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REVIEW

M2 macrophages and their role in rheumatic diseases

Shruti Bhattacharya[1] · **Amita Aggarwal**[1]

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Abstract
As a component of the innate immune system, macrophages play a crucial role in host defense against a variety of microbes. Conventionally, macrophages have been classified as M1 and M2 depending on their phenotype and role in immune regulation. M1 macrophages are generally pro-inflammatory, while M2 (also known as alternatively activated macrophages) are anti-inflammatory. M1 macrophages release pro-inflammatory cytokines, reactive nitrogen, and oxygen intermediates, and kill pathogens, whereas their M2 counterparts participate in the resolution of inflammation, remodeling of tissue, angiogenesis, and tissue repair. Macrophages are also crucial in the pathogenesis of immune-inflammatory disorders, such as, arthritis. In this review, we discuss the markers of human M2 macrophages, the role played by them in inflammation or progression of rheumatic diseases, their potential to act as biomarkers, and, finally, therapeutic strategies aiming at altering/enhancing the macrophage phenotype.

Keywords M2 macrophages · Rheumatic diseases · Spondyloarthropathy · Rheumatoid arthritis · Juvenile idiopathic arthritis · Systemic lupus erythematosus · Systemic sclerosis · Vasculitis

Introduction

Macrophages are important cells of the innate immune system that help in our fight against pathogens. The main functions of macrophages are phagocytosis, bacterial killing, production of cytokines, and presentation of antigen to naïve T cells for development of adaptive immune response. They were identified for the first time by Elie Metchnikoff in the year 1883 when he observed that the phagocytic mononuclear cells were proficient in killing bacteria and their killing capacity improved after infection [1]. This introduced the concept of 'macrophage activation' [2].

Macrophages are classified in different ways based on their location or their functional properties. Macrophages residing in tissues are called as tissue-resident macrophages. The tissue-resident macrophages have a long lifespan and are derived from the yolk sac. The tissue-resident macrophages have been given different names in different organs like microglial cell in brain, Kupffer cells in liver, and alveolar macrophages in lung [3]. Macrophages which are present in the tumor and promote tumor cell proliferation, metastasis, invasion, angiogenesis, etc., leading to tumor progression are referred to as tumor-associated macrophages. Macrophages were initially thought to only promote inflammation, but it was later discovered that they had the ability to both promote as well as resolve inflammation. This inflammation and resolution paradox was solved after the discovery of the two macrophage subsets, M1 and M2 [4].

The naïve (M0) macrophages can polarize under different conditions to become either M1 or M2 macrophages. The M1 or classical macrophages are pro-inflammatory as they have a role in killing microbes and causing inflammation. M1 macrophage subset is activated by microbial products such as lipopolysaccharide (LPS) or pro-inflammatory cytokines such as interferon-γ. They kill pathogens by releasing reactive oxygen and nitrogen species as well as pro-inflammatory cytokines [IL-6, IL-12, IL-23, IL-1β, and tumor necrosis factor (TNF)-α]. In addition, they skew the adaptive immune response towards the Th1 phenotype [5]. M1 macrophages have high expression of major histocompatibility class (MHC)-II as well as co-stimulatory molecules like CD80 and CD86 which help in efficient presentation of antigens to T cells [6].

On the other hand, the M2 macrophage subset, also known as alternatively activated macrophages, has major

✉ Amita Aggarwal
aa.amita@gmail.com

[1] Department of Clinical Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

roles in resolution of inflammation, angiogenesis, tissue remodeling, and repair. These macrophages are stimulated by cytokines like IL-4, IL-10, or IL-13, and, in turn, produce IL-10, arginase-1, macrophage colony stimulating factor (M-CSF), and transforming growth factor (TGF)-β. M2 macrophages possess high phagocytic capacity, express low levels of MHC-II compared to M1, but high expression of CD163, CD200R, macrophage galactose-type lectin (MGL)-1 and MGL-2, and kill extracellular parasites [5, 6].

M2 macrophage markers

Currently, M2 macrophages are identified on the basis of the transcription factors or specific proteins expressed by them such as, enzymes, transmembrane proteins, scavenger receptors, cytokines, or cytokine receptors. The markers used are CD200R, CD206, and CD163 on cell surface, and arginase-1, STAT-3, and IL-10 intracellularly. Among these, arginase-1, CD206 and CD163 are most commonly used, though different subsets of M2 macrophages have different markers (Table 1).

