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Macrophage involvement in idiopathic inflammatory myopathy: pathogenic mechanisms and therapeutic prospects

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Abstract

Idiopathic inflammatory myopathies are a group of systemic autoimmune diseases characterized by chronic muscle inflammation and diverse clinical manifestations. Macrophages, pivotal components of innate immunity, are implicated in immune responses, inflammation resolution, and tissue repair. Distinct macrophage polarization states play vital roles in disease progression and resolution. Mechanistically, activated macrophages release proinflammatory cytokines, chemokines, and reactive oxygen species, perpetuating immune responses and tissue damage. Dysregulated macrophage polarization contributes to sustained inflammation. Here, we reviewed the intricate contributions of macrophages to IIM pathogenesis and explored novel therapeutic avenues. We discussed emerging strategies targeting macrophages, including receptor-based interventions and macrophage polarization modulation, for IIM treatment. This review underscores the multifaceted involvement of macrophages in IIM pathogenesis and offers insights into potential therapeutic approaches targeting these immune cells for disease management.

Keywords Macrophage, Idiopathic inflammatory myopathies, Pathogenic mechanisms, Treatment

Introduction

Idiopathic inflammatory myopathies (IIMs) are a group of heterogeneous, systemic autoimmune diseases primarily characterized by muscle weakness, muscle enzyme elevations, inflammation on muscle biopsy, and extramuscular manifestations [1, 2]. Initially, IIMs included only dermatomyositis (DM) and polymyositis (PM). With the development of testing and examination technology, including assays for the myositis-specific autoantibodies (MSAs), immunohistochemical characterization of muscle biopsies (e.g. the expression of major histocompatibility complex class I (MHC I) molecules in muscle fibers and the subtyping of invading inflammatory cells) and magnetic resonance imaging (MRI) can be used to visualize muscle inflammation, classification criteria are being updated [3]. PM and DM cannot explain all phenotypes as the complexity of patient symptoms increases. In 1978, a clinical case described a unique form of inflammatory myopathy characterized by prominent quadriceps weakness and distal weakness, which is known as inclusion body myositis (IBM) [4]. Later, necrotizing myopathy with an "immune background" was suggested in the literature, and "immune-mediated necrotizing myopathy (IMNM)" emerged as a separate entity in IIM based on pathological criteria [5]. At present, the latest classification criteria for IIMs include DM, PM, IBM, IMNM and

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overlapping myositis (including anti-synthetase syndrome), which were proposed by Selva-O´ et al. in 2018 [6]. In general, IIM is considered to be a severe autoimmune disease involving multiple immune cells. The immunologic heterogeneity of IIMs and the associated immune-cell interactions have hindered the research of their risk factors and pathogenesis.

Recent studies have suggested that multiple adaptive immune, innate immune and nonimmune mechanisms are involved in the pathogenesis of IIMs [3, 7]. Traditional studies have emphasized the key role of adaptive immunity. T-cell phenotypes that accumulate in muscle tissue include proinflammatory, antiapoptotic and cytotoxic $CD28^{null}$ populations [8]. Several MSAs are associated with different clinical phenotypes [9, 10]. For example, antibodies to Mi-2 autoantigens are preferentially present in patients with DM, anti-signal recognition particle (SRP) autoantibodies are associated with necrotizing myopathy and anti-CADM-140 is associated with clinically amyopathic dermatomyositis (CADM). The presence of autoantibodies, T-cell infiltration and the upregulation of MHC I molecules on the sarcolemma suggest a role for adaptive immunity in pathogenic mechanisms [11, 12]. In addition, it is becoming increasingly clear that the innate immune system contributes to disease progression through multiple interconnected pathways. Toll-like receptors (TLRs), Type I interferons (IFNs) and various other cytokines have been shown to be involved in the occurrence of IIMs [13–16]. The overexpression of IFN regulatory proteins and cytokines was first described in the skin and muscles of patients with DM. Subsequently, evidence has shown that type I IFN signaling is upregulated in the muscle tissue and blood of patients with juvenile dermatomyositis, DM or PM [17–19]. Moreover, tumor necrosis factor-α (TNF-α) is tightly associated with IIMs, and the level of TNF-α is often connected with disease activity and the presence of interstitial lung disease (ILD) in DM patients [20]. The correlation between nonimmune-mediated mechanisms and IIMs is based on several key findings: (i) The pathological features of muscle biopsies are not always related to clinical severity. (ii) The effect of immunosuppressive therapy is limited. (iii) Several noninflammatory mechanisms, such as cellular stress and degenerative mechanisms, are evident in many muscle biopsies [21, 22]. In summary, IIMs are complex autoimmune diseases in which multiple interrelated pathways are involved in their development. The histopathological features of muscle tissue suggest that different disease mechanisms predominate in each IIM subtype, but the specific pathogenic mechanism is unclear. For example, PM is generally believed to be mediated by CD8+T cells, and it remains unclear whether the presence of autoantibodies is an epiphenomenon or a direct causative factor in the progression of the disease. Similarly, the mechanisms underlying macrophage infiltration and activation in various types of IIMs are not well understood. Therefore, our understanding of disease mechanisms needs to be improved, which will allow us to develop valid classification criteria, reliable prognostic biomarkers, and targeted therapeutic approaches.

