

## Review Article

# Relationship between Mast Cells and Autoimmune Diseases

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## Abstract

Mast Cells (MCs) are no longer considered as only effectors cell in allergic disorders, but also as important modulators of innate and adaptive immune responses. Increased numbers of MCs together with signs of their degranulation at sites of inflammation and tissue injury have been shown in studies of both human disease and animal models of autoimmune disorders. Despite this substantial evidence, MCs role in autoimmunity is still on debate. MCs can regulate the recruitment, survival and function of many immune cells. Therefore, they are able to enhance or suppress the initiation, magnitude and/or continuance of immune responses in autoimmune conditions. Further studies are essential to gain a more detailed understanding of MCs participation in autoimmunity. Targeting MC may be of value in future prevention and treatment of autoimmune diseases.

**Keywords:** Mast cells; Autoimmune diseases

## Autoimmune Diseases

Autoimmune diseases could be defined by inadequate or exacerbate excessive immune response against self-antigens. In this condition chronic diseases arise due the breakdown of host immune tolerance. The etiology of autoimmune disease is not clearly understood, but both genetic and environmental factors are implicated in autoimmune disease development [1,2]. Within many environmental factors described as a trigger of autoimmunity, we can detach chemical agents, drugs, UV radiation, however infectious agents could be considered as one of the main risk factors to autoimmunity pathology development [3]. A possible mechanism whereby infectious agents trigger autoimmunity is known as molecular mimicry. According to this concept microorganisms have molecular structure that cross-reacted with endogenous molecules [4]. Despite being considered a “rare” disease, the worldwide prevalence of autoimmune disease is around 5% and, curiously, of this total more than 70% are women. This elevated prevalence between women is attributed, at least in part, to hormonal changes throughout woman life [5]. Although each autoimmune disease shows specific characteristics depending on the affected tissue, all of them share a common pathologic mechanism, indicating a similar origin. The same environment and genetic inductors and also the same immune mediators of pathogenesis such as autoantibodies, leukocyte infiltrate and inflammatory pathway response are present in different autoimmune diseases context [6]. Activation of T and B cells plays an important role both in physiologic states and in response to pathogens but sometimes could trigger diseases, such as allergy and autoimmune diseases [3,7]. The organism has mechanisms that regulate all steps of lymphocytes activation and reduces deleterious effects possibility even in utero [8]. Tolerance is the major mechanism by which immune system control pathologic effects of T and B cells activation. Basically, tolerance acts by two ways: denominated central and peripheral tolerance. In the central tolerance, auto-reactive lymphocyte clones are deleted in the thymus.

In the case of peripheral tolerance, mature reactive clones cells are regulated by suppression or anergy mechanisms such as cytokines and different type of suppressive immune cells, wherein Treg cells have a pivotal role [9-11]. T-cell Receptors (TCRs) and B-cell Receptors (BCRs) recognize peptides presented by major histocompatibility complex molecules (MHC or HLA) to discriminate between self and non- self antigens. The V (D) J segments rearrange is a process that allows a wide variety of antigens to be recognized by the TCR and BCR. However, in some circumstances checkpoints in lymphocyte development fail and TCRs and BCRs self-reactive cells escape from tolerance [12,13]. MHC class I and II alleles also have been associated with increased susceptibility to autoimmune disorder, such as celiac disease, type 1 diabetes and rheumatoid arthritis [14,15].

In recent years, there has been demonstrated that innate immunity components also contribute for autoimmune diseases development. Toll-Like Receptors (TLRs), NOD-like receptors pathway and other Pattern Recognition Receptors (PRRs) are involved directly in the promotion of inflammatory milieu associate to autoimmune pathology, such as recruitment and activation of dendritic cells, macrophages, neutrophils and MCs that produce several amplifiers of autoimmunity [16]. Overall, both innate and adaptive immunity are mediators of complex mechanisms of autoimmune disease.

## Mast cell biology

MCs arise from CD34-positive hematopoietic progenitors in the bone marrow and are released into the circulation, from where they migrate to vascularized tissues or serosae cavities. MCs undergo terminal stages of their differentiation and/or maturation under the influence of microenvironmental conditions and through the action of Stem Cell Factor (SCF). In addition, cytokines such as interleukin IL-3, IL-4, IL-9, IL-10, Nerve Growth Factor (NGF), some chemokines and retinoid acid can regulate MCs differentiation [17]. MCs are widely distributed throughout vascularized tissues. On the basis of their location and protease content, MCs are subdivided

