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Review

Mast cells in rheumatoid arthritis: friends or foes?

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ABSTRACT

Mast cells are tissue-resident cells of the innate immunity, implicated in the pathogenesis of many autoimmune diseases, including rheumatoid arthritis (RA). They are present in synovia and their activation has been linked to the potentiation of inflammation in the course of RA. However, recent investigations questioned the role of mast cells in arthritis. In particular, animal models generated conflicting results, so that many of their pro-inflammatory, i.e. pro-arthritogenic functions, even though supported by robust experimental evidence, have been labelled as redundant. At the same time, a growing body of evidence suggests that mast cells can act as tunable immunomodulatory cells. These characteristics, not yet fully understood in the context of RA, could partially explain the inconsistent results obtained with experimental models, which do not account for the pro- and anti-inflammatory functions exerted in more chronic heterogeneous conditions such as RA. Here we present an overview of the current knowledge on mast cell involvement in RA, including the intriguing hypothesis of mast cells acting as subtle immunomodulatory cells and the emerging concept of synovial mast cells as potential biomarkers for patient stratification.

Contents

1. Introduction

1.1. Mast cells as effector cells of innate and adaptive immunity

Mast cells (MCs) are granulated tissue-resident cells of hematopoietic lineage, deriving from specific hematopoietic precursors [1]. They circulate as immature cells and migrate into vascularized tissues, where they complete their differentiation and reside in the proximity

Abbreviations: MCs, Mast cells; CIA, Collagen-induced arthritis; ACPA, anti-citrullinated protein antibodies; RF, Rheumatoid Factor; DT, Diphtheria Toxin; DTR, Diphtheria Toxin Receptor.

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of blood vessels and nerves. As they are present in all anatomic sites exposed to the external environment, they represent, together with dendritic cells, the first cells of the immune system to interact with environmental antigens, pathogens and toxins. Therefore, they can be considered "sentinels" of the innate immune system [2], positioned at the frontline, and ready to fight in response to infections and other stimuli. In fact, mast cells are able to sense danger signals via the classical pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) [3]. In addition, several other mechanisms of mast cells crosstalk with pathogens have been described. For example, it has been shown that viral and bacterial proteins can activate mast cells via specific receptors [4,5]. Following their activation by danger stimuli, mast cells react by quickly releasing a wide range of mediators, both pre-formed and newly produced. Some of these mediators (e.g. histamine, TNF-α, VEGF) contribute to the local vascular permeability and oedema at the site of inflammation, while chemokines (e.g. IL-8/CXCL8, eotaxin) induce the recruitment of other immune cells, such as neutrophils, NK cells and eosinophils. Importantly, mast cells can also participate to the direct killing of pathogens by different mechanisms, such as phagocytosis, the release of antimicrobial peptides or the production of extracellular traps similar to the ones described in neutrophils [6,7].

Even though many of these innate immunity functions of mast cells partially overlap with other immune cells (e.g. neutrophils, macrophages, dendritic cells), early evidence from animal models demonstrated that the absence of mast cells significantly impairs the ability to respond to bacterial infections [8,9], confirming their non-redundancy in the fight against pathogens.

In line with their importance in the response to pathogens, it is also worth noticing that mast cells are highly conserved throughout evolution [10]. In fact, MC-like cells, containing histamine and heparin, have been described in very simple invertebrates [11]. In higher species, with the evolution of adaptive immunity, mast cells acquire the expression of the high affinity receptors for IgE (FcεRI) [12]. Cross-linking of the FcεRI by IgE-antigen complexes induces mast cell activation and fast release of pre-formed mediators. Because of this property, together with circulating basophils, mast cells are mainly known as effector cells of IgE-mediated (Th2-like) responses, an arm of the adaptive immune system developed to fight helminths [13]. Moreover, mast cells are primary effector cells in hypersensitivity reactions [14]. However, it is important to remember that, before becoming effector cells of adaptive immunity, mast cells are key cells involved in the initiation and regulation of innate immunity responses [15].