The first detailed descriptions of patients with rare muscle disease (the acute form of myositis) with cutaneous lesions were reported by E. Wagner in 1863 and P. Potain in 1875 [23, 24]. They are characterized by many skeletal muscle lesions and skin manifestations, which became known to us later as PM and DM [25]. Pathology suggested that it is a myopathy and is associated with infiltration of varying numbers of lymphocytes and macrophages in most cases, but the reason for the accumulation of inflammatory cells was unknown. In 1965, Dawkins produced PM in guinea pigs and rats by injecting homologous or heterologous muscles with adjuvants, indicating that the pathogenesis of myositis may involve immune mechanisms and that macrophages are among the prominent cells involved in pathological lesions [26]. In 1984, Arahata et al. used immunohistochemistry and immunoelectron microscopy to show that lymphocytes and macrophages can cross the basement membrane and locally displace or crush muscle fibers, resulting in cell destruction in this region. These results indicated that the direct cytotoxic effect of macrophages and the synergistic effect of lymphocytes lead to muscle fiber damage [27]. In recent years, increasing evidence has shown that macrophages play an irreplaceable role in IIMs [28–33]. In the PM and IBM, cytotoxic CD8+T cells and macrophages intensively surround and invade nonnecrotic myofibers expressing MHC I [34, 35]. Anti-CD68 tissue staining indicated that macrophages were involved in the immune dysregulation of endothelial cells in IBM [36, 37]. Serological analysis of clinical patients has shown that interleukin-1 (IL-1), granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-10, C-C motif ligand 3 (CCL3) and CCL4 are significantly increased in IIM patients and are key biomarkers for distinguishing them from healthy individuals [31]. In an analysis of repeat muscle biopsies and blood samples from patients with IIMs before and after treatment, a reduction in CD68+macrophages in posttreatment biopsies were observed [38]. Studies in animal models have shown that inhibiting macrophage inflammatory infiltration can induce reactive oxygen species (ROS) degradation and decrease the expression of proinflammatory factors such as TNF-α and IL-6 [39]. These data may suggest that infiltrating macrophages in muscle tissue are involved in muscle weakness, but the underlying molecular mechanisms remain to be elucidated.

Previous studies have focused mainly on the analysis of macrophage-related cytokines and chemokines, possible molecular pathways of macrophage action, and related molecules that may affect the production and activation of macrophages. A major research advance in recent years has been the discovery that macrophages are a complex population with high heterogeneity and plasticity. During inflammation, macrophages undergo functional and morphological changes, including the expression of cell surface markers [40], antigen presentation to lymphocytes [41], and subsequent production of cytokines and chemokines. In the early stages, two distinct polarization states have been identified: classically activated macrophages (M1) and alternately activated macrophages (M2) [42]. M1 cells mainly produce proinflammatory cytokines such as TNF-α and IL-1. M2 cells exert anti-inflammatory effects by producing large amounts of anti-inflammatory cytokines such as IL-10 and transforming growth factor-beta (TGF-β). Pathology is often associated with dynamic changes in macrophage activation. M1 cells initiate and maintain inflammation, whereas M2 or M2-like cells are associated with the resolution of chronic inflammation [43]. In most myopathies, M1 plays a major role, but in anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR)-positive myopathy and macrophage-rich inflammatory myopathy, M2 tends to be abundant [44, 45]. The activation status of macrophages and the causal relationships among macrophages, inflammatory factors and autoimmunity in IIMs have attracted increasing attention from scholars. The M1/M2 paradigm is increasingly unable to account for the functional state of complex macrophages. Whereas in vitro, an M1 or M2 state may be present in differentiated cells stimulated by a single stimulus, macrophage activation in vivo is shaped by a broad tissue-specific environment consisting of a large network of signals from multiple cell types. A recent study using 28 different stimuli to activate human macrophages showed that macrophage activation could not be explained by a dichotomous model [46]. In addition, stimulus-specific naming systems for macrophage activation have been proposed. For example, macrophages stimulated in vitro, such as M (lipopolysaccharide (LPS)), are named by their inducer, whereas macrophages derived in vivo are described by a variety of markers rather than attempting to assign them to M1 or M2 types [47]. Thus, the history of the study of macrophage activation has evolved from dichotomous models to more precise systems linking stimuli to phenotypes. The challenge is to extend the phenotypic classification of macrophages to reflect their function at a particular point in time and in a particular environmental context.

Our article summarizes the role of macrophages in IIMs, describes new attempts to target macrophages, and describes new strategies for possible treatments.

Immunomodulatory effect of macrophages in IIM

As one of the main inflammatory infiltrates, macrophages can be found in all types of IIMs [1, 2, 48–50]. When tissue is damaged, inflammatory monocytes are recruited from the circulation and are converted into macrophages during migration. At the same time, most tissues of the body contain tissue-resident macrophages, which are extremely heterogeneous and indispensable for tissue function and homeostasis [51]. When tissue damage is limited, muscle-resident immune cells exert their stereotypic maintenance function to remove necrotic cells and establish immune tolerance. However, when tissue damage is too extensive to be handled by resident cells, they immediately recruit peripheral blood immune cells, which primarily constitute the first wave of immune cell influx [52]. Resident macrophages drive the influx of inflammatory leukocytes, and these monocytic-derived macrophages rapidly dominate inflammatory lesions, becoming the majority of macrophages. The importance of resident macrophages in initiating the inflammatory response has been illustrated by experimental studies [51]. Recent studies have revealed that high levels of creatine kinase released from skeletal muscle cells of patients with IIMs may represent danger-associated molecular patterns (DAMPs), which can activate macrophages as endogenous TLR ligands [7]. Activated macrophages tend to exhibit a proinflammatory phenotype in the early stage. They can have a direct killing effect by producing reactive oxygen species (ROS), nitrogen substances and proteases. Moreover, M1 macrophages which are primarily involved with pro-inflammatory immune progress, secrete various inflammatory mediators that drive autoimmune inflammation, including TNF-α, IL-1, IL-6, IL-12 and IL-23 [53]. CXC chemokines and CC chemokines also play a role in maintaining muscle inflammation [7]. The importance of various chemokines and cytokines in the pathogenesis of IIMs has been the focus of research over the last decade. Previous reports found that serum IL-6 levels are significantly increased in patients with IIMs and correlated with disease activity, whereas the high expression of IL-6 levels in pathological states may be mainly produced by infiltrating macrophages [54, 55]. Studies have shown that macrophages can regulate the proliferation and differentiation of satellite cells through the Janus tyrosine kinase-signal transducer and activator of transcription (JAK-STAT) pathway and affect muscle metabolism [43].