in two major subtypes in rodents: Mucosal MCs (MMC) that are associated with the epithelium of the lung and gastrointestinal tract, and which express chymases mMCP-1 and mMCP-2. The other subtype comprises the Connective Tissue MCs (CTMCs) that are found in the intestinal submucosa, peritoneum and skin. CTMCs are characterized by the expression of the chymase mMCP-4, an elastolytic enzyme (mMCP-5) and two tryptases (mMCP-6 and mMCP-7) as well as carboxypeptidase 3 (CPA3) [18]. In humans, MCs are classified as either  $MC_T$ , which express tryptase only, or  $MC_{TC}$ , which express tryptase, chymase and CPA3 [19]. The major mechanism of MCs activation is through antigen- and IgE-dependent aggregation of the high affinity IgE receptor, FcεRI, that triggers MCs degranulation [20]. However, MCs can also be differentially activated by complement system fractions (anaphylatoxins), immunoglobulin free light chains, hormones, neuropeptides and Toll Like Receptors (TLR) [21]. Thus, MCs can respond to different stimuli, and thereby participate in a wide variety of physiological and pathological processes. MCs activation can induce the release of various biologically active products. These include pre-formed molecules such as histamine, serotonin, TNF-α, kinins and proteases stored in secretory granules. Leukotrienes (LT), prostaglandins and Platelet Activated Factor (PAF) are synthesized during MCs activation from arachidonic acid. In addition, a number of cytokines (IL-1, 2, 5, 6, 8, 9, 13, 17, TNF and TGF-β1) chemokines (CCL1, CCL2, CCL3, CCL3L1, CCL4, CCL5, CCL7, CCL8, CCL11 and CXCL2) and growth factors (VEGF, PDGF, bFGF, EGF, IGF-1 and NGF) are synthesized *de novo* and released several hours after their stimulation [22]. MCs are no longer recognized only as eliciting allergy, but also as having many homeostatic functions, such as blood flow and coagulation, smooth-muscle contraction and peristalsis of the intestine, mucosal secretion, wound healing, as well as, regulation of innate and adaptive immune responses, peripheral tolerance and autoimmunity. MCs can regulate many aspects of the biology (recruitment, survival, development, phenotype or function) of immune cells, including granulocytes, monocytes/macrophages, dendritic cells, T cells, B cells, NKT cells and natural killer cells. Therefore, MCs are able to enhance or suppress the initiation, magnitude and/or maintenance of immune responses, inclusively autoimmunity [23].

### Mast cells crosstalk with other immune cells

Dendritic Cells (DCs) are likely to be one of the earliest target cells of MCs influence. These cells co-localize in most tissues, particularly at sites of Antigen (Ag) entry. Many lines of evidence have linked MCs or their products to the regulation of DC migration, maturation and function. MCs promote DCs migration by the release of TNF-α, IL-6 and IL-1β [24,25]. Indeed, MCs can induce the selective mobilization of specific DCs subsets [26]. By regulating DCs maturation, MCs are able to influence the ability of these cells to direct the quality of Th cell differentiation. Co-culture of activated MCs with DCs results in their maturation, demonstrated by increased expression of CD80 and CD86 [27]. Histamine has profound effects on DCs, which express all four of its receptors (H1-H4) [28,29]. *In vitro* data showed that histamine induces CD86 expression and chemokine production by immature DCs [27,28]. Besides preformed cytokines, metabolites from arachidonic acid and proteases, MCs granules also contain membrane vesicles termed exosomes [30]. MCs derived-exosomes were shown to induce immature DC to up-regulate MHC

class II, CD80, CD86, and CD40 molecules and to acquire a potent Ag presenting capacity to T cells [31]. MC-primed DCs stimulate CD4+ T cells to release high levels of IFN-γ and IL-17, indicating that MCs may promote Th1 and Th17 responses [32]. However, MCs can also induce the downregulation of IL-12 and stimulate the production of IL-10 by DC, resulting in a decrease in expression of the Th1 cytokine, IFN-γ, and an increase in the Th2 cytokine, IL-4, by T cells primed *in vitro* by these cells [33,34]. MCs can also directly influence T cell differentiation and function in a number of ways. T cell-MC co-culture experiments demonstrate that MCs significantly enhance T cell proliferation and cytokine production. MCs are infrequently found in lymph nodes and spleen, but they can migrate to these tissues during an immune response, where they mediated T lymphocyte activation [32]. MCs may also affect T-cell recruitment to sites of inflammation by direct release of chemotactic molecules [35,36], regulation of expression of adhesion molecules and induction of cytokine release by endothelial cells [37]. MCs can activate CD4+ or CD8+ T cells through Ag presentation by either MHC class II- or class I-context implying that they can actually serve as resident APCs [38-41]. Moreover, MCs expression of co-stimulatory molecules including members of the B7 family (ICOSL, PD-L1, and PD-L2) and the TNF/TNFR families (OX40L, CD153, Fas, 4-1BB, and glucocorticoid-induced TNFR) are important in regulating T cell activation and ultimate response [42,43]. Additionally, MCs produce the major cytokines involved in T-cells activation and polarization towards Th1, Th2, Th17 or Treg subsets [44]. The histamine released by MCs can promote Th1 cell activation through H1 receptors and suppress both Th1 and Th2 cell activation through H2 receptors [45]. MCs, in addition to cell-to-cell contact and cytokine release, can also regulate T-cell function by the secretion of exosomes [46]. MCs activation by adenosine receptors triggers IL-4 and IL-13 production which, in turn, induces the synthesis of immunoglobulin E (IgE) by B lymphocytes. Moreover, MCs protease I can enhance the production of IgG1 and IgE by B cells in the presence of IL-4 or LPS [47] in rats. These cells can also regulate CD40 surface expression on unstimulated B cells and the interaction between CD40 with CD40L on MC, together with MCs-derived IL-6, induce the differentiation of B cells into CD138+ plasma cells with selective secretion of IgA [48]. It was also demonstrated that MCs upon stimulation with IL-4 secrete exosomes that induce B cells proliferation and cytokine production [46]. Finally, some MCs-derived cytokines can influence B cell development, such as IL-4, IL-5, IL-6 and IL-13.