Arginase-1

Arginase-1 is considered as a classical M2 marker [7] and this helps the cell to produce ornithine from L-arginine upon activation [6]. Ornithine production promotes proliferation of cells, fibrosis, and tissue healing via the generation of collagen and polyamines [6, 8] (Fig. 1). Arginase-1 also has a role in downregulating the M1 macrophage response by depleting the substrate for the same, i.e., L-arginine [6].

CD206/mannose receptor (MR)

CD206 is a C-type lectin present on the surface of M2 macrophages [9]. $CD206^{+}$ macrophages are present in the placenta, skin, adipose tissue, heart, and peritoneum [10–13]. The CD206 expression on macrophages is associated with improved systemic insulin sensitivity via inhibition of adipocyte progenitor proliferation [14]. Mannose receptors helps in the degradation of the dermal collagen by M2 macrophages as a part of collagen degradation pathway [15]. Its expression increases in response to curcumin induced polarization of M0 and M1 macrophages toward M2 [16].

CD163

CD163 belongs to class B of scavenger receptor cysteine-rich superfamily and is expressed on the surface of most tissue-resident macrophages [17, 18]. It functions as a receptor for haptoglobin–hemoglobin complexes [19], and mediates cell-to-cell interactions between developing erythroblasts and macrophages in erythroblastic islands [20]. In case of bacterial infection, CD163 present on resident tissue macrophages acts as an immune sensor and induces local inflammation [21].

Dectin-1

Dectin-1 is a lectin immune receptor that recognizes and kills pathogenic fungi (*P. brasiliensis, C. albicans*, and *P. carinii*) via recognition of β-glucans on the fungal cell wall [22–25]. The function and expression of dectin-1 is enhanced in M2 macrophages [26].

Macrophage galactose C-type lectin (MGL)

Macrophage galactose-type lectin is a protein belonging to the C-type lectin receptor (CLR) family that recognizes the terminal α or β *N*-acetylgalactosamine residues present on tumor-associated antigens, viruses, bacteria, and helminths [27].

M2 macrophage subsets

M2 macrophages are further subdivided into four subtypes (M2a, M2b, M2c, and M2d) on the basis of cytokines that stimulate them as well as the roles played by them. The first subtype, M2a, is induced by IL-4 or IL-13, produces TGF-β and arginase and plays a role in tissue repair by production of extracellular matrix (ECM) components. The second subtype M2b, is induced by either immune complexes, IL-1R, or Toll-like receptor (TLR) ligation, produces IL-10, and reduces the production of IL-12, thus exerting anti-inflammatory properties. The third subtype, M2c, is induced via glucocorticoids, IL-10, TGF-β, and CCL-13, and shows anti-inflammatory effects via deactivation of M1 macrophages [5]. Finally, the fourth subtype, M2d, is induced by adenosine A_{2A} receptor agonists and TLR co-stimulation [28] (Table 1; Fig. 2).

M2 macrophages in rheumatic diseases

Innate immune system plays a major role, in both activation and regulation of immune response. Innate immune cells that mediate immune regulation include gamma–delta T cells, innate lymphoid cells (ILCs), and M2 macrophages. Among these, the role of M2 macrophages is currently being explored in the pathogenesis of various rheumatic diseases including spondyloarthropathy, macrophage activation syndrome (MAS), IgG4 mediated diseases, systemic sclerosis, and systemic lupus erythematosus (SLE).