TNF-α has also been shown to be upregulated in DM, PM and IBM, and serum TNF-α levels in DM patients have been shown to correlate with disease activity and

the presence of ILD [56]. In both the PM and IBM, macrophages actively invade nonnecrotic muscle fibers and express high levels of beta chemokines [36]. β-Chemokines play a proinflammatory role in IIMs, especially CCL2, whose levels measured by immunoassay are elevated in DM, PM, and IBM muscles compared to those in controls [57]. These inflammatory cytokines can not only directly bind to typical skeletal muscle cell receptors but also stimulate both necrotic and nonnecrotic muscle cells to highly express MHC I. MHC I presents autoantigens to drive T-cell-mediated cytotoxicity, which is closely related to the occurrence of PM [58]. Moreover, the binding of these receptors and abnormal overexpression of MHC I induce various signaling events, such as activation of the nuclear factor kappa B (NF-κB) pathway or the endoplasmic reticulum stress response, leading to proteasome activation and autophagy. Miller FW et al. reported that autophagy can mediate IIMs through dysregulation of skeletal muscle protein homeostasis, inflammasome activation, inflammatory cytokine production, and activation of cell death mechanisms (e.g., cellular pyroptosis) [7].

In addition, cytokines secreted by macrophages can induce the differentiation and expansion of Th1 and Th17 cells (T helper cells express IFN-γ and IL-17), promoting the development of inflammatory responses. Chevrel et al. confirmed the expression of IL-17 in DM and PM [59]. Peng et al. reported that the serum IL-23 level in patients with IIMs was significantly greater than that in healthy controls [60]. IL-17 and IL-23 promote the progression of the inflammatory response by inducing Th1 and Th17 cell differentiation [61]. Moreover, with the help of TH1 cells, B cells produce antibodies involved in the pathogenesis of IIMs, including MSAs in different forms of IIMs [10]. MSAs are closely related to different clinical features. The most common MSAs are anti-Jo-1 autoantibodies, which are directed against histidine-tRNA synthetase and are present in 20 to 25% of patients with PM or DM. Specific clinical phenotypes associated with various MSAs may also suggest the role of MSAs or their antigenic targets in the pathogenesis of myositis.

At the same time, the resolution of the immune response requires the synergistic effect of suppressing inflammatory factors and clearing necrotic cells and debris. Injury can result in multiple types of cell death, including direct tissue damage and subsequent depletion of the immune cells that infiltrate the tissue. Without timely clearance by phagocytes, such as macrophages, these apoptotic cells may undergo secondary necrosis, a transition that can promote persistent inflammation and trigger autoimmunity through sustained release of inflammatory mediators [42]. Proto et al. described a circuit by which regulatory T (Treg) cells enhance macrophage depletion of apoptotic cells during extinction [62]. Upon activation, Treg cells produce IL-13 and subsequently stimulate macrophages to upregulate IL-10. Macrophages retrieve this IL-10 and induce vav guanine nucleotide exchange factor 1 expression, which in turn regulates ras-related C3 botulinum toxin substrate 1 activity and actin polymerization. These findings indicate the regulatory role of immune cells in the treatment of autoimmune diseases such as IIMs through Treg cell enhancement strategies.

In summary, macrophage activation leads to the secretion of proinflammatory cytokines and chemokines, which in turn further recruit immune cells to an already mature environment and activate helper T cells as well as CD8+cytotoxic T cells to exert direct damaging effects. In addition, cytokines produced by these helper T-cell subsets further induce macrophage activation and contribute to disease progression. Treg cells have also been found to regulate macrophage phagocytosis, and dysregulation of Treg cells also provides ideas for the occurrence and development of diseases. Figure 1 visually demonstrates these effects of macrophages.

The effect of macrophage polarization in IIM

Normally, macrophages often exhibit a proinflammatory phenotype in the early stage of tissue damage. To counteract tissue destruction, macrophages undergo apoptosis or switch to anti-inflammatory phenotypes to alleviate the inflammatory response and promote tissue repair. However, as observed in many chronic inflammatory and autoimmune diseases, the response of inflammatory macrophages is not rapidly controlled, leading to their pathogenicity and promoting disease occurrence and development [63]. Previous studies on macrophage polarization were mostly limited to the M1 and M2 paradigms. That is, TLR and IFN-γ stimulate the differentiation of macrophages to the M1 phenotype, whereas IL-4 and IL-13 induce the M2 phenotype [43]. The M1 phenotype is characterized by high expression levels of proinflammatory cytokines, high production of reactive nitrogen and oxygen intermediates, promotion of Th1 responses, and inhibition of M1 polarization, which can alleviate the inflammatory response [64]. In contrast, M2 macrophages are thought to be involved in promoting tissue remodeling and to have immunomodulatory functions. Classically activated M1 cells are associated with the initiation and maintenance of inflammation, and M2 or M2-like cells are related to the resolution of chronic inflammation [65].