### Mast Cells in Rheumatoid arthritis

Rheumatoid Arthritis (RA) is the most common autoimmune disease in the world. RA is a chronic inflammatory disease that affects the joints and is characterized by autoantibody production and destruction of cartilage and bone [49,50]. Despite of established adaptive immunity participation in RA, different cells of innate immunity, including MCs, has been implicated in RA progress [50-52]. Patients with RA have a higher number of MCs at synovial cavity than health individuals [53,54]. Besides, animal experimental models studies (K/B×N model of arthritis e.g.) showed that MCs produce several mediators that are implicated in RA pathogenesis [55,56]. Histamine deficient mice developed a moderate form of arthritis when compared to the wild-type controls, and the use of pharmacological antagonists of the histamine receptors showed

that H4 is the most important for development of arthritis in autoantibody-induced arthritis [57-59]. The levels of tryptase in synovial fluid are increased in RA patients and was demonstrated that tryptase has an antiapoptotic effect on RA synovial fibroblasts through the activation of Rho, inducing hyperplasia of synovial tissue [60]. Tryptase can also activate synovial cells expressing PAR-2, enhancing tissue inflammation [60,61]. A tryptase member family, hTryptase- $\beta$ , was able to activate zymogen forms of MMP-3 and MMP-13, which are constitutively present in articular cartilage [62]. MCs produce many relevant cytokines in RA context, such as TNF- $\alpha$ , IL-6, IL-1 $\beta$ , IL-17 and IL-33. The TNF- $\alpha$  importance in RA development is demonstrated by RA treatment with anti-TNF- $\alpha$  antibody. The activated MCs have an enhanced production of TNF- $\alpha$  that may activate other innate effectors cells [63-65]. IL-33, a member of IL-1 family, exacerbates arthritis by activating MCs [64,66,67]. Interesting, MCs are the major producing of IL-17 in RA synovia, opposite to what is observed in others sites where Th17 are the main IL-17 source [68-71]. The presence of autoantibodies such as rheumatoid factor and anti-citrullinated protein antibody (ACPA) is related to RA progression, since these antibodies may trigger MCs activation through Fc $\gamma$ R and Fc $\epsilon$ R that are expressed in synovial MCs [49,72,73].

### Mast cells in neurological autoimmunity

Multiple sclerosis (MS) is the most prevalent autoimmune disease of those affecting Central Nervous System (CNS), featured by inflammatory, demyelinating lesions localized in the brain and axonal loss [74,75]. In the brain, MCs reside on the brain side of the blood-brain barrier (BBB), and interact with different cells of CNS [76]. A considerable amount of literature has demonstrated that MCs are implicated in MS disease, wherein MCs are found within the demyelinated plaques, in normal white matter, and tryptase was significantly elevated in cerebrospinal fluid of MS patients [77,78]. Mouse model of Experimental Autoimmune Encephalomyelitis (EAE) have contributed to the understanding of MS development [79]. However, the observed MS functions in EAE models are very confusing. Previous studies using MCs-deficient W/W<sup>v</sup> mice showed that MCs are important for early onset and severe disease in MS. The phenomenon observed in W/W<sup>v</sup> mice model was correlated with activation of CD4 and CD8 T cell, IFN- $\gamma$  production as well as IL-4 expression and neutrophil recruitment by MCs. In this mice model all these mechanisms described are decreased when compared with wild type animals developing EAE [79-82]. In contrast to the data with W/W<sup>v</sup> mice model, Kit W-sh/W-sh mice have an increased EAE development due to absence of immune suppression and there is evidence that chymase protects from post-traumatic brain inflammation. These studies suggest that MCs play a regulator role in EAE [83-86]. There is still some works showing that MCs could not contribute to EAE, this conclusion comes from studies using W/W<sup>v</sup>, W-sh and Cre-Lox system [87,88]. More studies will be needed to assess these divergent data.

