact on the expression of the α-subunit, and no effect was observed on the expression of the γ-subunit. This down-regulation of FcεRI resulted in reduced responsiveness during late phase response characterized by infiltration of leukocytes and measured by tumor necrosis factor alpha (TNF-α) release. However, the immediate responses (that is, the release of granular content) were not altered, as measured by β-hexoaminidase release [6]. In the case of IL-10, it was shown that FcεRI downregulation was STAT3 dependent and also induced reduction of STAT5, Akt, Syk and Fyn in mast cells [12]. The latter four molecules are part of different pathways known to be involved in IgE-mediated degranulation [47–49]. However, the effect of IL-10 treatment had a significant impact on the immediate response to IgE [12]. Lastly, TGF-β impacts the rate of protein synthesis of the IgE receptor and not RNA expression, suggesting that TGF-β may regulate mast cells functions via posttranslation mechanisms [7]. The effects of TGF-β on protein synthesis have recently been shown to be SMAD dependent [50].

These observations clearly show that, during dominant tolerance, T^{reg} not only play an important role in suppressing effector T-cell development and function but are also needed to regulate the responsiveness of mast cells to IgE. That T^{reg} have a diminished suppressive capacity in atopic patients [51–53] could, therefore, contribute to increased mast cells

degranulation and thus aggravating allergic inflammation, whereas in graft tolerance, the T^{reg} suppress this proinflammatory response by suppressing FcεRI expression.

Possible contributions of mast cells to dominant tolerance

Although it is clear that T^{reg} can directly influence mast cells function, little is known about the effects of mast cells on T^{reg}. Here, we discuss some of the possible mechanisms that mast cells employ to regulate acquired peripheral tolerance.

Mast cells produce IL-10 and TGF-β, two suppressive cytokines. As such, mast cells are able to suppress T-cell proliferation and could possibly generate aT^{reg} via the production of these cytokines. Indeed, mast cells can downregulate antigen-specific T-cell proliferation after mosquito bites in an IL-10-mediated fashion, suggesting that IL-10 is one of the immune suppressive mediators released by mast cells [54]. That IL-10 plays an important role in suppressing immune responses was emphasized by a study [9] in contact dermatitis, in which IL-10 derived from mast cells significantly reduced the skin disease as measured by leukocyte infiltration and inflammation. Moreover, this group [9] and others [55,56] showed in both rodents and humans that low levels of either ultraviolet A (UVA) or UVB irradiation lead to activation of mast cells in the skin with the subsequent release of both IL-10 and histamine. Additionally, type I interferons (IFNs) induce IL-10 and TGF-β secretion by human mast cells; however, it also downregulates OX40L [57]. As has been shown in the murine bladder carcinoma (MB49) model, tumors can induce IL-10 production by the infiltrating leukocytes, thereby contributing to the immunosuppressive environment [58]. Although the role of mast cells in tumors is not clear yet, their presence has been linked to a bad prognosis. IL-10 derived from mast cells could contribute to the generation of tumor-specific aT^{reg}. Therefore, next to the T^{reg}, it is likely that one of the main sources of IL-10 during tumor development is the mast cell [59,60]. The possible positive effects of immune suppression in transplantation have mostly been attributed to the presence of T^{reg}, whereas the negative effect of fibroses and intima hyperplasia mostly point at the mast cells [43,61–64]. However, the actual impact of the mast cells-derived IL-10 and TGF-β on dominant tolerance has yet to be established.

Mast cells express the serotonin-specific transporter (SERT) that enables them to take up and store serotonin. When mast cells get activated by IgE, the stored serotonin can be released. Serotonin is considered an accessory ‘third’ signal for T-cell proliferation and is involved in early T-cell activation of both naive $CD4^+$ and $CD8^-$ T cells [65–67]. It is, therefore, plausible that under tolerant conditions mast cells actively deplete the local environment of serotonin needed for robust T-cell responses.

Moreover, the ability to present antigen in the context of major histocompatibility complex class II (MHC-II) could also imply that they are able to influence T-cells responses. More recently, it has been shown that mast cells express other costimulatory molecules of both the TNF superfamily [OX40L, CD30 ligand (CD30L), Fas and glucocorticoid-induced TNF receptor (GITR)] as well as the B7 family [CD80, CD86, PD ligand 1 (PD-L1) and PD-L2], making them bona fide antigen-presenting cells [68]. Recently, Nakano *et al.* [69••] showed that Notch signaling was required for upregulation of both MHC-II and OX40L on mast cells. However, these mast cells skewed naive T cells to a Th2 phenotype, inducing the production of IL-4, IL-10 and IL-13 and suppressing the production of IFN-γ. It is known that the environment in a graft is Th2 skewed [70], therefore suggesting that antigen presentation by mast cells, under tolerant conditions, could benefit graft acceptance.

Lastly, the release of a wide array of de-novo-generated (proteolytic) enzymes could modulate the direct cytokine environment. Although nothing is known about the role of mast cell proteases in organ transplantation, we observed upregulation of monocyte

chemoattractant protein 1 (MCP1) and MCP5 in tolerated allogeneic grafts [5]. Recently, the study [71] of a patient who had received a kidney transplant also showed elevated levels of mast cells tryptases in the blood, although no correlation was found with graft function.

