Autoimmunity Reviews 14 (2015) 751–759

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Revisiting the role of mast cells in autoimmunity

Xinhua Yu [a,b,*], Anika Kasprick [a], Frank Petersen [a,*]

[a] Priority Area Asthma and Allergy, Research Center Borstel, 23845, Borstel, Germany
[b] Laboratory of Autoimmunity, The Medical College of Xiamen University, Xiamen University, 361005 Xiamen, China

ARTICLE INFO

Article history:
Received 6 April 2015
Accepted 14 April 2015
Available online 23 April 2015

Keywords:
Mast cells
Autoimmune diseases
Mouse models
Autoimmunity
Kit signaling

ABSTRACT

Beside their well known role in allergy, mast cells (MCs) are capable to sense multiple signals and have therefore the potential to be involved in many immune responses. MCs are actively present in the target tissues of some autoimmune disorders, suggesting a possible function in the manifestation of such diseases. This idea is strengthened by the evidence that KIT-dependent MC-deficient mice are protected from disease in many mouse models of autoimmunity, including multiple sclerosis, rheumatoid arthritis and autoimmune skin blistering diseases. Thus, the essential role of MCs in autoimmunity not only significantly extends the knowledge of MCs in the immune response but also provides novel therapeutic targets for the treatment of such diseases. However, recent studies using a new generation of KIT-independent MC-deficient strains could not confirm an essential participation of MCs in autoimmune diseases. Therefore, it is necessary to clarify the observed discrepancies and to elucidate the role of MCs in autoimmune diseases. Here, we review the impact of MCs on the development of autoimmune diseases with focus on the controversial effects of MC deficiency in different mouse models of autoimmune diseases. We also try to clarify contradictory findings in mouse studies to finally elucidate the role of MCs in autoimmunity.

Contents

1. Introduction: Mast cells . . . 752
2. MCs in human autoimmune diseases . . . 752
   2.1. MCs in multiple sclerosis . . . 752
   2.2. MCs in rheumatoid arthritis . . . 752
   2.3. MCs in autoimmune blistering diseases . . . 752
3. MC-deficient mice . . . 752
   3.1. KIT-dependent MC-deficient mice . . . 753
      3.1.1. WBB6F1-Kit$^{W/W\text{-}v}$ and WCB6F1-Mgf$^{Sl/Sl\text{-}d}$ mice . . . 753
      3.1.2. C57BL/6-Kit$^{W\text{-}sh}$ mice . . . 753
   3.2. KIT-independent MC-deficient mice . . . 753
      3.2.1. Cpa3^{Cre} mice . . . 753
      3.2.2. Mcpt5^{Cre} mice . . . 754
      3.2.3. Mas-TRECK mice . . . 754
4. MCs in the mouse models of autoimmune diseases . . . 754
   4.1. Therapeutic evidence of the role of MCs in mouse models of autoimmune diseases . . . 754
   4.2. Pathogenesis of autoimmune diseases in MC-deficient mice . . . 754
      4.2.1. Autoimmune diseases in Kit$^{W/W\text{-}v}$ mice or Mgf$^{Sl/Sl\text{-}d}$ mice . . . 754
      4.2.2. Autoimmune diseases in Kit$^{W\text{-}sh}$ mice . . . 755
      4.2.3. Autoimmune diseases in KIT-independent MC-deficient mice . . . 756
5. Conclusion and outlook . . . 756
   5.1. Conclusion . . . 756
      5.1.1. Do MCs play a role in the mouse models of autoimmune diseases? . . . 756
      5.1.2. Do MCs play a role in human autoimmune diseases? . . . 757

* Corresponding authors at: Priority Area Asthma and Allergy, Research Center Borstel, 23845 Borstel, Germany. Tel.: +49 45371882520.
E-mail address: xinhuayu@fz-borstel.de (X. Yu).

http://dx.doi.org/10.1016/j.autrev.2015.04.008
1568-9972/

5.2. Outlook . . . 757
Take-home messages . . . 758
References . . . 758

1. Introduction: Mast cells

Mast cells (MCs) derive from precursors of the hematopoietic lineage in the bone marrow [1]. The precursors circulate in blood and the lymphatic system before homing to their target tissues where they develop into mature MCs. This maturation process is regulated by various factors including several cytokines among which the stem cell factor (SCF) may be the most important one. As a ligand of the cell surface-expressed KIT, this growth factor serves as the main driver of MC differentiation [2]. MCs are distributed throughout almost all tissues and are specifically located at the interfaces of the body where they reside in proximity to nerves, blood and lymphatic vessels [3]. MCs are even present in the brain under physiological conditions.

Due to the expression of the high-affinity IgE receptor (FcεRI), MCs are well known for their role in IgE-mediated anaphylaxis and allergic reactions [4]. However, apart from FcεRI, MCs also express a plethora of further receptors, e.g. complement receptors, FcγR, and Toll-like receptors allowing them to respond to diverse stimuli [3,5]. Given their wide tissue distribution and large capacity to be activated, MCs are the major immune cell type sensing danger signals at the body interfaces and therefore play an essential role in the defense against potential pathogens [3].