### Mast cells in inflammatory bowel disease

Inflammatory bowel diseases (IBD), Crohn's disease and ulcerative colitis are chronic noninfectious inflammations manifested in the gastrointestinal tract [89]. The IBD etiology is unknown, however we know that interaction of several factors like heredity,

environment, intestinal microbiota and immune system cells can lead to IBD development [89]. The intestinal immune system has a dual function at the same time maintain the food antigens and commensal microorganism tolerance, but also protecting against pathogenic organisms. Thus when an unbalance in the homeostasis mechanism of gastrointestinal tract arises, the host became more susceptible to IBD pathology [90,91]. A large body of literature has investigated the participation of adaptive immune system in IBD, there is an strong association between exacerbated activation of T cells and IBD progress. In this context a mix of Th1/Th17 response is increased and is deleterious for intestinal mucosa Crohn's disease and ulcerative colitis [90,92]. Nowadays, the innate immune cells also has been implicated in IBD pathology, once that macrophage, DC and other innate immune cells have been implicated in IBD [93]. MCs are present in different regions of gastrointestinal tissue and together with other cells assist in this homeostatic maintenance [94,95]. Several studies have suggested that IBD patients present an increase in MC mediators, such as tryptase, chymase and histamine [94,96,97]. Besides that, *in vitro* and *in vivo* experimental models data also shown that MCs are important inflammation sources in IBD, whereas release of proteases, PAR-2 activation pathway and TNF- $\alpha$  contribute to deleterious effects of disease [98-101]. Interesting, recent works have examined the extracellular ATP's role, a known danger signal, in mediating MCs activation in the context of intestinal inflammation. This mechanism occurs by activation of P2 purine receptors (P2X7), and this ATP-induced activation of P2X7 exacerbates MCs inflammation induced [102].

### Mast cells in Type 1 diabetes

Type 1 Diabetes (T1D) is caused by the immune-mediated destruction of insulin-producing  $\beta$  cells in the pancreas. The selective immune response to  $\beta$ -cells develops by the emergence of islet antigen-reactive T cells concomitantly to an impairment of immune regulation. Susceptibility to T1D is conferred by a combination of genetic background and environmental factors [103]. Studies in NOD mice and biobreeding (BB) rats, which develop T1D with common characteristics to the human disease [103, 104], have identified roles for several different immune cell types in  $\beta$ -cell destruction. More important, it seems that the pathogenesis of T1D involves a considerable crosstalk between these cells. CD4+ and CD8+ T cells are pivotal for T1D onset and are considered to be the final executors of  $\beta$ -cell destruction. T1D can only be transferred from diabetic NOD mice to immune compromised syngeneic recipients by a combination of both T cell subsets [105,106]. Although being the source of the autoantigens that drive T1D,  $\beta$ -cells are unable to directly prime diabetogenic CD4+ or CD8+ T cell responses, making necessary the involvement of cross-presenting APCs (B lymphocyte, macrophage and DC) for the disease to develop. NOD mice deficient in B lymphocytes or depleted from DC and macrophages are protected from the onset of T1D [107-110]. MCs could be another innate immune cell involved in T1D. MCs reside in the peri-acinar space, pancreatic interstitium and mesentery and have already being implicated to pancreas inflammation and cancer [111-114]. The existent evidence that indicate a role of MCs in T1D is somewhat indirect. Transcripts associated with MCs were differentially expressed in the Pancreatic Lymph Nodes (PLN) of prediabetic BB rats [115]. In a subsequently study, the same group showed that MCs

