

## Crucial roles of macrophages in the pathogenesis of autoimmune disease

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### Abstract

Macrophages are key players in various immune responses. In addition to functions in innate immunity such as antigen phagocytosis and cytokine production, antigen presentation by macrophage represents a link between innate and acquired immunity. During inflammatory processes, naïve monocytes differentiate into pro-inflammatory M1 and anti-inflammatory M2 macrophages. Resident monocytes/macrophages contribute to immune response that maintains tissue-specific homeostasis. In the target organs of autoimmune diseases, macrophages have dual functions in both the induction and suppression of autoimmune responses, which are mediated by production of various cytokines and chemokines, or by interaction with other immune cells. This review focuses on selected autoimmune diseases, such as systemic lupus erythematosus, multiple sclerosis, rheumatoid arthritis, and Sjögren's syndrome, to illustrate the key roles of macrophages in the cellular or molecular pathogenesis of autoimmunity. In addition, the contribution of macrophages to each autoimmune disease is compared.

**Key words:** Macrophage; Autoimmunity; Differentiation; Cytokines; Chemokines

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**Core tip:** Macrophages are well known as phagocytic cells and the source of cytokines and other immunomodulators of the innate immune system. There are many reviews of macrophage function, but not many that focus on their role in autoimmunity and autoimmune disease. This review focuses on the role of tissue resident macrophages in autoimmunity both in general and

several selected autoimmune diseases, develops a novel context for evaluation and a slightly different way of thinking of the complex interactions involved in "mistaken self-identity".

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## INTRODUCTION

Autoimmunity proceeds *via* a complex interaction of immune responses by a variety of immune cells in both lymphoid and target organs<sup>[1]</sup>. In some autoimmune diseases, T-cell-mediated autoimmune responses are involved in the onset or development of disease. Auto-reactive T cells are generated in the thymus and other peripheral lymphoid organs in an environment that includes other immune cells, stromal cells, and various epithelial cells<sup>[2,3]</sup>. Because the activities of autoreactive T cells are regulated by interactions with regulatory T (Treg) cells, dendritic cells, macrophages, and B cells, the pathogenesis of autoimmune diseases cannot be considered simply as a T-cell-mediated immune response<sup>[4]</sup>. The interactions of T cells with other immune cells in the pathogenesis of autoimmune disease have been described in many research reports<sup>[5]</sup>.

Macrophages differentiate from bone marrow-derived monocytes or tissue resident cells that are derived from yolk sac or fetal liver, such as histiocytes, Kupffer cells, microglia, alveolar, peritoneal, and synovial macrophages<sup>[6,7]</sup>. In the innate immunity system, macrophages function as phagocytic cells that engulf and digest cellular debris, foreign substances, microbes, and pathogens<sup>[8]</sup>. They also secrete cytokines and chemokines that modulate the activities of other immune cells in the inflammatory lesions<sup>[8]</sup>. The third macrophage function in innate immune system is antigen presentation to T cells which represents a link between innate and acquired immunity as well as dendritic cell<sup>[8]</sup>. Macrophages also contribute to the recovery of injured tissue by promoting angiogenesis or fibrosis<sup>[9]</sup>. The functions of tissue-resident macrophages have been the topic of recent reviews.

Classically activated (M1) macrophages produce pro-inflammatory cytokines, such as interleukin (IL)-1 $\beta$ , interferon (IFN)- $\gamma$ , and tumor necrosis factor (TNF)- $\alpha$  that promote various inflammatory responses<sup>[6,10]</sup>. Alternatively activated (M2) macrophages produce anti-inflammatory cytokines, such as IL-10 and IL-4. There are three macrophage subsets (M2a, b, and c) with characteristic stimuli or cytokine profiles<sup>[6,10]</sup>.