Many clinical trials have attempted to elucidate the macrophage activation phenotype in IIMs based on this theory. Zhang et al. reported increased expression of TLR4 and IFN-γ signaling pathway genes in IIM patients and suggested that M1 macrophages may participate in the pathogenesis of IIM [44]. Experiments by Torres-Ruiz

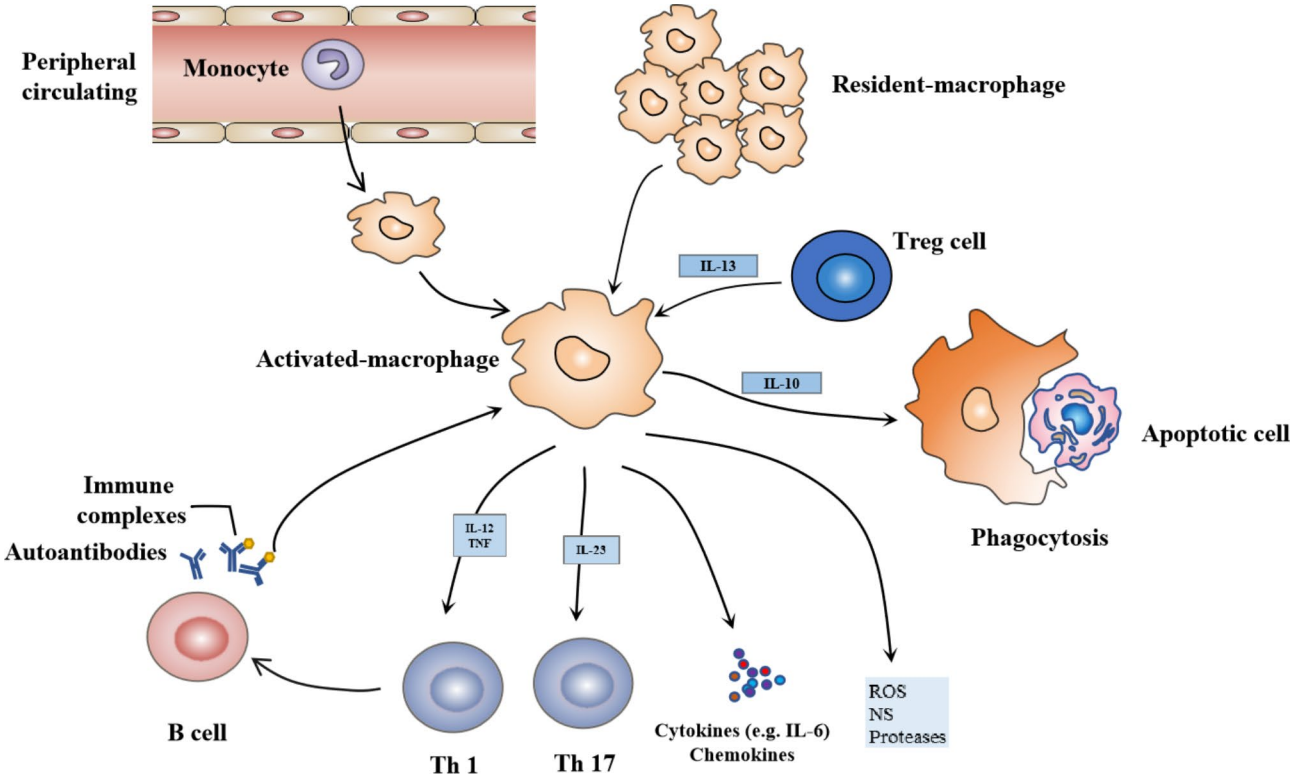

Fig. 1 The role of macrophages in IIMs. When tissue is damaged, inflammatory monocytes are recruited from the circulation and are converted into macrophages during migration. At the same time, resident tissue macrophages proliferate while recruiting peripheral blood immune cells, which primarily constitute the first wave of immune cell influx. Activated macrophages tend to exhibit a proinflammatory phenotype at an early stage. They can exert direct killing effects by producing ROS, NSs and proteases. In addition, macrophages secrete a variety of inflammatory mediators to drive autoimmune inflammation, and cytokines secreted by macrophages can induce the differentiation and expansion of Th1 and Th17 cells and promote the development of inflammatory responses. On the other hand, the phagocytosis of apoptotic cells by macrophages can be enhanced by Tregs. All these factors contribute to the progression of inflammation. ROS, reactive oxygen species; Treg, regulatory T cells; NS, nitrogen species; Th1 and Th17 cells, T helper cells that express IFN-γ and IL-17; IL-6, interleukin-6; IL-10, interleukin-10; IL-13, interleukin-13; IL-12, interleukin-12; IL-23, interleukin-23; TNF-α, tumor necrosis factor-α

et al. revealed that circulating intermediate monocytes were expanded in IIM patients, and these intermediate monocytes mainly differentiated into M1 macrophages, suggesting a pathogenic role of inflammatory macrophages in IIMs [50]. Previous studies have shown that human monocytes can be divided into three subclasses based on the expression of the surface markers CD14 and CD16: classical monocytes (CD14++CD16-), intermediate monocytes (CD14++CD16+), and nonclassical monocytes (CD14+CD16+) [66]. Intermediate monocytes have phagocytic and proinflammatory properties because they secrete IL-1β, TNF-α, and IL-6; in addition, they express CD80, CD86, and HLA-DR and are able to differentiate into M1 macrophages [67]. In contrast, in animal models of muscle injury, nonclassical monocytes are recruited to muscle to promote muscle repair after tissue injury [68]. Thus, the expansion of intermediate monocytes may contribute to the proinflammatory environment in the peripheral blood of IIM patients, and the greater proportion of nonclassical monocytes in these patients may reflect muscle damage [69]. These studies suggest that there are different monocyte phenotypes at different stages of the disease or that the proportion of cells with different phenotypes changes with the stage of the disease. Analysis of the characteristics of macrophage subtypes in PM and DM muscle revealed that these cells express myeloid-related protein 14 and 27E10 (M1-type macrophages) early and activate 25F9 (M2-type macrophages) late, as well as inflammatory markers such as inducible nitric oxide synthase and TGF-β [40, 70]. This suggests that different functional states of macrophages are present in myositis muscle and that their relative proportions may vary according to the stage of the disease process.