found in the PLN from diabetic rats presented a gene expression profile indicative of activation and that treatment with cromolyn, a MC degranulation inhibitor, delayed the onset of T1D [116]. MCs could be involved in the development of T1D by directly eliciting  $\beta$ -cell destruction or by modulating the proinflammatory response against  $\beta$ -cell antigens. Cytokines immediately released upon MCs degranulation or newly synthesized may be important mediators of  $\beta$ -cell damage. MCs produce the three major cytokines involved in T1D development, TNF- $\alpha$ , INF- $\gamma$  and IL-1 $\beta$ . Treatment of neonatal NOD mice with recombinant TNF- $\alpha$  accelerated diabetes [117]. TNF- $\alpha$  stored in MCs granules may induce  $\beta$ -cell cytotoxicity via generation of nitric oxide (NO) [118] or by increasing the ability of APCs to activate  $\beta$ -cell-specific T cells [119,120]. There are data that support a synergistically effect of both IFN- $\gamma$  and TNF- $\alpha$  in the induction of  $\beta$  cell apoptosis [121]. NOD mice bearing a null mutation of the INF- $\gamma$  receptor  $\alpha$  chain showed a marked inhibition of insulinitis and no signs of diabetes [122]. It was shown that MCs can be a source of IFN- $\gamma$ , which secretion does not depend on IgE-mediated activation [123]. *In vitro* experiments demonstrated that IL-1 $\beta$  induction of NO production [124] and ER stress response [125] activates cell death programs and modifies the expression of several genes that may affect both function, viability and  $\beta$ -cell recognition by the immune system [126]. Moreover, IL-1R deficiency slows development of diabetes in NOD mice by blocking IL-1 $\beta$ -mediated induction of iNOS by TNF- $\alpha$  and IFN- $\gamma$  [127]. MCs production of IL-1 $\beta$  may be mediated by an inflammasome-dependent mechanism. IL-1 $\beta$  produced by these cells is primarily responsible for the cutaneous inflammation in the cryopyrin-associated periodic syndromes (CAPS), caused by mutations in the NLRP3 gene that lead to overactivation of inflammasome [128]. IL-1 $\beta$  is secreted as an inactive precursor, and processing of pro-IL-1 $\beta$  depends on cleavage by proteases. Interestingly, human MCs chymase is able to rapidly and specifically convert IL-1 $\beta$  precursor in its active form [129]. In contrast to the data that indicate a pathogenic function of MCs in T1D, recently, it was documented that repeated administration of anti-Fc $\epsilon$ R1 antibodies resulted in protection against diabetes in NOD mice by a mechanism that was partially dependent on IL-4 [130]. Authors concluded that this effect was due to activation of both basophils and MCs, although they have not evaluated exactly which cells were involved in that process. Thus, the exact role of MCs in T1D development still remains to be ascertained.

### **Mast cells in Systemic lupus erythematosus (SLE)-mediated glomerulonephritis**

SLE is an autoimmune disease with manifestations derived from the involvement of multiple organs including kidneys, joints, nervous system and hematopoietic organs. The combination of genetic, hormonal and environmental factors is involved in the activation of both innate and adaptive immune responses, resulting in loss of tolerance to ubiquitous self-antigens, particularly anti-double-stranded DNA [131]. Defective clearance of cell debris results in secondary necrosis and an overload of self-antigens. In SLE patients, nuclear particles, specially double-stranded DNA, are taken as viral particles and elicit a (pseudo) antiviral immune response that involves all antigen-presenting cells, particularly DC and B cells [132]. Activation of the innate immune system results in enhanced antigen presentation to T cells and the release of proinflammatory

cytokines, including type I IFNs. The expansion of T and B cell clones with specificities for predominantly nuclear autoantigens account for the production of antinuclear antibodies, immune complexes and T cell-dependent tissue damage. Antigen-antibody complexes mediate the injury to organs and tissues by binding to complement and attracting macrophages and neutrophils [133]. Immune complexes may also bind to receptors expressed by tissue-specific cells and alter their function [132]. Lupus Nephritis (LN) occurs in approximately 50% of adult and 80% of pediatric patients with SLE [134]. In the kidneys, Immune Complexes (IC) can deposit in the mesangial area, subendothelial and subepithelial spaces or in peritubular capillaries. IC deposition induce complement- and FcR-mediated inflammatory cascades that cause activation or injury of renal resident cells, which in turn release inflammatory factors, leading to the recruitment of inflammatory cells [135]. Cytotoxic T cells, Th17 T cells, as well as B cells infiltrate the kidney in LN. Long term renal damage is caused by continuous inflammation, vascular injury by systemic and local mediators, hypoxia and fibrosis [136]. MCs numbers were shown to be increased in kidney biopsies of patients with LN [137,138]. However, it was not evaluated if MCs accumulation was involved in the development of LN or if it was merely a response to subsequent autoimmune-mediated tissue injury. It was demonstrated that MCs-deficient mice subjected to the pristane-induced model of LN developed renal disease comparable to their WT counterparts, including glomerulonephritis, immune deposits, and proteinuria [139]. Thereafter, MCs contribution to LN needs to be evaluated.