Although macrophages are involved in inflammatory stimuli, including autoimmunity, the lesions accompanying such responses are not induced by macrophages only. In addition, these cells also support tissue repair

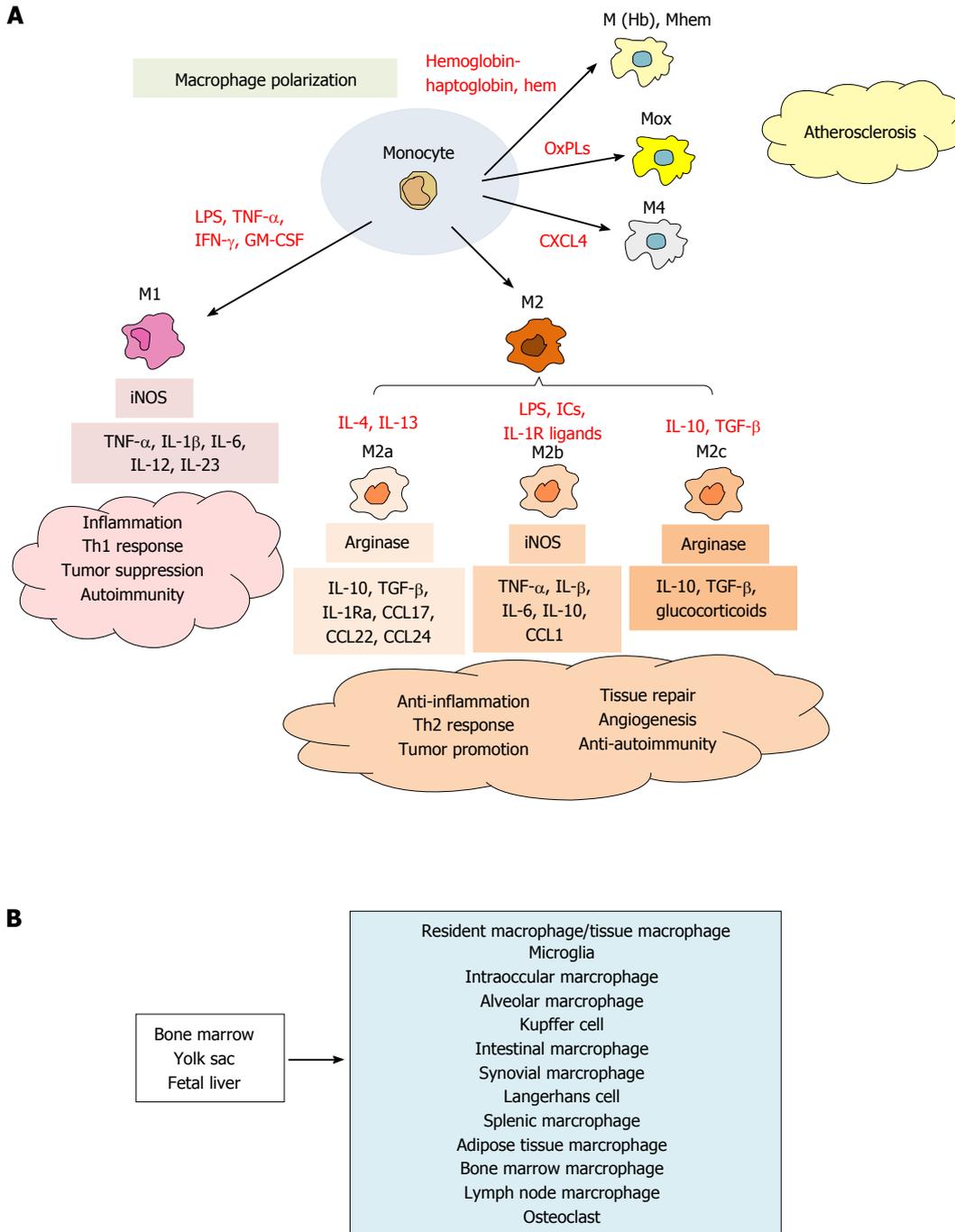
and immune homeostasis restoration. Therefore, the complex pathogenesis of autoimmune diseases can be seen as reflecting macrophage dysfunction. Further, the comparison regarding the contribution of macrophages to the pathogenesis between representative autoimmune diseases would be important for understanding the cellular mechanisms of the onset or development of autoimmune diseases. We review recent studies elucidating the role of macrophages in cellular and molecular mechanisms of autoimmune disease; moreover, we discuss potential novel clinical approaches to treat autoimmune diseases by targeting macrophages.

