Review

The multifaceted role of mast cells in the pathogenesis of rheumatoid arthritis

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ABSTRACT

Mast cells (MC) are tissue duelling cells playing an active role in both innate and adaptive immune system. They act as first players in different microbial infections and exert a crucial role in allergy, chronic inflammation, fibrosis, and rheumatic diseases (RD), including rheumatoid arthritis (RA). MC are normally present in human synovia and they increase in the joints of RA patients, contributing to inflammatory and remodelling processes. Due to their great plasticity and multifunctionality, MC exert a wide range of roles in different stages of the disease. To date, the results obtained by in-vitro and in-vivo studies have contributed to better clarify the dynamic role of MC in local arthritis of RA and have improved our knowledge on different aspect of the disease. Although different mice models have been extensively used to investigate the contribution of MC in different stages of RA, those models often fail to reproduce the complexity and the heterogeneity of the human disease. Here, we provide an overview on different roles of MC in RA pathogenesis and how these cells might influence some clinical features of the disease.

Role of MC in innate and adaptive immune responses

Mast cells (MC) are innate immune cells derived from $CD34^+$ haematopoietic stem cells in the bone marrow (1), circulating as immature form in the blood stream and in the lymphatic system, before completing their differentiation and maturation in tissues. Most of MC progenitors already express in their membrane c-Kit and FcεRI, crucial receptors for cell survival and activities. Although different cytokines, chemokines and adhesion molecules (*e.g.* IL-4, IL-5, IL-6, IL-15, TNF-α, CCL-2 and VCAM-1) derived from the tissue microenvironment regulate the expansion, homing and maturation of MC precursors, the binding of stem-cell factor (SCF) to the c-Kit receptor remains the strongest signal for their differentiation, proliferation and survival (2, 3).

Due to their strategic localisation at the host-environment interface, mature MC represent a first line of defense against harmful pathogens (4), producing antimicrobial peptides and releasing an array of pre-formed and newly synthesised mediators (5). By binding to pathogen-derived peptides, MC exert their anti-bacterial activities via Toll-like receptors (TLRs): peptidoglycans from Gram-positive bacteria trigger MC degranulation through TLR2, while lipopolysaccharide (LPS) from Gram-negative bacteria promotes release of TNF-α, IL-1β, IL-6 and IL-13 via TLR4.

Although MC are historically recognised to play a crucial role as effector cells in innate immune system, their role in autoimmune diseases is gaining more interest. In particular, these cells have a great ability to interact with dendritic cells, T and B cells, by physical contact and/or by releasing of soluble mediators (*i.e.* TNF-α, IL-4, IL-6 and metalloproteinases) (2, 4, 6-8). Furthermore, CD4+ T cells induce MC degranulation through OX40-OX40L binding, and *vice-versa* MC contribute to CD4+ T cells proliferation and cytokines production by releasing soluble TNF-α. Although these cells play a pivotal role in the maintenance of homeostasis in different tissues, MC might contribute to the development of autoimmunity by breaking peripheral immune tolerance. In fact, following MC-T cells contact via OX40-OX40L binding, T regulatory cells (Treg) lose

their Foxp3 expression as well as their capacity to suppress T cell activities, promoting autoimmunity (9, 10).
Moreover, MC actively regulate the adaptive immune response by supporting the development, survival and activities of B cells through the release of IL-4, IL-5, IL-6, and IL-13 cytokines as well as activation of CD40-CD40L axis (9). Furthermore, MC are able to influence T and B cells activities by releasing exosomes that might modulate dendritic cells phenotype and their functional maturation (11). MC-derived exosomes are also able to promote *in-vitro* differentiation of T naïve cells into Th2 phenotype and to induce IgE and IgA production by activated B cells (12).