As research progresses, it has increasingly been discovered that the M1-M2 binary classification model fails to adequately describe macrophage activation. Many macrophages in homeostatic or pathological states or during disease progression do not show a clear M1 or M2 phenotype [47]. Xue et al. used the transcriptional program of macrophages activated by 28 different stimuli, including pattern recognition receptor ligands, cytokines, and

metabolic cues, to obtain a dataset of 299 macrophage transcriptions. Network modeling of this dataset extends the current model of M1 versus M2 polarization to a "spectral model" that includes at least nine different macrophage activation programs [46]. As an extension of the multidimensional model, stimulus-specific naming systems for macrophage activation have been proposed, in which macrophages are named according to specific stimuli in vitro, such as M (LPS) and M (IL-4), while in vivo, they are described by multiple markers [71]. Sanin et al. developed a predictive model to map macrophage activation to 12 mouse tissues and 25 biological conditions and found a common limited number of transcriptional profiles, modeled as stages of four conserved activation pathways, including "phagocytosis," "inflammation," "oxidative stress," and "remodeling [72]." With the increase in the macrophage activation phenotype, the role of macrophages in inflammatory myopathy needs to be further elucidated.

There's a lot of confusion here. First, how exactly macrophages play a role in IIMs, whether there is an imbalance between polarizations, or whether there are macrophage phenotypes that play different dominant roles in various myopathies require further investigation. Second, there is a lack of dynamic observations of macrophage phenotypes. There has been no research on the proportion of macrophage phenotypes and their changes at different stages of the disease in IIM patients or animal models. The specific molecular mechanism of macrophage phenotypic transformation, its relationship with the occurrence and development of diseases, and the changes in the expression of other immune cells and immune molecules associated with the phenotypic transformation of macrophages are still unknown. The role of macrophages with different phenotypes in IIMs needs to be further elucidated.

Clincal application of targeting macrophage strategies in IIM

Treatments designed for macrophages are not initially targeted or specific, and these off-target examples provide insights and lessons for developing more targeted approaches. At present, the targeted therapy of macrophages mostly focuses on reducing the production of macrophages and inflammatory factors and regulating the polarization of macrophages, which will be described

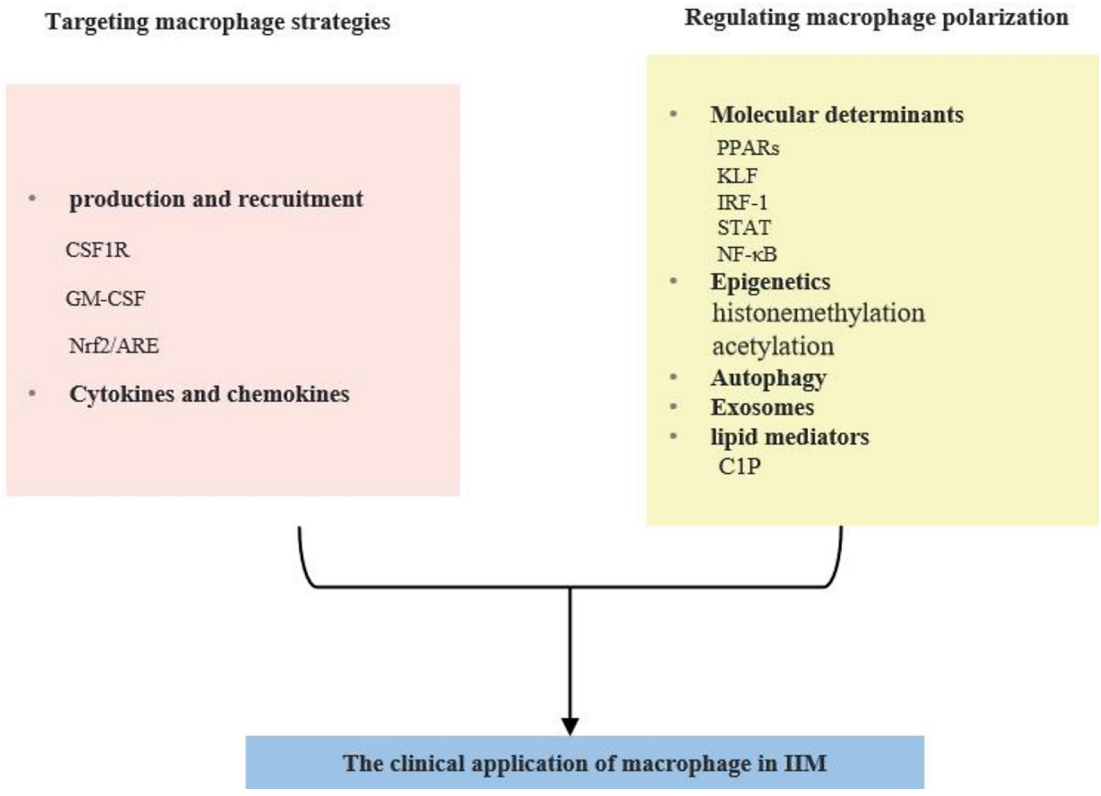

Fig. 2 Therapeutic effects on macrophages in IIMs. These attempts have focused mainly on macrophages or regulating macrophage polarization. Monoclonal antibodies or inhibitors can be used to block the inflammatory pathway and reduce the production of proinflammatory factors. By regulating the molecular level, genetic modifications, autophagy and exosomes, the proinflammatory macrophage septum is shortened, or more differentiation into an anti-inflammatory macrophage phenotype occurs. PPARs, peroxisome proliferator-activated receptors; KLF, Krppel-like factor; IRF-1, interferon regulatory factor 1; STAT, signal transducer and activator of transcription; C1P, ceramide 1-phosphate

in detail below and Fig. 2 demonstrates these treatment strategies.