Table 1 Characteristic of human macrophage subsets

	M1 macrophage	M2 macrophage	M2a macrophage	M2b macrophage	M2c macrophage	M2d macrophage
Phenotype	Classical	Alternative				
Activated by	LPS, IFN-γ, GM-CSF	Immune complexes, IL-4, IL-13, c-Myc, IRF-4	IL-4, IL-13	Immune complexes, TLR's	IL-10, glucocorticoids	A_{2A}, TLR
Cytokine production	TNF, IL-1β, IL-6 (pro-inflammatory)	IL-10, IL-1RII, IL-1RA (anti-inflammatory)	IL-10, Decoy IL-10RII, IL-1Ra	IL-10, TNF, IL-1, IL-6	IL-10, TGF-β	CD206, Fizz1, arginase-1 dectin-1
Chemokine production	CXCL-1, CXCL-10, CCL5	CCL17, CCL-18, CCL-22, CCL-24	CCL17, CCl22, CCL24	CXCL1, CXCL2, CXCL3, CCL1, CCL20	CCL18	Il-10, VEGF
Marker expression	CD80, CD86, CD68, IL-1R, TLR2, TLR4, iNOS, MHC-II	CD163, MHC-II, CD206/MMR, CD200R	CD163, MHC-II, CD206/MMR, CD200R, IL-1R2	CD86, MHC-II	CD163, TLR 8, TLR1	VEGF
Presentation of antigen	Yes	No	No	No	No	No
Nitric oxide production	Yes	No	No	No	No	No
Primary function	Pro-inflammatory Phagocytic Bactericidal	Anti-inflammatory Matrix remodeling Pro-angiogenesis Pro-wound healing	Inflammation Allergy Anti-parasitic	Immunoregulation	Immunoregulation Tissue remodeling	Proangiogenic activity

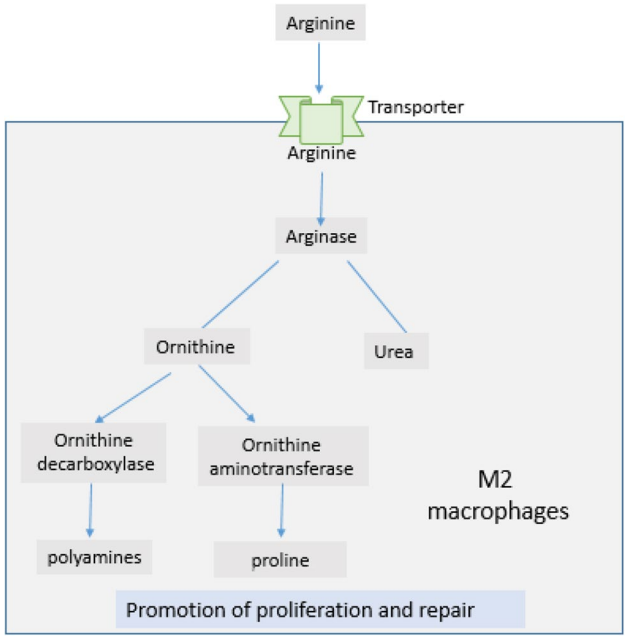

Fig. 1 Arginine metabolism by arginase in M2 macrophages

In this review, we have focused on the role of M2 macrophages in pathogenesis of rheumatic diseases and the therapeutic strategies which aim at altering the M1/M2 macrophage balance or enhancing the M2 macrophage phenotype.

Search strategy

PUBMED database was searched for review as well as original articles from start to April 2018. The search strategy used was M2 macrophages AND rheumatic diseases OR rheumatoid arthritis OR systemic lupus erythematosus OR systemic sclerosis OR vasculitis OR spondyloarthropathy OR Sjogren syndrome OR juvenile arthritis OR rheumatic disease treatment. Non-English articles were excluded. Among English articles, abstracts were first screened for relevance and only those having relevant information were included. Article in references of these articles which met our search criteria were also included.

Spondyloarthropathy (SpA)

Spondyloarthropathy (SpA) are a group of diseases that are characterized by inflammatory back pain, sacroiliitis, arthritis, and enthesitis. It encompasses different forms of arthritis like reactive arthritis, ankylosing spondylitis (AS), psoriatic arthritis, inflammatory bowel disease (IBD) associated arthritis, juvenile spondyloarthropathy, and undifferentiated spondyloarthropathy. It is considered an auto-inflammatory disease due to lack of autoreactive T and B cells.