The role of MC in the pathogenesis of rheumatic diseases

Due to their modulatory roles in the innate and adaptive immune systems, MC are actively involved in the pathogenesis of rheumatic diseases (RD) in which autoimmunity and/or inflammation are implicated. In the synovial tissue of patients with spondylarthritis (SpA), in which inflammation is the main pathogenic feature, MC are dramatically increased and are one of the main cellular sources of IL-17, crucial pro-inflammatory cytokine in RD (13). MC can contribute to the pathogenesis of these diseases also through their pro-fibrogenic activities as demonstrated in primary Sjögren's syndrome (pSS). In the salivary glands of these patients, MC are highly present in the tissue and actively contribute to the development of fibrotic processes by stimulating the production of extracellular matrix (ECM) components via $TGF\beta_1$ release (14). Moreover, in minor salivary glands, MC promote fibroblast chemotaxis in CCR7-positive cells through the release of CCL19 and CCL21 chemokines, supporting the direct role of MC in the development of tissue fibrosis, one of the main histopathological hallmark of pSS (15).
In parallel, the pro-fibrogenic activity of these cells has been also demonstrated in IgG4-related disease (IgG4-RD), an immune-mediated disorder in which salivary and lachrymal glands might be involved. Even if the mechanisms underlying their pathogenesis are different, in the gland tissue of both pSS and IgG4-RD MC are increased, and they actively contribute to promote fibrotic processes (16). However, besides their role in fibrosis, MC contribute to IgG4-RD pathogenesis by modulating type 2 inflammation (17, 18). In fact, a large number of MC expressing Th2 and Treg cytokines have been detected in submandibular gland of IgG4-RD patients where they locally can be activated by non-specific IgE binding, leading to lymphoplasmacytic infiltration and IgG4 production (19). Furthermore, by investigating the crosstalk between cells from the innate and adaptive immune systems in IgG4-RD pathogenesis it has been proved that CD4+ T and B cells, particularly plasmablasts, might contribute to tissue fibrosis by releasing pro-fibrotic mediators (20, 21). Due to the tight interaction between MC and B or T cells in different tissues (2, 4, 6-10), we can suggest an indirect effect of MC in IgG4-RD, by promoting the pro-fibrogenic activity of B and/or T CD4+ cells. The key role of MC in this context is also supported by recent reports, suggesting potential roles of anti-IgE therapy in subtypes of IgG4-RD. In this context the dissociation of pre-bound IgE from FcεRI with omalizumab, an anti-IgE mAb nowadays approved for severe asthma, chronic spontaneous urticaria and nasal polyps, might reduce activation of MC and consequent decrease in the release pro-fibrotic cytokines, including $TGF\beta_1$. Therefore, the pharmacological activity of omalizumab might suggest a potential usefulness of this biological drug in IgG4-RD treatment, particularly in those patients with high levels of IgE in a context of Type 2 inflammatory phenotype (22).
Due to their widespread tissue localisation, MC are easily involved in different pathogenetic mechanisms of other RD. For example, in systemic sclerosis (SSc), these cells are increased in the skin even in the very early stage of the disease, when the fibrosis is not yet established (23). As proven in biopsies of esophagus from SSc patients, MC are one of the main cells expressing an inflammatory gene signature, supporting their pro-inflammatory activities beyond their pro-fibrogenic ones (24).
Even if several reports suggest the active role of MC in different RD, rheumatoid arthritis (RA) remains the autoimmune disease in which MC are widely investigated. This is partially due to the availability of different animal model useful to reproduce the disease in animal strains.

The role of MC in rheumatoid arthritis: from inflammation to tissue remodelling

Several evidences support an active role of MC in the pathogenesis of RA, where chronic inflammation and tissue remodelling are the main features (25) (Fig. 1). MC are normally present in human synovia, but they are increased since the early stage of RA. Different mechanisms of MC hyperplasia were proposed, including recruitment of MC progenitors into the inflammatory tissue (26), and prolonged MC survival once these cells infiltrate the joints (27, 28). Due to their heterogeneity, MC may display different phenotypes, and several signals derived from the tissue environment might modulate their activities. If MC tryptase (MC_T) are mainly present in the early stage of RA (29, 30), where they correlate with synovial hyperplasia and T-cells infiltration, MC tryptase/chymase (MC_{TC}) are detected in fibrotic areas of synovial tissue, particularly in those patients with a severe or rapidly progressive disease (31, 32).
Different triggers can be responsible for MC activation, including cellular and humoral components. For instance, human MC co-cultured *in-vitro* with naïve B cells promote B cell activation and their differentiation with consequent production of anti-citrullinated protein antibodies (ACPA), mainly via cell-cell contact (33). In turn, ACPA may induce MC activation by binding Fcγ receptors (5), process that might be amplified by TLR4 and HSP70 binding (34). In this complex scenario, complement components might contribute to the activation of MC. This is the case of anaphylatoxin C5a which induces MC to release pro-inflammatory mediators by acting on C5a receptor in synergy with