Targeting macrophage production and recruitment

Pharmacologically targeted therapies for macrophages are currently understood, and most of these therapies target panmacrophage markers, such as colony-stimulating factor 1 receptor (CSF-1R) and GM-CSF [73, 74]. CSF-1 can recruit macrophages, which inhibit inflammation by promoting angiogenesis and the secretion of immunosuppressive cytokines. Therefore, the CSF-1 pathway is an attractive therapeutic target. CSF1R inhibitors or CSF1R monoclonal antibodies are under clinical study. For example, imatinib and pexidartinib (PLX-3397) are multitarget receptor tyrosine kinases of CSF-1R. Sotuletinib (BLZ-945) is a selective inhibitor of CSF-1R. Cabiralizumab (FPA-008) is a humanized monoclonal antibody that binds human CSF-1R with high affinity [75]. These inhibitors or antibodies can inhibit inflammation by binding to their corresponding receptors.

Other potential targets for macrophages are also under development. Liu Y et al. reported that ROS in macrophages were reduced when nuclear factor E2-related factor 2 (Nrf2) was overexpressed in a rat model of autoimmune myositis. In this study, macrophages with high expression of Nrf2 were isolated from autoimmune myositis mice. Nrf2 inhibits macrophage invasion, induces ROS degradation, and controls the expression of proinflammatory cytokines by activating the Nrf2/antioxidant response element pathway [76]. All of the above targets function by reducing the production or recruitment of inflammatory macrophages. Considering the heterogeneity between animal models and humans, more clinical studies are needed to verify these findings.

Targeting inflammatory factors

Blocking inflammatory factors secreted by macrophages also contributes to treatment. Previous studies have confirmed the role of IFN I in the pathogenesis of IIMs. By analyzing the IFN I signal in whole blood, it was found that the expression of Siglec 1 in macrophages was highly upregulated. After blocking STAT1 with small interfering RNA or drugs, the expression of this protein was significantly decreased. In the study of Manuel et al., the ability of macrophages to produce IFN I was significantly controlled after the overexpression of Siglec 1. The use of Siglec-1 may provide a new approach for treatment [77]. Experiments in conventional mouse models have shown that the production of TGF-β1 contributes to inflammatory healing and is associated with the inhibition of proinflammatory cytokines. The excessive production of TGF-β1 by M2 macrophages may be a factor in excessive fibrosis. Nilotinib is a kinase inhibitor with antifibrotic activity that can block the effect of TGF-β1, reduce muscle fibrosis and hinder the progression of chronic inflammation [78].

Studies have confirmed that β-chemokines and their receptors, such as cc-chemokine receptor-2 (CCR2), which are strongly expressed in both the PM and IBM, are highly expressed in IIMs [37, 79]. They regulate the migration and infiltration of macrophages and can inhibit inflammatory macrophage transport by using anti-CCL2 or CCR2 antibodies. In in vitro experiments, IL-6 deletion or STAT3 knockdown attenuated CCL2 and CCL3 expression in activated macrophages, thereby reducing inflammatory cell migration and muscle damage. Tocilizumab, the world's first humanized monoclonal antibody against the IL-6 receptor, has been approved for the treatment of patients with systemic juvenile idiopathic arthritis [80].

These studies suggest that the inhibition of proinflammatory cytokines secreted by macrophages may alleviate disease activity, but related therapeutic drugs and the specific therapeutic effect of blocking this site need to be developed. There is still a lack of reports on the exact therapeutic effect of existing drugs on IIM patients. More clinical intervention trials are needed to study the effect of blocking inflammatory factors, and the timing and course of medication are also crucial.

Targeting macrophage polarization

Inducing macrophage polarization is a promising strategy for macrophage-targeted therapy [81]. A study revealed that the polarized phenotype was reversible in vitro and in vivo [82, 83]. The molecular determinants that are currently known to induce phenotypic switching in macrophages include peroxisome proliferator-activated receptors (PPARs), Krppel-like factor, IRF-1, STAT, and NF-κB. PPARs are a family of ligand-activated transcription factors. PPARs are among the most popular molecules under investigation. These compounds play essential roles in lipid metabolism and inflammation regulation because of their anti-inflammatory functions. PPAR-γ is highly expressed in macrophages, and its expression is increased in IL-4-treated macrophages, thereby reducing inflammatory cell migration, driving an alternating activated phenotype and increasing oxidative metabolism [84, 85]. The regulation of polarization also involves epigenetic modifications, such as histone methylation and acetylation. However, targeted therapy for macrophage polarization is in its infancy. Some clinically approved treatment strategies, including PPAR-γ inhibitors, statins and zoledronic acid, may affect the functional status of macrophages. However, the extent to which their effects on macrophages explain their clinical efficacy remains to be defined.

Recent studies have suggested that autophagy may be a potential therapeutic approach for IIM. Autophagy

refers to a series of strictly regulated catabolic processes in which cytoplasmic components are transported to lysosomes for degradation. Recent studies have shown that autophagy can change the intracellular metabolic state and regulate macrophage polarization. At present, more than 40 proteins encoded by autophagy-related genes (ATGs) have been identified to be involved in the regulation of autophagy at different stages [86]. Genes associated with macrophage polarization are also under investigation. Chen et al. demonstrated that the differentiation and phagocytic function of macrophages depend on autophagy mediated by unc-51, such as autophagy activating kinase 1 and ATG7, and specific ATG7 knockout mice exhibit a change in the ratio of proinflammatory M1-type macrophages [87, 88]. Autophagy may be directly or indirectly involved in regulating macrophage polarization through the NF-κB pathway, adenosine monophosphate-activated protein kinase/mammalian target of rapamycin (AMPK/mTOR) pathway, NOD-like receptor family pyrin domain containing 3 inflammasome and miRNAs [89–92]. Recent studies have focused on modulating macrophage polarization through autophagy to participate in inflammatory responses [87, 89]. Whether autophagy genes may be participated in the regulation of macrophage polarization signaling pathways or whether autophagy may lead to the degradation of essential proteins involved in macrophage polarization will provide a new research direction for the treatment of diseases.