1.2. Mast cells and the modulation of adaptive immune responses

In addition to their functions as effector cells, recent evidence suggest that mast cells modulate adaptive immunity, therefore representing an important link between these critical arms of the immune system [16]. For example, mast cells express MHC class II and have been shown to induce antigen-specific T cell activation [17–19]. Vice versa, mediators derived from cells of the adaptive immunity can influence mast cell activation, as shown by the ability of IgG to activate mast cells through the FcγRs [3,20]. In the crosstalk between mast cells and adaptive immunity, the protective role of mast cells in the response against pathogens, i.e. their ability to orchestrate Type 2 responses against helminths [17,21], can become harmful when the immune response is dysregulated. In fact, mast cells can contribute to the responses leading to allergy [22] and autoimmunity [23].

A great deal of evidence indicates that mast cells have deleterious effects in these contexts, given their ability to release mediators with clear pro-inflammatory effects, such as histamine, and several other pro-inflammatory prostaglandins and cytokines.

Albeit mostly known for their pro-inflammatory roles, many of these mediators have been also shown to have opposite effects. For example, histamine is well known for its pro-inflammatory functions (e.g. vasodilation, increased vascular permeability, bronchospasm etc), but it can also exert immunomodulatory effects [24]. Accordingly, we have recently shown that basophil-derived histamine is able to suppress the pro-inflammatory activation of monocytes [25], thereby contributing to the homeostatic down-regulation of immune responses.

This is in keeping with the processes involved in the resolution of inflammation that start early in its course in order to restore homeostasis, prevent tissue damage, and facilitate wound repair.

In line with this concept, mast cells have been shown to produce mediators known for their immune regulatory effects and pro-resolving inflammation [26], such as IL-10, and mast cell-derived IL-10 has been shown to have protective effects in vivo [27–31].

Overall, this evidence suggests that mast cells should be considered more than simple effector cells, as they are able to orchestrate both innate and adaptive immune responses, acting as immunomodulatory cells that can be finely tuned by multiple stimuli [15,32,33].

2. Mast cells as immunomodulatory cells in RA

Mast cells have been implicated in the pathogenesis of various rheumatic diseases, including Rheumatoid Arthritis (RA) [34]. The synovial membrane is the primary inflammatory site in RA and synovitis is characterized by thickening of the lining layer, with cellular hyperplasia and infiltration of immune cells in the sub-lining [35]. Mast cells are among the immune cells found in the inflamed RA synovia, which are known to be present as resident cells in healthy synovia [36], with a considerable increased number in various joint diseases, including osteoarthritis [37], spondylarthritis [38], and RA [39–42]. Consequently, many attempts have been made to elucidate their specific role in the pathogenesis of the disease. Here we will present an overview of the state of the art describing current experimental evidence obtained through different approaches, starting from animal models of arthritis, followed by human experimental data both in vitro and ex vivo. Finally we will discuss the relevance and potential translation to patients with RA.

2.1. Mast cells contribution to arthritis: results from animal models

The role of mast cells in the development of arthritis has been extensively debated in the past years, mainly because of controversial results obtained in different animal models. Table 1 offers an overview of the various mouse strains and mast cell depletion strategies, together with the main findings and issues upon arthritis induction.

Initially, a significant reduction in the severity of K/BxN serum-induced arthritis was observed in animals deficient in mast cells because of spontaneous mutations affecting the structure or expression of c-KIT ($Kit^{W/W\text{-}v}$), indicating that mast cells are essential for the development of arthritis [43]. However, these results were rapidly challenged by the observation that Collagen-Induced Arthritis (CIA) was not affected by MC deficiency. Moreover, the results with K/BxN serum-induced arthritis could not be replicated in another MC-deficient strain ($Kit^{W\text{-}sh/W\text{-}sh}$) [44–46], generating a controversy that left the question of mast cell involvement in arthritis unanswered for many years. Upon further investigations, some of these inconsistencies were ultimately attributed to the phenotype of mast cell deficient mice [47]. In fact, the mutations in cKIT determined a profound MC deficiency together with a variety of phenotypic abnormalities. In particular, $Kit^{W/W\text{-}v}$ mice were found to be neutropenic, which in itself could majorly contribute to the reduction of arthritis severity observed in MC-deficient animals. On the contrary, $Kit^{W\text{-}sh/W\text{-}sh}$ mice were found to be neutrophilic, which reciprocally could mask the effect of MC deficiency. Thus, overall, no definitive conclusions can be drawn from these experiments.

In recent years, new 'KIT-independent' MC specific depletion models have been developed. The first set of experiments in these new strains questioned the contribution of mast cells to various autoimmune conditions [48] including arthritis [49,50].