## MACROPHAGE SUBSETS

Monocytes differentiate into classically activated (M1) or alternatively activated (M2) macrophages following exposure to polarization signals such as cytokines, chemokines, hormones, bacterial products, and lipids (Figure 1A). Exposure of naïve monocytes to IFN- $\gamma$ , TNF- $\alpha$ , or lipopolysaccharide (LPS) induces M1 development. M1 macrophages produce pro-inflammatory cytokines, including TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-12 and IL-23, which in turn promote development and responses of Th1 cells<sup>[6,9]</sup>. By contrast, M2 macrophages are further classified into three subpopulations, depending on the response to various stimuli<sup>[6,10]</sup>. Exposure of naïve monocytes to IL-4 and IL-13 promotes M2a macrophages which express arginase I and produce IL-10, TGF- $\beta$ , IL-1Ra, CCL17, CCL22 and CCL24 to promote Th2 cells, eosinophils and basophils (Figure 1A)<sup>[6-10]</sup>. M2b macrophage development is induced by LPS, immune complexes (ICs), or apoptotic cells. In turn, M2b macrophages express inducible nitric oxide synthase and produce high level of IL-10, TNF- $\alpha$ , IL-1 $\beta$ , IL-6 and CCL1, which then promote recruitment of eosinophils and Treg cells (Figure 1A)<sup>[6-10]</sup>. M2c macrophages are elicited by IL-10, TGF- $\beta$ , or glucocorticoids and express arginase I. M2c macrophages exert an immunosuppressive function by promoting the development of Th2 cells and Treg cells (Figure 1A)<sup>[6-10]</sup>.

## TISSUE MACROPHAGES

In addition to the functional macrophage subtypes, there are subpopulations of tissue resident macrophages. These include microglia in the brain, intraocular macrophage in the eye, Langerhans cells in the skin (dermal DCs), salivary macrophage in the salivary glands, alveolar macrophage in the lung, splenic macrophages, Kupffer cells in the liver, intestinal macrophages, subcapsular sinusoidal macrophages and medullary macrophage in the lymph nodes, bone marrow macrophages, and osteoclasts in bone, all of which contribute to various tissue-specific immune surveillance (Figure 1B)<sup>[9]</sup>. For example, alveolar macrophages remove foreign antigens or allergens in the lung; Kupffer cells contribute to clearance of pathogens and toxin in the liver<sup>[8,9]</sup>. Recent studies demonstrate that resident macrophages derives from yolk sac and fetal liver in addition to bone marrow (Figure



**Figure 1 Macrophage differentiation and resident macrophages.** A: Naïve monocytes differentiate into M1, M2 and atherosclerosis-related macrophages [M(Hb), Mox, and M4] by various stimuli. M1 macrophages enhance inflammation through producing TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-12 and IL-23. M2 macrophages polarize to three subsets (M2a, M2b and M2c) by cytokines or ICs to suppress inflammation and repairs tissues through producing regulatory cytokines, such as IL-10, TGF- $\beta$ , IL-1R ligands and IL-6. Macrophage precursors (monocytes) are circulating, and quickly migrate into all tissues of the body, in which monocytes differentiate into mature macrophages with unique functions in each tissue; B: Resident /tissue macrophages are derived from bone marrow, yolk sac, and fetal liver to settle in various tissues. Resident macrophages contribute to homeostasis in the tissues. OxPLs: Oxidized phospholipids; ICs: Immune complexes; IFN: Interferon; TNF: Tumor necrosis factor; IL: Interleukin; MCP-1: Monocyte chemoattractant protein-1; LPS: Lipopolysaccharide; iNOS: Inducible nitric oxide synthase.