In vitro, exosomes appear to play a role in macrophage phenotypic switching. Mesenchymal cell-derived exosomes (MSC-Exos) can regulate adjacent and different cells by transferring DNA, mRNA, noncoding RNA, proteins and lipids from parent cells to recipient cells. Accumulating evidence suggests that MSC-Exo-mediated macrophage polarization can promote tissue injury healing. In vitro, MSC-Exos inhibit CD68+/HLA-DR+M1 cells and promote CD206+/CD163+M2 cells [93, 94]. A miRNA study of endothelium-derived exosomes revealed that miR-10a can inhibit the activation of proinflammatory macrophages by targeting the NF-kB pathway. MiR-182 can mediate the transformation of macrophages to a suppressive inflammatory phenotype [95]. In addition, exosomes from adipose-derived stem cells can induce macrophages to suppress inflammation polarization by carrying active STAT3 or activating arginase 1 [96]. In summary, exosomes have great potential as a cell-free therapy for IIMs.

Alternatively, lipid mediators play a key role in regulating the onset and resolution of inflammation. They are rapidly produced by immune cells and have direct receptor-mediated effects on immune cells, including macrophages [97]. Giannakis et al. characterized the mediator lipidome in two mouse muscle injury models (CTX and eccentric exercise-induced injury) during the transition of skeletal muscle injury from inflammation to resolution and regeneration. The production of proinflammatory lipid mediators (e.g., leukotrienes and prostaglandins) and specialized proresolving lipid mediators (e.g., resolvins and lipotoxins) was also observed. The dynamic changes in $Ly6C^{high-}$ and $Ly6C^{low-}$infiltrating macrophages in muscle at different time points after injury revealed a unique signature of $Ly6C^{lo}$ macrophage expression. The integration of transcriptomics and lipidomics results suggested that Ly6C+macrophages are both sources and sensors of lipid mediators, which may contribute to macrophage population phenotype transition [98]. Naturally, phosphorylated sphingolipids are among the many lipid metabolites released under inflammatory conditions, and ceramide 1-phosphate (C1P) is a biologically active sphingolipid metabolite. C1P is considered a DAMP whose expression rapidly increases in injured tissues [99]. The phosphorylated sphingolipids C16-C1P and C8-C1P (a natural long-chain ceramide and shorter synthetic analog, respectively) are known to possess chemoattractant, antiapoptotic, and mitogenic activities [100]. In experiments by Ortiz Wilczynski et al., C8-C1P was found to reduce proinflammatory markers (CD44, CD80, and HLA-DR, as well as IL-6 secretion) in CD14+monocytes isolated from humans challenged with LPS. Even in the presence of inflammatory pathogen-associated molecular patterns and DAMPs, C8-C1P-triggered monocyte differentiation toward prolytic macrophages is biased by increasing anti-inflammatory and proangiogenic gene expression patterns. These results suggest that C8-C1P can inhibit M1-skewing-promoting tissue repair and proangiogenic macrophage programs [101]. Hanksins et al. reported that C8-C1P selectively blocks the TLR4-NF-kB axis and decreases mitogen-activated protein kinase activation and cytokine expression, which is consistent with the findings of the abovementioned study showing the downregulation of CD44, CD80, HLA-DR, and IL-6 expression in monocytes after LPS stimulation [102]. The C1P analogs PCERA-1 and ONO-SM-362 inhibited TNF-α production and induced the release of the anti-inflammatory cytokine IL-10 in macrophages [103, 104]. All of the above findings suggest that lipid metabolites may be key players in regulating the inflammatory/anti-inflammatory and lytic macrophage balance. Future studies should aim to characterize the emerging and diverse signaling roles of lipid mediators in controlling these different stages of the inflammation-involution-repair response, elucidate the specific lipid mediator characteristics of innate immune cell subsets, and provide new ideas for possible therapeutic modalities.

Prospects and challenges

Macrophages are critical immune cells involved in the initiation and regression of inflammation. The role of macrophages has received increasing attention. Current studies on the mechanism of macrophages in IIMs have focused mainly on the fact that macrophages are essential cells of innate immunity and play a proinflammatory role. With the discovery of different polarization phenotypes of macrophages, studies have begun to investigate whether changes in polarization types are involved in pathogenesis. Both prolonged proinflammatory phenotypes and induced polarization can contribute to the development of inflammation. The specific function of macrophages in IIMs needs to be further studied, and these cells may play different roles in different types of myopathies. Numerous high-throughput sequencing methods using mainly single-cell sequencing can be used to further characterize the molecular subtypes of macrophages in IIMs. Only a clearer understanding of macrophage heterogeneity is available, and targeted treatment plans can be designed for different IIMs.

Macrophage-targeted therapy is still in its infancy. Targeted therapy mainly focuses on inhibiting macrophage production, inducing polarization, directly targeting macrophage receptors or indirectly targeting cytokines secreted by macrophages. In the past few years, most strategies to address the pathogenic effects of CSF-1/CSF-1R and IL-34/CSF-1R have focused on CSF-1R. However, because CSF-1R is involved in various biological processes, specific therapies targeting CSF-1R have adverse effects [105]. This has drawn attention from the scientific community to other players in this complex, particularly its ligands CSF-1 and IL-34 [106]. Usually, there are several neutralizing biological agents for cytokine targeting therapy (e.g. infliximab, etanercept, adalimumab, and tocilizumab) [107]. The ability of macrophages to reduce cytokine production has also been studied but has not yet reached the stage of clinical development. Both blockade of macrophage infiltration (e.g., inhibition of the CCL2/CCR2 chemokine axis), repolarization of macrophages (e.g., blockade of CD47 or stimulation of CD40 or TLRs), and depletion of macrophages have been investigated [108].