A barrier with addressing the role of mast-cell-derived mediators in tolerance and immunity is the ability to conditionally control the production of defined mediators by mast cells. However, with the development of mast cells-specific protease driven Cre knock-in mice [72•,73•], the technology to temporally, conditionally and spatially control mast cells synthesis of mediators *in vivo* is now possible.

Conclusion

There is little doubt that mast cells are regulators of adaptive immune responses. Figure 1 shows the described interactions between mast cells and T cells in a very simplified form. Many results come from observations without having defined the mediators that underlie the phenomena. However, it is recognized that there is a complex set and series of interactions between mast cells and T^{reg}. The two faces of mast cells, either as inducers of inflammation or regulators of tolerance, are likely based on whether mediators are released by degranulation or secretion, the nature of the subsets of mast cells that are involved and other environmental cues that control mast cells phenotype. Defining the molecular basis for mast cells regulation of immunity and tolerance is the quest for the future.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 449).

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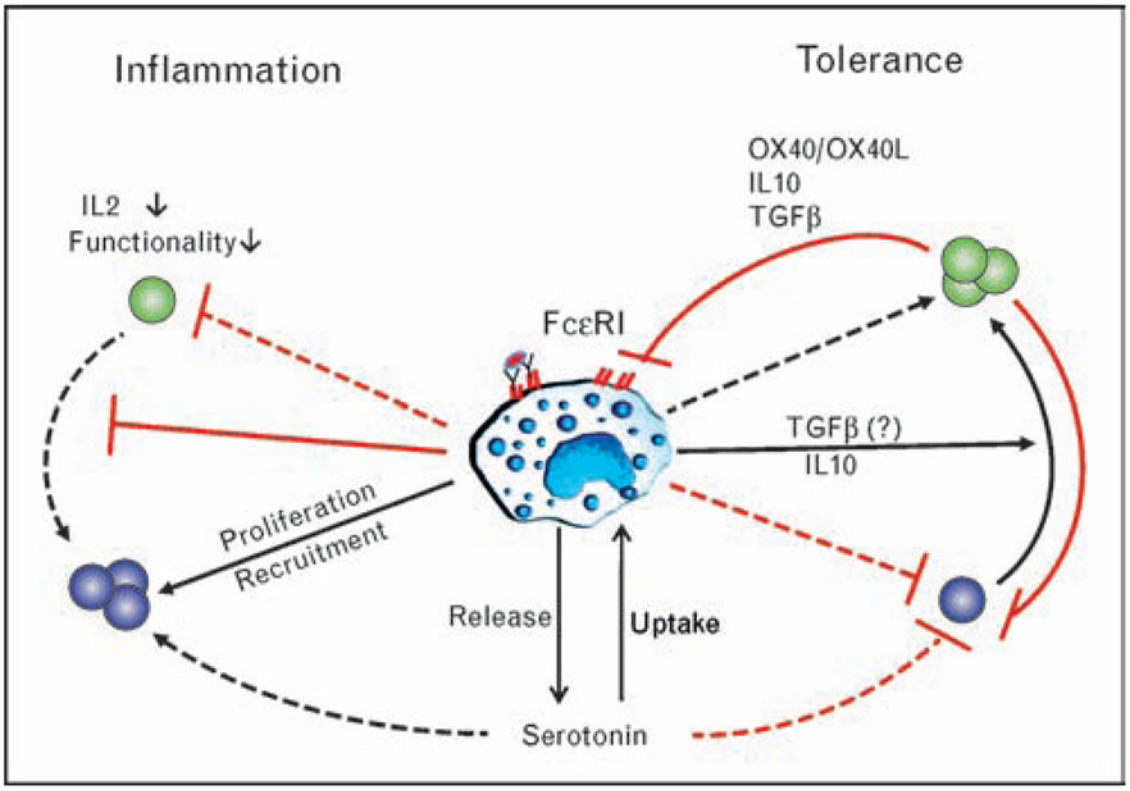

Figure 1. Interaction of mast cells with T cells under inflammatory and tolerant conditions

The binding of allergen IgE to the high affinity IgE receptor FcεRI arms the MC. Subsequent encounter with the allergen leads to the immediate release of granular content leading to a proinflammatory response as seen in allergies. This response leads to suppression of T^{reg} functionality and recruitment and proliferation of T^{eff} among other proinflammatory leukocytes. However, under tolerant condition, the MCs are needed to establish an immunosuppressive environment. The T^{reg} present in the graft not only suppress T^{eff} but also the proinflammatory properties of the MC mainly by influencing the expression of the FcεRI. IL, interleukin; IgE, immunoglobulin E; MC, mast cell; OX40L, OX40 ligand; T^{eff}, effector T cell; T^{reg}, regulatory T cell; TGF-β, transforming growth factor beta. ●, regulatory T cell; ●, effector T cell; ●, mast cell.