1B)<sup>[7]</sup>. Adipose tissue macrophage (ATM) are involved in the pathogenesis of metabolic diseases such as obesity and type 2 diabetes, in which accumulation of M1 ATMs promote inflammation and insulin resistance<sup>[11,12]</sup>. Resident macrophages are located in the all tissues, and play important roles in immune surveillance function to maintain the homeostasis.

Macrophage accumulation within the vascular wall is a hallmark of atherosclerosis. The lesional macrophages are derived from both blood monocytes and smooth muscle cells, and accumulate lipoproteins by macropinocytosis, phagocytosis, and binding to scavenger receptors, such as SR-A, SR-BI, CD36, and LOX1<sup>[13]</sup>. The vascular subsets include M(Hb) and Mhem macrophages that are

resistant to lipid loading and are induced by hemoglobin-haptoglobin complexes and hem<sup>[13-15]</sup>. The Mox macrophage subset is induced by exposure to oxidized phospholipids and is characterized by expression of high levels of heme oxygenase-1<sup>[13,16,17]</sup>. In addition, M4 macrophage is induced by CXCL4, and associated with the pathogenesis of atherosclerosis (Figure 1A)<sup>[13,16-18]</sup>.

Macrophages are also a functional link between inflammation and cancer. There is strong evidence that tumor-associated macrophages (TAMs) can promote tumor progression<sup>[19,20]</sup>. Cytotoxic killing by M1 TAMs, has an antitumor effect, but angiogenesis stimulated by vascular endothelial growth factor produced by M2 macrophages promotes tumor growth<sup>[21,22]</sup>. A number of diverse macrophage-associated phenotypes contribute to tumorigenesis in the complex tumor microenvironment.

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## IMPAIRED ENGULFMENT BY MACROPHAGE AND SYSTEMIC ERYTHEMATOSUS

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Impaired engulfment of dead cells by macrophage results in activation of autoimmune responses leading, severe autoimmune anemia, and chronic arthritis<sup>[23-26]</sup>. Apoptotic cells release "find me" signals, such as lysophosphatidylcholine, to attract phagocytes and expose "eat me" signals on the cell surface that stimulate engulfment<sup>[23,27]</sup>. One of the "eat me" signals is phosphatidylserine, which is exposed on the cell surface during apoptosis. Macrophages recognize phosphatidylserine, engulf the apoptotic cells, which are transferred to the lysosomes and degraded by lysosomal enzymes. Bridging molecules such as milk fat globule EGF factor 8 (MFG-E8) and growth arrest-specific 6 (Gas6) protein mediate binding between phosphatidylserine on the apoptotic cells, and integrin and tyrosine-kinase receptors on macrophages<sup>[23,26]</sup>. The clearance of apoptotic cells in the body is controlled by complex molecular and cellular interaction with macrophages.

If apoptotic cells are not engulfed, then they undergo secondary necrosis, in which the plasma membrane disintegrates with release of the cellular contents, which then bind to immunoglobulins and complement proteins, and activate macrophages and B cells. In addition to Fc receptors and B cell receptors, also Toll-like receptors are able to recognize the necrotic cell components and activate macrophages and B cells. The activated macrophages secrete cytokines that stimulate B cells to produce autoantibodies able to cause pathological conditions such as systemic erythematosus (Table 1)<sup>[23,26]</sup>. In addition, if lysosomal digestion is defective, the dead cell components accumulate in the lysosomes, leading to intracellular activation of pro-inflammatory cytokines such as IFN- $\beta$  and TNF- $\alpha$  production by the innate immune system<sup>[23,26]</sup>. Thus, both extracellular activation of immune responses by apoptotic cells that are not phagocytized and intracellular activation of macrophages by impaired processing of apoptotic cells contribute to the onset or development of autoimmunity.