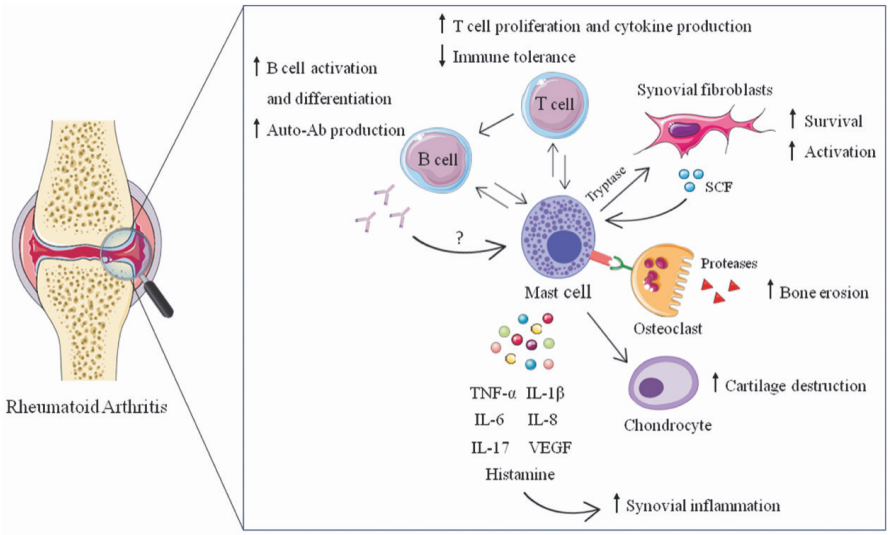

Fig. 1. Cross-talk between MC and other immune cells in RA.

Table I. MC and animal models of arthritis.

Role of MC	Arthritis model	Susceptible strain	References
Required	K/BxN arthritis	W/Wv and Sl/Sld	(56)
	CIA	Red MC basophil mouse	(59)
	CIA	mMCP4-deficient mice	(60)
	mBSA/IL-1β-induced arthritis	mMCP-6^{-}/mMCP-7^{-} C57BL/6 mice	(61)
Not required	K/BxN arthritis	KitW-Sh/KitW-Sh	(57)
	K/BxN arthritis	Cre-Master mice	(58)

CIA: collagen-induced arthritis; mBSA: methylated bovine serum albumin; IL-1β: interleukin-1beta; MC: mast cells; mMCP4: mouse MC protease 4; mMCP-6: mouse MC protease 6; mMCP-7: mouse MC protease 7; Cre-Master: Cre-mediated MC eradication.

the activation of the Fcγ receptor (35). In parallel, IL-33, an alarmin involved in RA pathogenesis and produced in the inflammatory tissue, induces MC to release an array of pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, and IL-17 (36-40).

Besides the various evidences of the role of MC in the inflammatory processes, some other studies suggest other anti-inflammatory activities of these cells in RA. For example, following IL-33 stimulus, MC gain the ability to suppress monocyte activation by releasing both the anti-inflammatory cytokine IL-10 and histamine. There are also evidences showing an inverse correlation in RA joints between MC genes expression and disease activity (41), as well as a negative correlation between levels of tryptase and C-reactive protein (CRP) in patients with early RA not yet treated with disease-modifying anti-rheumatic drugs (DMARDs) (42).

It is recognised that the direct contribution of MC in RA pathogenesis is also due to their pro-fibrogenic effects. For example, MC-derived tryptase is able to exert an anti-apoptotic activity on synovial fibroblasts, promoting their survival and activation in the tissue. In turn, synovial fibroblasts contribute to the survival of MC by the production of SCF and to their tissue recruitment by releasing chemoattractant mediators (43-47).