### **Mast cells in psoriasis**

Psoriasis is one of the most common chronic inflammatory skin disorders and is characterized by scaly, reddened patches, papules, and plaques derived from excessive growth of skin epithelial cells [140]. Many stressful physiologic and psychological events and environmental factors are associated with onset and disease worsening. Carriage of HLA-Cw6 [141] and environmental triggers, such as  $\beta$ -haemolytic streptococcal infections [142] are major determinants of disease expression. Psoriasis is primarily a T cell-mediated autoimmune disease, and arises by the interaction of epidermal keratinocytes and mononuclear leukocytes [141]. At the psoriasis lesion it is observed a marked infiltration of mononuclear leukocytes (T cells and DC) into the dermis and elongated/hyperplastic blood vessels in the papillary dermal region [143]. The majority of the T cells infiltrating the dermis are of the CD4+ T cells subtype, whereas CD8+ T cells predominate in the injured epidermis. CD8+ T cells are likely to be the ultimate effectors cells that recognize autoepitopes presented by the binding pockets of HLA-Cw6 or other HLA class I molecules on the keratinocyte surface [142]. There are compelling evidences of the involvement of MCs in the pathogenesis of psoriasis. MCs, particularly the MC<sub>TC</sub> subset, are enriched in the papillary dermis of psoriasis lesions in humans [144-146] and show signals of degranulation, denoted by increased interstitial levels of histamine [147], in early eruptive and recurring lesions [146]. Increased expression of SCF by keratinocytes, endothelial cells and fibroblasts may account for the accumulation and activation of MCs in plaques lesions [148]. MCs may contribute to psoriasis development by the production of cytokines. For instance, MCs in psoriatic skin are strongly positive for interferon INF- $\gamma$  [149], believed to be one of the most important mediators in the cytokine

cascade of psoriasis [150]. Moreover, most of IL-17 producing cells in normal and psoriatic skin are MCs [151], not T cells. IL-17 induces the synthesis of antimicrobial peptides (i.e., defensins, lipocalin, and S100 proteins) [152] and also regulates a group of neutrophil-attracting CXCL chemokines [153] expression by keratinocytes. This cytokine is believed to be an important effector factor in psoriasis pathogenesis [154] and blockage of its pathway has been shown to be therapeutic on psoriasis [155]. Furthermore, tryptase released upon degranulation is believed to activate keratinocytes and endothelial cell by means of PAR-2 activation [156].

### Mast cells in bullous pemphigoid

Bullous pemphigoid (BP) is an acquired autoimmune skin disease associated with an IgG autoimmune response and characterized by detachment of the epidermis from the dermis and an intense inflammatory cell infiltrate in the upper dermis. Autoantibodies from BP patients react with two hemidesmosomal components: transmembrane collagen XVII (BP180 or BPAG2) and plakin family protein BP230 (BPAG1) [157]. BP pathogenesis include complement activation, recruitment of inflammatory cells and liberation of proteolytic enzymes that cleave and degrade type XVII collagen [158]. The activation of complement seems to play a central role in this disorder since mice depleted of complement did not develop BP following injection with pathogenic rabbit anti-BP180 antibodies [159]. Autoreactive T and B cell responses to BP180 have been found in patients with BP [160] although it was shown that these lymphocytes subtypes were not necessary for the emergence of subepidermal blistering in an experimental model [161]. Besides complement activation, lesion formation in BP depends upon MCs degranulation [162] and accumulation of neutrophils [163] and eosinophils. Mice deficient in neutrophils or MCs are resistant to experimental BP [161]. MC degranulation is a common feature of BP [164,165] and precedes neutrophil infiltration and subsequent dermal-epidermal separation [162]. MCs degranulation in BP was dependent on complement activation [162]. Moreover, MCs may also be activated by FcεRI cross-linking. In addition to IgG autoantibodies, most BP patients also produce IgE class autoantibodies that also react with BP180 and total IgE levels are often elevated in the disease [166]. IgE autoantibodies were found at the basement membrane zone and coating MCs in injured skin [167]. Upon degranulation, MCs release a variety of mediators such as leukotrienes, PAF and cytokines that contribute directly or indirectly to neutrophils recruitment [162,168,169]. Activated neutrophils release proteolytic enzymes that cause the splitting of epidermis from the dermis [157]. Elastase and gelatinase B (MMP-9) were found to be crucial for neutrophils induction of blisters [170]. Interestingly, MCs chymase MCP-4 can activate MMP-9 and also directly degrade BP180 *in vitro* [171]. Mice lacking specifically this protease were resistant to experimental BP [171].