Higher frequency of M2a macrophages ($CX3CR1^+$ $CD163^+$ cells) has been observed in peripheral blood [29] as well as ileal biopsies of AS patients with chronic gut

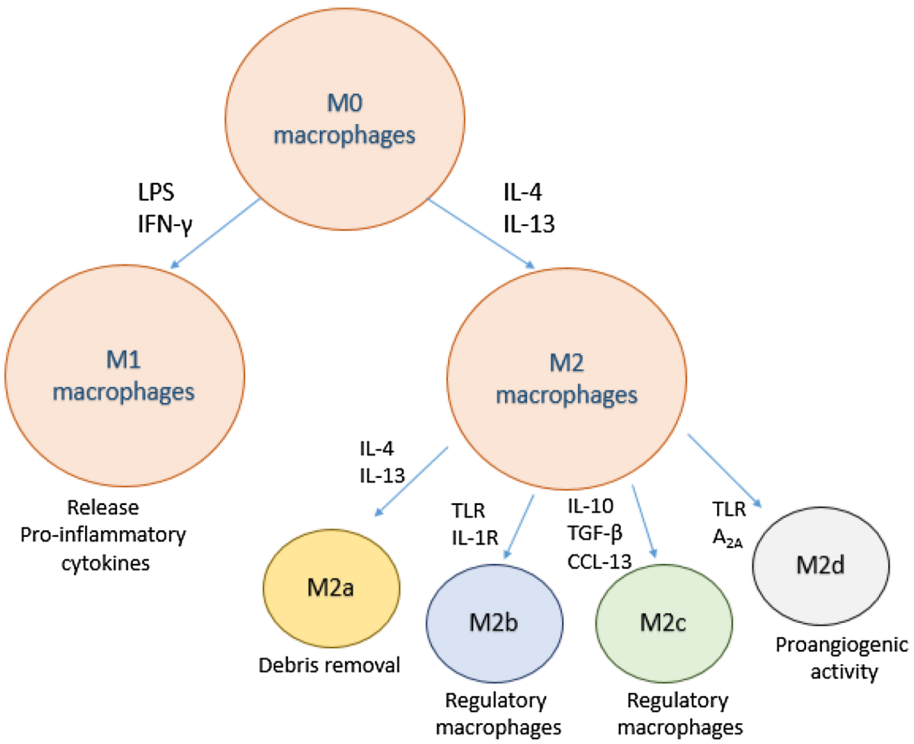

Fig. 2 Macrophage classification and polarization. M0 macrophages undergo polarization depending on the stimulus that they receive. On stimulation with microbial products like LPS or IFN-γ, they polarize towards M1 macrophages. M1 macrophages produce pro-inflammatory cytokine release. M0 macrophages on stimulation by IL-4 and IL-13 mature into M2 macrophages. M2 macrophages can further undergo differentiation into M2a (induced by IL-4 and IL-13 which have a role in removal of debris), M2b (induced by TLR and IL-1R and have a role in regulation of the immune response), M2c (induced by IL-10, TGF-β, and CCL-13, and have a role in immune response regulation) and M2d (induced by TLR agonists or A_{2A} receptor activation and have a role in angiogenesis)

inflammation. Frequency of M2 macrophages in blood also correlated with inflammatory parameters in AS patients [30]. SpA patients with chronic synovitis have higher numbers of M2c macrophages (IL-10 polarized with CD163 expression) in the intimal lining layer of the synovium [31]. The M2a macrophages ($CD200R^{+}CD163^{+}$) derived from AS patient's synovium when co-cultured with healthy macrophages change the phenotype of healthy macrophages. These co-cultured healthy macrophages have enhanced expression of CD163 in response to IL-10 [32].

Increased frequency of M2a ($CD163^{+}$ $CD209^{+}$ $CD206^{+}$) macrophages have been observed in the skin of patients with psoriatic arthritis [33]. IL-33 enhances M2 polarization and patients with IBD have reduced serum IL-33 levels, indicating a dysregulation in M1–M2 macrophage balance [34]. In animal models of colitis, administration of M2 macrophages ameliorates the disease [35]. In 2,4,6 trinitrobenzene sulfonic acid-induced IBD murine model, there is increase in M2 macrophage population ($CD86^{+}CD163^{+}$) which prevents colitis. On the other hand, $STAT6^{-/-}$ mice have increased number of $CD16^{+}$ macrophages which correlate with fibrosis, suggesting that M2 macrophages prevent fibrosis [36].