If we consider the complex mechanisms involved in tissue remodelling, including joint cartilage destruction and bone erosion, we can hypothesise a role of MC also in advanced stages of RA when the disease is already established. In fact, MC are present at the site of cartilage destruction (48, 49), where they seem to actively contribute to the degradation of cartilage proteoglycans (50). Indeed, analysis of cartilage-pannus specimens have revealed areas of MC aggregates at the sites of erosion with deposition of extracellular tryptase (51). This can lead to modulate chondrocyte metabolism by releasing vascular endothelial growth factor (VEGF), one of the main pro-angiogenic mediators involved in RA (52).

To date, it is unclear if MC contribute to bone erosion via activation of osteoclasts, although MC were found to be possible sources of RANKL, a major protein implicated in osteoclasts activation (53). However, the increased bone loss that characterises patients with systemic mastocytosis suggests a potential role of MC in accelerating bone turnover (54,55), and new achievements derived from this haematological disorder might help to better understand the role of MC in the bone erosion in RA.

MC in animal models of arthritis

Different animal models of experimental arthritis have been developed in order to better clarify the role of MC in RA. However, the results obtained are often controversial, due to the different methodologies used in the experimental models of arthritis, that only in part reproduce the complexity of RA (Table I).

In K/BxN mice, in which inflammatory arthritis is induced by injection of arthritogenic serum from KRN and NOD mice, the inflammatory process and clinical manifestations of the disease were abrogated in MC deficient mice, and then restored by transferring bone marrow derived wild-type MC into MC-deficient mice (56). However, further studies performed in other animal models were not able to confirm these observations. In fact, in a MC-deficient mice due to defect in kit signalling (KitW/KitW-v mice), the lack of the development of arthritis was explained by the reduction in neutrophils recruitment, and not by the deficiency of MC (57).

In order to overcome the limits of these experimental models using Kit-mutant mice, other *in-vivo* systems, independent of the c-Kit, have been developed. By using the Cre-mediated MC eradication (Cre-Master) mice, an increased susceptibility to antibody-induced autoimmune arthritis was observed, despite the lack of MC and the reduction in the basophils count (58). To better clarify the contribution of MC in the different

stages of the disease, these cells were depleted in CIA model during different phases of arthritis. When MC depletion was reached in a preclinical phase, circulating CD4+ T cells, monocytes, IL-6 and IL-17 levels were drastically reduced, with consequent beneficial effects on arthritis, while these effects were not observed in the established arthritis, supporting the contribution of MC mainly in the early phase of the disease (59).

By using mice deficient in MC protease 4 (mMCP4), the homologue of chymase in humans, it was possible to demonstrate *in-vivo* the potential role of MC-chymase in the development of severe autoimmune arthritis, mainly by its direct effect on inflammation, cartilage erosion and bone turn-over (60). In parallel, arthritis was markedly reduced in transgenic mice lacking heparin and mMCP-6 and mMCP-7, the corresponding human tryptase forms in mice, suggesting potential therapeutic beneficial effects of inhibiting MC-restricted tryptase in RA joint inflammation (61).

Conclusion

Several lines of evidence support the hypothesis of a direct role of MC in inflammatory and remodelling processes of RA. Nonetheless, we have to take into account that MC are complex cells and besides their well-known pro-inflammatory roles, they can exert anti-inflammatory activities, mainly through IL-10 production. Up to now, data obtained *in-vivo* and *in-vitro* strongly support different roles of MC in different stages of the disease. Further insight into the role of MC in RA can be obtained in genetically manipulated animal models of RA. However, these models, besides their limits in reproducing the human disease, are highly heterogeneous both in the mechanisms of RA induction and in modulation of MC number/activities. For example, the *Kit* mutants strains display abnormalities of several c-kit expressing cells, while the Cre-Master mice have a selective deficiency of MC. Thus, the conflicting results we reported are expected, and further studies, using more selective gene targeting, may be required to gain a full picture of the involvement of MC in RA.

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