Inspiration may be obtained from other researches for the treatment of myositis. For example, regulating the state of macrophages through metabolic pathways is a possible therapeutic target. Transcriptomic studies in mice have shown that changes in the inflammatory state of macrophages are closely related to transcription and metabolic reprogramming. Specifically, the proinflammatory state is characterized by high glycolytic activity, which differs from the anti-inflammatory state associated with phosphorylated oxidation [109]. However, it remains to be determined whether this change in metabolism is a consequence or one of the drivers of inflammatory changes. In Gaetan Juban's study, specific inactivation of the gene encoding the AMPK-α1 subunit (the only catalytic subunit expressed in macrophages [110]) in macrophages prevented inflammatory state changes in vitro and in vivo, leading to defects in muscle regeneration in mice [111, 112]. In addition, exosomes derived from macrophages with an anti-inflammatory phenotype are also noteworthy. Proinflammatory macrophage-derived nanovesicles can target tumor tissue and repolarize M2 into M1 macrophages, thereby secreting proinflammatory factors and stimulating antitumor immunity [113]. This method was inspired by previous methods. Exosomes isolated from macrophages with an anti-inflammatory phenotype can be used as drug carriers for the treatment of inflammatory diseases [114, 115]. Li et al. developed M2 exosomes derived from M2 macrophages as carriers to codeliver IL-10 plasmid DNA and chemotherapeutic drugs for the treatment of rheumatoid arthritis [114]. Considering the common pathogenic role of inflammatory macrophages in diseases, anti-inflammatory macrophage phenotype-derived exosomes may promote the conversion of more macrophages to the anti-inflammatory macrophage phenotype to inhibit disease progression in patients with IIMs.

To improve the target accuracy, a unique drug delivery system has been developed. Antibody–drug conjugates (ADCs) are novel drug delivery systems that can take advantage of the specificity of antibodies to deliver small molecules directly to the target. The use of ADC technology to transport immunomodulatory molecules in macrophages in inflammatory diseases is also developing. Maria et al. demonstrated the efficiency of coupling drugs by targeting drugs to CD163+macrophages in animal models [116]. However, macrophage-targeted therapy also faces some difficulties. First, the M1/M2 classification is insufficient to explain macrophage plasticity in many studies. Macrophages can adopt an intermediate phenotype with mixed characteristics of M1 and M2 phenotypes, and the phenotype can change depending on the microenvironment. There is a lack of consensus on how to define macrophage activation. Except for the short description of the differentiation of macrophages in vivo, interspecific differences and the lack of conservative surface markers between species hinder the translatability of animal research to humans [117]. For example, only mouse macrophages express high levels of F4/80, while the human homolog mucin-like hormone receptor 1 is mainly expressed by eosinophils [118]. Through transcriptome analysis of mouse m1 and m2 macrophages, Jablonski et al. reported that CD38, G-protein coupled receptor 18 and Formyl peptide receptor 2 are M1-type-specific genes, while c-Myc and early growth response protein 2 are M2-type-specific genes, which may provide

a new strategy for better inhibition of macrophages [119]. However, there are few reports on targeted macrophage therapy for IIMs. In the future, it will be necessary to further research the key mechanism of macrophages in IIMs, build a better animal model, and explore the therapeutic effect of targeting macrophages in this disease.

In conclusion, the intricate involvement of macrophages in the pathogenesis of IIMs presents a multifaceted landscape that significantly influences disease progression and clinical manifestations. Our review sheds light on the pivotal role of macrophages in perpetuating inflammation, tissue damage, and immune dysregulation in IIMs. Macrophage polarization states underscore their dynamic contribution to disease severity and resolution. Targeting macrophages has emerged as a promising therapeutic approach, with potential interventions ranging from receptor-based therapies to macrophage polarization modulation. However, the diversity of terminology and inconsistency in the use of markers to describe macrophage activation hinder research in several ways, and the challenges posed by macrophage plasticity and interspecies differences necessitate further investigation. These insights provide a foundation for advancing IIM management strategies by directing therapies toward macrophage-mediated processes, offering renewed hope for improved patient outcomes. Continued research into deciphering the intricate interactions between macrophages and the immune microenvironment holds promise for transforming the landscape of IIM treatment.

Abbreviations

IIMs	Idiopathic inflammatory myopathies
DM	Dermatomyositis
PM	Polymyositis
IBM	Inclusion body myositis
IMNM	Immune-mediated necrotizing myopathy
MSAs	Myositis-specific autoantibodies
MHC	Major histocompatibility complex class I
MRI	Magnetic resonance imaging
CADM	Clinically amyopathic dermatomyositis
IFNs	Type I interferons
TLRs	Toll-like receptors
TNF-α	Tumor necrosis factor-α
ILD	Interstitial lung disease
IL-1	Interleukin-1
GM-CSF	Granulocyte-macrophage colony-stimulating factor
CCL3	C-c motif ligand 3
ROS	Reactive oxygen species
TGF-β	Transforming growth factor-beta
HMGCR	Anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase
LPS	Lipopolysaccharide
DAMPs	Danger-associated molecular patterns
JAK-STAT	Janus tyrosine kinase-signal transducer and activator of transcription
NF-κB	Nuclear factor kappa B
Treg cells	Regulatory T cells
CSF1R	Colony-stimulating factor 1 receptor
Nrf2	Nuclear factor E2-related factor 2
CCR2	Cc-chemokine receptor-2
PPARs	Peroxisome proliferator-activated receptors
ATGs	Autophagy-related genes
AMPK/mTOR	Adenosine monophosphate-activated protein kinase/mammalian target of rapamycin
MSC-Exos	Mesenchymal cell-derived exosomes
C1P	Ceramide 1-phosphate
ADCs	Antibody–drug conjugates

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Ziqi Li wrote and reviewed the paper. Geng Yin, Qibing Xie and Huan Liu supervised the study and edited the paper. All the authors have read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

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The authors declare no competing interests.

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