Juvenile idiopathic arthritis (JIA)

One of the major complications seen in systemic onset juvenile idiopathic arthritis (SoJIA) is occurrence of macrophage activation syndrome (MAS). MAS is considered as a secondary or acquired hemophagocytic lymphohistiocytic (HLH) disorder characterized by defective NK and CD8 T-cell cytolytic function, hyper-activation of T lymphocytes, and macrophages that show hemophagocytosis [37]. Elevated levels of soluble CD163 (sCD163) are seen in primary and secondary forms of HLH [38]. sCD163 levels reflect the level of expansion and activation of phagocytic macrophages [39]. sCD163 level in serum is also elevated in patients with active SoJIA, some of whom later develop MAS. Thus, they may act as markers of subclinical MAS [40, 41]. However, in another study, it did not perform as well as soluble CD25 in predicting subclinical MAS [42].

M2 macrophages expressing CD163 also contribute to iron metabolism in bone marrow. Thus, they may play a role in anemia of chronic disease observed in SoJIA and other rheumatic diseases, chronic infection, and malignancy. CD163 mediates the internalization of hemoglobin–haptoglobin complex, and later the complex undergoes lysosomal degradation with release of hemoglobin and recycling of CD163 back to surface. The released iron either binds to ferritin or is exported out and binds to ferroportin for transfer to developing red blood cells. IFN-γ, a cytokine, that is produced in large amount in MAS inhibits ferroportin thus reducing availability of iron [43].

Studies from our laboratory have shown that CD163 mRNA expression is 6.5-fold higher in the synovial fluid mononuclear cells (SFMC) as compared to peripheral blood mononuclear cells (PBMC) from children suffering from enthesitis-related arthritis (ERA) category of JIA [44]. Furthermore, a higher level of soluble CD163 was observed in serum from patients with ERA as compared to healthy volunteers. Synovial fluid also had levels higher than serum validating the mRNA data [44]. This suggests that M2 macrophages may have a role in pathogenesis of ERA.

Rheumatoid arthritis (RA)

Rheumatoid arthritis is an auto-immune inflammatory disorder characterized by synovial inflammation, degradation of cartilage, and bone erosion by osteoclasts leading to joint damage. RA patients display an increased M1/M2 ratio which promotes osteoclastogenesis [45]. A study done by Mottonen and colleagues found 68% of macrophages like synoviocytes (MLS) from synovial fluid (SF) of RA patients to be of M1 phenotype [46]. As compared to osteoarthritis (OA), the RA SF has higher M1/M2 macrophage ratio [47].

Anti-citrullinated protein antibodies (ACPAs) are highly specific for RA and are used for the diagnosis and prognosis of disease. ACPAs from SF of RA patients induce IRF5 activity and lead to increase in M1 polarization of cultured peripheral blood monocytes, This results in increased M1/M2 ratio and skewing of macrophages to pro-inflammatory phenotype [47]. Vogelpoel et al. have, however, shown that M2 macrophages on simultaneous exposure to Toll-like receptor (TLR) ligands and immune complexes (ICs) produce pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β) and promote Th17 responses in RA [48]. This suggests that, in the presence of TLR ligands, ICs can modify the M2 macrophage phenotype to pro-inflammatory phenotype.

In TNF transgenic mouse which is an animal model of RA, it was shown that M1 macrophages in the synovium have active Notch signaling. Notch activation promotes polarization of M0 macrophages towards the M1 phenotype. However, in the absence of Notch or in the presence of Notch inhibitor, macrophages develop into M2 phenotype [49].

The mitochondrial membrane protein known as translocator protein (TSPO) is highly expressed on M0 macrophages, activated M2 macrophages, and fibroblast like synoviocytes in the synovium of RA. This can help in assessing synovitis by positron emission tomography (PET) using TSPO radioligand 11C-PBR28 [50].