### Mast cells in vasculitis

Vasculitis comprises a diverse group of conditions characterized by inflammation and necrosis of blood vessels that leads to vessel occlusion and ischemia of tissues. Vessels of any kind in any organ can be affected, which accounts for the heterogeneity of signs and symptoms of the disease. Vasculitis may occur as a primary condition or as a component of other diseases [172] and are categorized on the basis of the predominant type of vessel (large, medium or

small) affected [173]. Small-vessel vasculitis may be caused by IC-mediated inflammation as in the case of anti-glomerular basement membrane disease (Goodpasture's syndrome), IgA vasculitis (Henoch-Schönlein purpura) and vasculitides secondary to systemic immune complex diseases such as SLE, dysproteinemias, cryoglobulinaemias, and chronic infections. Vasculitis can also be induced by antibodies directed to autoantigens like in Anti-Neutrophil Cytoplasmic Antibody (ANCA)-associated small vessel vasculitis, which includes granulomatosis with polyangiitis (originally Wegener's granulomatosis), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome) [172]. The Anti-Neutrophil Cytoplasmic Autoantibodies encountered in ANCA-associated vasculitis are mostly directed against the neutrophil azurophilic granule proteins proteinase 3 (PR3) and Myeloperoxidase (MPO). The inoculation of mice with hybridomas producing monoclonal IgG rheumatoid factors induces the development of a leukocytoclastic skin vasculitis caused by the deposition of cryoglobulins. The binding of IC by FcR positive cells stimulates the secretion of inflammatory mediators that recruit Polymorphonuclear (PMN) cells, which damage blood vessels. In this model of hypersensitivity angiitis, vascular inflammation was dependent on MC recognition of IC by FcγRIII and release of pre-formed TNF-α stored within its granules [174]. Administration of mercuric chloride (HgCl<sub>2</sub>) to Brown Norway rats causes a Th2-induced autoimmunity characterized by high IgE concentrations and production of multiple IgG autoantibodies to MPO. Animals develop polyarthritis and a leukocytoclastic vasculitis which predominantly affects the intestine. Vasculitis in this model has some similarities to human Churg-Strauss syndrome. It has been suggested that MC play a role in the pathogenesis of early disease [175,176], which is αβ T-cell and neutrophil independent [177,178]. Nontoxic concentrations of HgCl<sub>2</sub> can induce CTMC mediator release and cause up-regulation of IL-4 mRNA expression *in vitro* [172]. Besides, HgCl<sub>2</sub> administration induced an increase of serum rat MC protease II (RMCP II) [175] and reduction of toluidine blue positively stained cells (interpreted as MC degranulation), indicating *in vivo* MC activation [176]. Moreover, the use of the MC-stabilizing agents G63 and doxantrazole resulted in amelioration of early cecal vasculitis caused by HgCl<sub>2</sub> [175]. On the other hand, MC depicted a protective role in the development of focal necrotizing glomerulonephritis (GN) in ANCA-associated vasculitis. MC-deficient Kit W-sh mice developed augmented anti-MPO GN, characterized by enhanced renal injury compared to MC-intact C57BL/6 mice. Moreover, mice reconstitution with bone marrow derived-MC attenuated glomerular injury indicated by fewer abnormal glomeruli and less fibrin deposition. It was suggested that MC migrate from sites of MPO presentation to draining LN where they could modulate T regulatory cells function through secretion of IL-10, and these cells, in turn, would decrease MPO T effector cells capacity to produce proinflammatory cytokines [179].

### Mast cells in other autoimmune conditions

MCs have been implicated in other autoimmune conditions in which were observed their accumulation in the vicinity of affected tissues. In Thyroid-Associated Ophthalmopathy (TAO), an extra thyroidal manifestation of Graves' disease, MC were among the cells that infiltrate the orbit [180-182]. It was shown a significant correlation between the numbers of MCs in minor salivary glands