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## MACROPHAGES IN MULTIPLE SCLEROSIS

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Multiple sclerosis (MS) is a debilitating neurological disorder of the central nervous system (CNS). It is a T-cell-mediated autoimmune disease with clinical signs and symptoms characterized by weakness and progressive paralysis<sup>[28,29]</sup>. Studies of experimental autoimmune encephalomyelitis (EAE), an animal model of MS, have demonstrated that autoreactive T cells against myelin proteins play a key role in disease development<sup>[30,31]</sup>. Th1 and Th17 cells trigger autoreactive responses within the CNS through pro-inflammatory cytokines including IFN- $\gamma$ , IL-17, IL-12, and IL-23. At later phases of MS, Th2 and Treg cells contribute to controlling inflammation.

Macrophages participate in the pathogenesis of EAE<sup>[32,33]</sup>. Indeed, there are few infiltrating macrophages in the CNS under physiological conditions. However, during induction and exacerbations of EAE, macrophages infiltrate the meninges surrounding the CNS, the perivascular space, and the choroid plexus<sup>[34,35]</sup>. The number of infiltrating macrophages in the CNS decreased during remissions in parallel with the decrease in lymphocyte infiltrates<sup>[34,35]</sup>. The expression of chemokines and chemokine receptors by CNS macrophages contributes to the induction and progression of EAE<sup>[36]</sup>. EAE studies have demonstrated that up-regulation of CCR2, CCL2, CCL3, CCL4 and CCL22 induces macrophage accumulation and effector function in the CNS<sup>[37,38]</sup>. Moreover, CCR4, a receptor for CCL17 and CCL22, is up-regulated in macrophages present in the CNS lesions<sup>[39]</sup>. *CCR4* gene knockout mice exhibit lower macrophage infiltrates in the CNS, and exhibit milder EAE symptoms than those seen in wild type mice<sup>[40]</sup>.

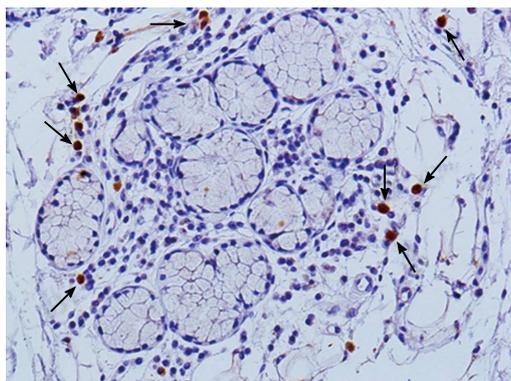
Both M1 and M2 macrophages play important roles in enhancing and regulating the pathogenesis of EAE. TNF- $\alpha$ , IL-1 $\beta$ , IL-12 and nitric oxide, expressed by activated M1 macrophages, induce inflammation and tissue damage in the CNS<sup>[41-43]</sup>. Fewer M2 than M1 macrophages are present in the CNS during exacerbations in EAE mice. An increase in the M2 macrophage population contributes to anti-inflammatory effect associated with increased production of IL-4, IL-10, IL-13 and TGF- $\beta$ <sup>[44]</sup>. Moreover, M2 macrophages are thought to have more regulatory function in the pathogenesis of EAE<sup>[45]</sup>. In addition to tissue repair, the anti-inflammatory cytokines produced by M2 macrophages drive differentiation and recruitment of Th2 and Treg cells to suppress the autoimmune response in EAE<sup>[45]</sup>. Adoptive transfer of M2 macrophages into EAE mice significantly inhibits disease development<sup>[41,44]</sup>. Thus, macrophages play key roles in the pathogenesis of MS (Table 1).

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## MACROPHAGE IN RHEUMATOID ARTHRITIS

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Rheumatoid arthritis (RA) is a chronic autoimmune



**Figure 2 Macrophages in autoimmune lesions.** CD68<sup>+</sup> macrophages infiltrate in the salivary gland tissue from SS patients. Immunohistochemical analysis using paraffin-embedded sections from lip biopsy materials was performed by staining with anti-CD68 antibody (DAKO). Biotinylated antibody and horseradish peroxidase (HRP)-conjugated streptavidin (LSAB kit, DAKO) was used as a secondary antibody, and then CD68<sup>+</sup> cells were detected by using 3,3'-Diaminobenzidine (DAB) as a substrate. Counter staining was performed with hematoxylin. Original magnification is  $\times 400$ . Arrows show CD68<sup>+</sup> macrophages.