Osteoarthritis (OA)

Osteoarthritis is characterized by articular cartilage loss, bony overgrowth (osteophyte formation), joint effusion, and weakness of muscles and tendons. M2 macrophages are observed to be elevated in the synovium as well as knee joint capsule of OA patients and show positive association with osteophyte progression [51]. TGF-β produced by synovial M2 macrophages promotes the formation of osteophytes [52]. However, other studies have shown infiltration of $CD68^+$ macrophages (M1) in OA synovial tissue [53]. M1 macrophages damage the cartilage by production of IL-1β, MM13, IL-6, and a disintegrin, and metalloproteinase with thrombospondin motifs-5 (ADAMTS5) in OA. Administration of M2 macrophages did not inhibit the effects of M1 macrophage on OA cartilage [54]. M1 macrophages are the mediators of anti-chondrogenic effect observed in mesenchymal stem cells of OA synovium [55]. Thus, it seems that M2 macrophages promote new bone formation but may not inhibit cartilage damage.

Gout

Gout is another auto-inflammatory disease characterized by repeated attacks of joint inflammation. Synovial fluid of gout patients show presence of both M1 and M2 macrophages [56]. The resident M1 macrophages produce TNF-α, IL-6, and IL-1β which drives the early pro-inflammatory phase of acute gout [57]. Both M1 and M2 macrophages do not produce IL-1β after urate crystal phagocytosis, but, if stimulated in addition with LPS, M2 macrophages produce IL-1β. M2 macrophages had lower caspase level as compared to M1 macrophages [58].

Vasculitis

Vasculitis, inflammation of the blood vessel wall presents with multisystem involvement associated with systemic symptoms. Crescentic glomerulonephritis (CGN) seen in vasculitis is characterized by renal macrophage infiltration. M2 macrophages which are seen in proliferative glomerular lesions, cellular-fibrous crescents, and tubulointerstitial area show negative correlation with estimated glomerular filtration rate [59]. Patients with IgA nephropathy also show increased number of CD163 macrophages in acute tubulointerstitial lesions and glomerular lesions. The number of CD163 macrophages correlated positively with the percentage of crescents, proteinuria, and negatively with estimated glomerular filtration rate and serum albumin [60]. $CD163^+$ macrophages also localize to the sites of glomerular fibrinoid necrosis and normal appearing glomeruli in case of early pauci-immune necrotizing glomerulonephritis [61]. All these suggest that M2 macrophages promote glomerular damage in vasculitis.

Systemic lupus erythematosus (SLE)

Systemic lupus erythematosus is a systemic auto-immune disorder characterized by the presence of multiple autoantibodies including anti-nuclear antibodies. Defect in disposal of apoptotic cells by macrophages leading to increased load of nuclear self-antigens is one of the important factors in pathogenesis. In pristane-induced lupus, there is impaired phagocytosis of apoptotic cells, which can be seen both in vitro and in vivo. In contrast, mice given non-lupus inducing inflammatory hydrocarbon oil do not show this abnormality. This was related to the inability of pristane to allow conversion of M1 macrophages towards the $CD138^+$ anti-inflammatory M2 phenotype [62]. In activated leukocyte-derived (ALD)-DNA induced SLE mouse models of lupus nephritis (LN), intra-renal macrophages show polarization towards the M2b phenotype as evidenced by enhanced production of IL-10 and suppression of the pro-inflammatory cytokines, viz., TNF-α, monocyte chemoattractant protein (MCP)-1, and IL-6 [63].

SLE patients have elevated levels of sCD163 in serum as compared to healthy individuals [64]. Patients with LN also show high levels of soluble MER and CD163 in serum which correlate with SLE disease activity score [65]. The mRNA and frequency of M2 macrophages are significantly increased in the skin of lupus patients.

Renal biopsies of LN patients have high numbers of ($CD163^+CD68^+$) M2c macrophages compared to $CD206^+CD68^+$ (M2b) macrophages which also correlate with disease progression. Alternatively, the elevated glomerular $CD163^+$ macrophage numbers correlate with the severity of nephritis as determined by the active biopsy index [66]. The sCD163 levels in the urine also correlate strongly with the glomerular $CD163^+$ cell counts, urinary monocyte chemoattractant protein-1 level, and histological disease score [67]. Studies from our lab have also shown that sCD163 can be used as a urinary biomarker for assessment of LN disease activity [68].