**Table 1:** Overview of autoimmune disease in whose development Mast cells may be involved.

| Disease                                 | Animal model   | Evidence of MC participation  | Ref.            |
|---|--|---|-----------------|
| Type I Diabetes (T1D)                   | Spontaneous development of autoimmune insulinitis in Biobreeding rats.                             | Increased expression of MC transcripts in pancreatic lymph nodes from rats with T1D.  | [115]           |
|   |  | Treatment with MC stabilizer delayed disease onset.   | [116]           |
| Systemic lupus erythematosus (SLE)      |  | MC increased numbers in kidney biopsies of patients with lupus nephritis.   | [137,138]       |
| Psoriasis                               |  | MC enriched in the papillary dermis of psoriatic lesions in humans.   | [144-146]       |
| Bullous pemphigoid (BP)                 | Injection with pathogenic anti-BP180 IgG.  | Degranulated MC in cutaneous lesions from patients with BP.   | [164]           |
|   |  | Presence of histamine in the blister fluid of BP lesions.   | [165]           |
|   |  | Mice deficient in MC or lacking mMCP-4 were resistant to experimental BP.   | [161, 162, 171] |
| Vasculitis                              | Inoculation of mice with hybridomas producing monoclonal IgG rheumatoid factors.                   | Disease development was dependent of MC recognition of IC by FcγRIII and release of pre-formed TNF-α  | [174]           |
|   | Administration of HgCl <sub>2</sub> to Brown Norway rats.  | MC stabilization resulted in amelioration of early caecal vasculitis.   | [175]           |
|   |  | Direct correlation between MC degranulation and early caecal vasculitis.  | [176]           |
| Thyroid-associated ophthalmopathy (TAO) | Genetic immunization of outbred NMRI mice with cDNA encoding the human thyrotropin receptor (TSHr) | MC were among the cells that infiltrate the orbit in patients with TAO.   | [181]           |
|   |  | MC infiltrated the extraocular muscles from hyperthyroid animals.   | [182]           |
| Sjogren's syndrome (SS)                 |  | Association of MC presence with fibrosis and cell acid infiltration in the minor salivary glands of patients with primary SS.   | [183]           |
| Pemphigus vulgaris (PV)                 |  | Increased numbers of MC in skin lesions from patients with PV.  | [184]           |
| Scleroderma                             |  | Increased MC density in the skin of patients with scleroderma.  | [185]           |
| Rheumatoid arthritis (RA)               | K/BxN mice   | Higher number of mast cells at synovial cavity of RA patients.  | [54,56]         |
|   |  | In MCs deficient animal models, mice were resistant to joint inflammation development.  | [78]            |
| Multiple sclerosis (MS)                 | EAE  | MCs presence in demyelinated plaques.<br>Animal models showing conflicting data. It has been demonstrated both deleterous as a regulatory effect or even none mast cells involvement. | [80,82,84,88]   |
| Inflammatory bowel disease (IBD)        | Dextran sodium sulfate (DSS) and trinitrobenzene sulfonic acid (TNBS) induced colitis              | MCs mediators presence in patients.   | [96,97]         |
|   |  | Treatment with MCs inhibitors mediators reduces disease progression.  | [98,102]        |

and the degrees of fibrosis and lymphoid infiltration in Sjogren's syndrome [183]. MCs infiltration was also found in skin lesions from patients suffering from pemphigus vulgaris [184]. These cells were also present in increased numbers or in an activated state in the dermis of patients with scleroderma [185].

### Alternative function of mast cells in autoimmune diseases

The presence MCs or of their products at the site of inflammation were readily considered as an indicative of MCs participation in disease onset. However, this evidence is supportive, but not definitive of a direct role of MCs in the development of autoimmunity. Instead of contributing to the initiation of autoimmunity, MCs could actually be recruited and activated in response to the inflammatory milieu, participating solely in the subsequent tissue damage associated with disease progression. In agreement to this, MCs induce human

orbital fibroblasts to produce increased levels of prostaglandin E<sub>2</sub> and hyaluronan, indicating that these cells are involved in tissue remodeling that occurs in TAO [186]. In scleroderma, it is likely that MCs play a major role in the clinical progression of skin changes, through regulation of fibroblast production of extracellular matrix [187,188].

### Autoimmune disease study in MC-deficient mice

Kit mutant mice have been considered for decades as a powerful tool to evaluate *in vivo* MCs functions [189]. However, Kit is also involved in the development and function of many stem and mature cells inside and outside of the immune system [190]. Thereafter, some of the phenotype outcomes from Kit mutation are unrelated to MCs deficiency. Recently, it was generated a mice strain deficient in MCs (Cre-Lox system) which is independent of alterations in Kit thus

permitting direct analyses of the functions of MCs. Interestingly, some key data obtained earlier with Kit mutant mice were not confirmed with this new strain, inclusively data regarding the pathogenic role of MCs in experimental models of autoimmune arthritis and encephalomyelitis [191]. Of course, these results do not discredit all of the available MCs literature obtained with Kit mutant mice. But certainly, a re-evaluation of MCs immunological functions attributed based on the results obtained with this mice strain is necessary.

## Conclusion

Due to the widespread expression of inhibitory and activation cell-surface receptors on MCs [21], they will respond variably depending on the physiologic setting [192]. Additionally, MCs can release an impressive array of mediators, many of which can mediate proinflammatory, anti-inflammatory and/or immune regulatory functions [22]. Together, these morphological features of MCs translate to distinct effects they may exert in autoimmune diseases. Despite the substantial data from studies of both human disease and animal models that indicated a role of MCs in autoimmunity, there still is a debate regarding the actual function of MCs in those conditions [193]. Further studies are essential to gain a more detailed understanding of MC role in autoimmunity. Targeting MCs may be of value in future prevention and treatment of disease. The use of MCs-stabilizing agents would offer a possibility for the prevention of autoimmune conditions in whose development MCs may be involved (Table 1).

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