disorder characterized by inflammation of the synovial lining of the joint capsule. Pathological characteristics of RA lesions include immune cell infiltration, synovial cell hyperproliferation, fibrosis (pannus formation), and destruction of cartilage and bone<sup>[46]</sup>. Various immune cells are observed in RA lesions, including CD4<sup>+</sup> T cells, CD8<sup>+</sup> T cells, B cells, natural killer (NK) cells,  $\gamma\delta$ T cells, mast cells, dendritic cells, and macrophages<sup>[47,48]</sup>. Monocyte/macrophage-derived cytokines, such as TNF- $\alpha$ , IL-1 $\beta$ , IL-12, IL-6, IL-15, IL-18 and IL23, trigger and enhance the activation and recruitment of Th1 and Th17 T cells in the synovial tissues of RA patients and animal models<sup>[49]</sup>. In addition, activated macrophages also play an important role in controlling Treg cells in the pathogenesis of RA<sup>[49,50]</sup>.

Synovial macrophages are resident cells in the synovial tissues of healthy joints<sup>[49]</sup>. The macrophages become activated and polarized to form M1 or M2 phenotype within RA lesions. However, inflammatory synovial macrophages have not yet been classified into a phenotype. Many M1 macrophages that produce TNF- $\alpha$  and IL-1 $\beta$  are observed in the synovial tissues of RA patients along with M2 macrophages that produce IL-10. The ratio of M1 to M2 macrophages present in synovial lesions varies in relation to disease stage. IFN- $\gamma$  and TNF $\alpha$  promote polarization to M1 macrophages during synovial inflammation in early stage disease<sup>[51,52]</sup>. IFN regulatory factor (IRF) 5 is thought to be a key transcription factor for M1 macrophage differentiation<sup>[53]</sup>. IL-10, IL-4, IL-13 and ICs promote polarization to M2 macrophages and suppression of synovial inflammation at later stage<sup>[54]</sup>. M2 macrophage differentiation is controlled by a lot of number of transcription factors, including IRF3, IRF4, and nuclear factor (NF)- $\kappa$ B (Table 1)<sup>[55-57]</sup>.

Therapies targeting monocyte/macrophage have been used to treat RA. Inhibition of TNF- $\alpha$  produced by synovial inflammatory macrophages promotes IL-10 expression

by CD4<sup>+</sup> T cells, enhances Treg cell function, promotes monocyte apoptosis *via* transmembrane (tm)TNF- $\alpha$ , and is associated with an antiosteoclast effect<sup>[58-63]</sup>. Inhibition of IL-6 signaling enhances the frequency of Treg cell, and monocyte apoptosis<sup>[64-69]</sup>. Abatacept [cytotoxic T-lymphocyte antigen 4-Ig (CTLA4-Ig)] inhibits both the interaction between monocytes/macrophages and T cells, and monocyte differentiation into osteoclasts<sup>[70]</sup>. Therefore, macrophages contribute to the pathogenesis of RA directly or indirectly. Clinical use of agents that target macrophage function would likely be effective for treating RA.