Systemic sclerosis (SSc)

Systemic sclerosis is an auto-immune disease characterized by fibrosis and vasculopathy in multiple organs. SSc patients have higher numbers of M2 macrophages in their PBMCs, probably induced by type I interferons and TLR

agonists [69]. A 2010 study showed an increase in the M2a subtype of M2 macrophages ($CD163^+$ $CD204^+$) in the skin biopsies of SSc patients [70]. M2 macrophages promote fibrosis by the release of pro-fibrotic mediators like TGF-beta [71]. Increased levels of serum sCD163 correlate with progression of the disease [72]. $CD14^+$ monocytes from patients suffering from SSc-interstitial lung disease (ILD) express elevated levels of CD163 compared with controls [73]. CD206, a marker of M2 macrophages, is increased in SSc-associated pulmonary arterial hypertension patients and correlates with degree of pulmonary arterial hypertension [74]. Treatment with rolipram (PDE4 inhibitor) has shown reduction in dermal fibrosis in a dose-dependent manner in bleomycin-induced skin fibrosis model in mice. This was mediated by inhibition of monocyte differentiation towards M2 phenotype and IL-6 secretion [75]. Thus, M2 macrophages in SSc promote fibrosis in skin and lung.

IgG4 related disease (IgG-RD)

IgG4 related disease is generally characterized by increased levels of serum IgG4- and IgG4-positive plasma cell infiltration in multiple organs. IgG4-related dacryoadenitis and sialadenitis is characterized by bilateral swelling of the glandular tissues associated with extensive fibrosis. $CD68^+$/$CD163^+$ M2 macrophages have been observed to be distributed around the ectopic germinal centers in salivary gland of patients with IgG4-related disease [76]. M2 macrophages induce fibrosis and antibody synthesis via production of IL-10, IL-13, and CCL-18 [77]. CCL-18 induces collagen production by fibroblasts, thereby mediating fibrosis [78]. CCL-18 has been found to be elevated in serum of patients with IgG4-RD and it correlates with disease activity [79]. In contrast, in primary Sjogren syndrome, another disease that presents with sialadenitis M2 macrophages is significantly reduced in the labial salivary gland and inversely correlates with the disease activity [80].

Deficiency of adenosine deaminase 2 (DADA2)

Deficiency of adenosine deaminase 2 is an auto-inflammatory disease which present with the early onset vasculitis along with livedoid skin rashes. Adenosine deaminase 2 (ADA2) is produced by myeloid lineage cells. It acts as a growth factor inducing the proliferation of monocytes and differentiation into M2 phenotype. In the absence of ADA2, increased frequency of M1 macrophages is observed [81]. Monocytes of ADA2-deficient patients showed a normal differentiation into M1 phenotype, but their M2 phenotype differentiation is impaired [82]. This can lead to sustained inflammation of the vessel wall.

Treatment strategies for diseases involving M2 macrophages

Different strategies are being explored to increase M2 macrophages to control continued immune-inflammation in rheumatic diseases, though most are still being tested in cell culture or animal models. Mannose ligand-grafted polyethylenimine nanoparticles mediated delivery of CD163 plasmid to primary human monocytes and THP-1 cells led to conversion of monocytes to M2 phenotype. This was confirmed by an increase in IL-10, IL-1 receptor antagonist (IL-1ra), and reduced MCP-1 production in response to LPS stimulation [83]. Dendrimers (highly branched polymers with potential of drug delivery) are being explored for targeting monocytes in arthritic mouse models. Intravenous injection of azabisphosphonate (ABP)-capped dendrimer inhibited the development of arthritis in IL-$1ra^{-/-}$ mice as well as K/BxN serum transfer-mediated arthritis. The disease amelioration was identified by reduction in inflammatory cytokines, absence of bone erosion and cartilage destruction, and normal synovial membrane histology [84].

In the presence of an antigenic stimulus, macrophages undergo metabolic reprogramming which is responsible for their pro-inflammatory phenotype. This reprogramming causes macrophages to shift from oxidative phosphorylation to glycolysis for ATP production while increasing succinate levels. Increased mitochondrial oxidation of succinate by succinate dehydrogenase together with elevated mitochondrial membrane potential drives ROS production. Use of dimethyl malonate promotes an anti-inflammatory response. Use of rotenone to block ROS production also inhibits the inflammatory phenotype [85].