MCs can be activated both in a receptor-dependent or -independent manner. Upon their activation they release a wide spectrum of mediators which can be categorized into three groups according to the time kinetic of their release [4,6]. The first group contains preformed mediators like histamine, proteases such as tryptases and chymases as well as some cytokines, e.g. tumor necrosis factor α (TNF-α), that are stored in the numerous MC granules and can be released immediately after cell activation. The products of the second group are also released relatively fast and comprise rapidly synthesized bioactive metabolites of arachidonic acid such as prostaglandins and leukotrienes. The final group contains products which are newly synthesized via unregulated gene expression in response to stimulation, including most cytokines and chemokines. The different biological functions of these products characterize MCs not only as simple effector immune cells but enables them to regulate both innate and adaptive immunity [7,8].

2. MCs in human autoimmune diseases

Given the wide distribution of MCs and the broad spectrum of their mediators, it is reasonable to speculate that MCs are potentially involved in many immune activities, including autoimmunity [5,8]. Autoimmune diseases are disorders of the immune response mediated by autoreactive T cells and/or autoantibodies. Indeed, there is accumulating evidence arguing for an involvement of MCs in the pathogenesis of human autoimmune diseases.

2.1. MCs in multiple sclerosis

Multiple sclerosis (MS), a CD4+ T cell-dependent autoimmune disease affecting the central nervous system, is characterized by lymphocyte infiltration, chronic inflammation and eventual demyelination [9,10]. Several myelin components, like the myelin basic protein (MBP), the myelin oligodendrocyte glycoprotein (MOG), and the myelin proteolipid protein (PLP) are regarded as candidates for autoantigens in MS and have been successfully used to induce experimental autoimmune encephalomyelitis (EAE), a mouse model of MS, in susceptible animal strains [11]. Studies in patients and mouse models suggest a critical role of the cellular adaptive immunity, especially T helper 1 (Th1) and T helper 17 (Th17) cells, as well as the humoral immunity by B cells and autoantibodies in the pathogenesis of the disease [12–14]. Moreover, several diagnostic findings imply an involvement of MCs in MS. For instance, MCs have been observed in the plaques of MS patients where their amount and distribution correlated with the severity of the disease [15–17]. In addition, activity of MC-associated proteases including tryptase and chymase have been shown to be accumulated in the cerebrospinal fluid of MS patients [18] and transcriptional analysis of brain biopsies revealed the upregulation of some MC-related genes [15,19]. Taken together, these findings suggest that MCs are actively present in the target tissues of MS patients.

2.2. MCs in rheumatoid arthritis

Rheumatoid arthritis (RA) is a systemic autoimmune disease primarily affecting synovial joints and is characterized by chronic inflammation and cartilage destruction [20]. Although joint-specific as well as systemic antigens have been defined and successfully employed to establish several experimental models of RA [21], it should be noted that the definite autoantigens of RA still need to be identified. This heterogeneity reflects the complexity of the pathogenesis of RA which is based on both, the humoral and the cellular autoimmunity [22].

MCs are resident cells in the synovial joint. Moreover, evidence for a role of MCs in RA is given by findings in patients. Here, levels of MCs are elevated in the inflamed synovium [23] and associated with an increased local production of MC-derived mediators which have the capacity to initiate or amplify the inflammatory response [24,25]. In addition, according to two recent studies MCs represent the main producers of IL-17A in RA [26,27], a cytokine essentially involved in the pathogenesis of RA [28].

2.3. MCs in autoimmune blistering diseases

Autoimmune blistering diseases are a group of autoimmune diseases targeting structure proteins in the skin that mediate either cell–cell or cell–matrix adhesion [29]. The autoantibodies against those structure proteins impair the adhesion in an inflammation-dependent or -independent manner [29] resulting in a loss of the skin barrier integrity. Bullous pemphigoid (BP) is the most prevalent autoimmune blistering disease characterized by autoantibodies against type XVII collagen (also named BP180, COL17A) and BP230 [30]. A role of MCs in BP is supported by their increased number in lesional skin and elevated levels of MC-derived mediators and proteases in the blister fluids of BP patients [31]. Moreover, most patients produce specific anti-COL17A IgE autoantibodies which are capable to mediate disease manifestation [32], further implying a potential role of MCs in the pathogenesis of BP.

3. MC-deficient mice

Various mouse models have been established for different types of autoimmune diseases during the last 50 years [33]. To address the role of MCs in these models, MC-deficient mouse strains were used as indispensable tools. While the first generation of MC-deficient mouse types were generated by interfering with the KIT signaling pathway, in later developed strains a specific loss of MC was achieved by transgenic approaches. An overview on the different types of MC-deficient mouse lines and their phenotypes are summarized in Table 1.