## MACROPHAGES IN SJÖGREN'S SYNDROME

Sjögren's syndrome (SS) is a chronic autoimmune disease that targets exocrine glands, such as salivary and lacrimal glands, and also causes systemic autoimmune lesions<sup>[71]</sup>. The mononuclear cell populations infiltrating the salivary gland tissues of SS patients include CD4<sup>+</sup> T cells, CD8<sup>+</sup> T cells, Treg cells, B cells, NK cells, DCs and macrophages<sup>[72]</sup>. Among them, infiltration of CD4<sup>+</sup> T cells, Treg cells, B cells, DCs and macrophages is correlated to lesion severity<sup>[73]</sup>. SS is triggered by T-cell-mediated autoimmune responses; however, also other immune cells contribute to the onset or development of SS, including macrophages. Macrophages are observed in the autoimmune lesions of the salivary gland tissues from SS patients (Figure 2). Indeed, an elevated expression of macrophage-derived molecules, such as chitinase-3-like protein 1 and chitinase 1, is associated with increased severity of SS lesions, suggesting that macrophages are involved in the pathogenesis of SS<sup>[74]</sup>. In addition, pro-inflammatory cytokines produced by macrophages, such as TNF- $\alpha$ , IL-1 $\beta$ , IL-6 and IL-12, have been associated with the induction of autoimmune lesions in the target glands of MRL/lpr/lpr mice, a murine model of SS<sup>[75]</sup>. In a SS model using autoimmune regulator (*AIRE*) gene knockout (KO) mice, many macrophages in addition to CD4<sup>+</sup> T cells infiltrated the corneal stroma, limbus, and lacrimal glands<sup>[76]</sup>. Adoptive transfer of CD4<sup>+</sup> T cells from *AIRE* KO mice into immunodeficient recipient mice resulted in local infiltration of macrophages in the target tissue<sup>[76]</sup>. Moreover, *in vivo* depletion of macrophages by injection of clodronate liposome into *AIRE* KO mice attenuated dry eye symptoms<sup>[76]</sup>. Therefore, autoreactive T cells may elicit macrophage infiltration into the target organs of macrophage-associated autoimmune lesions (Table 1).

Aromatase is an enzyme that converts androgens to estrogens. Aromatase gene knockout (*ArKO*) mice develop marked abdominal adiposity, suggesting that aromatase regulates lipid metabolism<sup>[77,78]</sup>. *ArKO* mice also spontaneously develop an autoimmune disease in exocrine glands, such as salivary and lacrimal glands that resembles SS<sup>[79]</sup>. We reported significantly increased expression of mRNA encoding pro-inflammatory cytokines, IL-1 $\beta$ , IL-6, IFN- $\gamma$ , TNF- $\alpha$ , and monocyte che-

**Table 1** Autoimmune diseases and macrophages

Autoimmune disease	Remarks of macrophage
SLE	Impaired engulfment, IFN- $\beta$ , TNF- $\alpha$ , B cell activation
MS	M1 (CCR4, TNF- $\alpha$ , IL-1 $\beta$ , IL-12, NO), M2 (IL-4, IL-10, IL-13, TGF- $\beta$ )
RA	M1 (TNF- $\alpha$ , IL-1 $\beta$ , IRF5), M2 (IL-10, IL-4, IL-13, IRF3, IRF4, NF- $\kappa$ B)
SS	M1 (IL-1 $\beta$ , IL-6, TNF- $\alpha$ , MCP-1)

SLE: Systemic erythematosus; MS: Multiple sclerosis; RA: Rheumatoid arthritis; SS: Sjögren's syndrome; IFN: Interferon; TNF: Tumor necrosis factor; IL: Interleukin; IRF: IFN regulatory factor; MCP-1: Monocyte chemotactic protein-1.

motactic protein-1 (MCP-1) in white adipose tissue of ArKO mice<sup>[80]</sup>. We also found an increased number of inflammatory M1 macrophages in white adipose tissue of ArKO mice, and significant enhancement of MCP-1 mRNA expression in the salivary gland tissue<sup>[80]</sup>. The severity of autoimmune lesions in a murine SS model exacerbated by administration of an aromatase inhibitor, and the percentage of macrophages in the spleen of SS model mice treated with aromatase inhibitor was significantly higher than that in control mice<sup>[80]</sup>. Collectively, the data indicates that aromatase may be involved in the pathogenesis of SS-like lesions by controlling the target organ- and adipose tissue-associated M1 macrophages.

## CONCLUSION

Macrophages have dual functions in promotion and regulation of inflammation. The differentiation and distribution of macrophages influence the onset or development of systemic and organ-specific autoimmune diseases. Macrophages serve as a bridge between innate and adoptive immunity to maintain immunological homeostasis, and macrophage dysfunction or impairment leads to the induction of severe immune disorder. Clinical interventions targeting macrophages may result in discovery of novel treatments of immune disorders, including autoimmune diseases.

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