Anti-TNF therapy reduces the M1 phenotype and inflammatory parameters in AS patients [29]. Zhang and colleagues have achieved the conversion of M1 to M2 macrophages via IL-35 produced by regulatory T cells in a murine psoriasis model [86]. A shift from M1 to the M2 phenotype can reduce colitis by IL-10 production, thus providing a unique approach towards IBD treatment [36] (Table 2).

Human umbilical cord blood stem cells are being explored as a promising therapeutic option for the treatment of RA as they mediate polarization of naïve macrophage towards the M2 phenotype in collagen-induced arthritis [87]. Non-viral gene transfection strategy has shown the ability to repolarize M1 macrophages towards M2. IL-10 encoding plasmid DNA was encapsulated in non-condensing alginate-based nanoparticles. The surface of these nanoparticles was modified with tuftsin peptide for specific targeting of macrophages. Enhanced localization of these nanoparticles occurred in

Table 2 Therapeutic strategies involving M2 macrophages [29, 60–66]

S. no.	Author	Strategy	Observation	Model/cells/tissue used
M1–M2 polarization				
1	Alvarado Vasquez (2017) [83]	Nanoparticle targeted CD163 delivery	Monocytes → M2 macrophages	Macrophages
2	Shin (2017) [87]	Stem cells (human umbilical cord blood)	Naïve macrophages → M2 macrophages	Collagen-induced arthritis
3	Jain (2015) [88]	Alginate-based nanoparticles	M1 → M2 polarization	Arthritic rat model (male Lewis rats)
4	Sun (2017) [49]	Thapsigargin	M1 → M2 polarization	RA mouse model (Hes1-GFP/TNF-Tg mice)
5	Li (2014) [89]	2-Deoxy-D-galactose	M1 → M2 polarization	Collagen-induced arthritis
6	Sultana (2017) [90]	Withaferin A (steroidal lactone with mannosylated liposome incorporation)	Synovial macrophages → M2 macrophages	Human synovial macrophages
7	Tong (2018) [91]	Silibinin	M1 → M2 polarization	RAW 264.7 cell line
8	Utomo (2016) [54]	Dexamethasone	M1 → M2 polarization	Human osteoarthritis cartilage explants
9	Siebelt (2015) [92]	Triamcinolone acetonide	M2 polarization	Osteoarthritis rat model (papain induced)
10	York (2007) [93]	(TNF-α-induced protein 8) TIPE overexpression	M2 polarization	Resolution (ALD-DNA SLE mouse model)
11	Zhang (2016) [86]	IL-35 (Treg cells)	M1 → M2 polarization	Psoriasis (murine psoriasis model)
Enhancement of M2 phenotype/ M2 supplementation				
1	Park (2017) [94]	SIRT-1	Acetyl CoA/AMPK phosphorylation Enhances M2 phenotype	Arthritis
2	Li (2015) [95]	M2 macrophage transplantation		Reduce disease severity (ALD-DNA induce SLE mouse model)
Decrease in M1 phenotype				
1	Zhao (2017) [29]	Anti-TNF therapy	M1 phenotype reduction	Ankylosing spondylitis
2	Hayder (2011) [84]	Dendrimers	Inhibition of pro-inflammatory cytokine production	IL-1ra$^{-/-}$ mice K/Bxn serum transfer mice model
3	Mills (2018) [85]	Rotenone	Block ROS production by M1 macrophages	Bone marrow derived macrophages (wild type C57Bl/6 mice)
4	Mills EL (2018) [85]	Dimethyl malonate	Promotion of anti-inflammatory response	Bone marrow derived macrophages (wild type C57Bl/6 mice)
5	Dhanasekar (2015) [93]	Morin (flavanol)	Reduction of intracellular reactive oxygen species	Acute gouty arthritis in vitro model

the inflamed paws of arthritic rats. Approximately 66% of arthritis rat synovial macrophages were found in M2 state compared to 9% in untreated rats. This strategy may be beneficial for the treatment of chronic inflammatory diseases like RA [88].

Targeting Notch signaling to promote M2 macrophages can be a new therapeutic approach in inflammatory arthritic disorders. In Hes1-GFP/TNF-Tg mice (RA mouse model carrying the *Hes1*-GFP transgenic Notch reporter), the administration of Thapsigargin (Notch inhibitor) caused reduction in M1 phenotype and promoted M2 phenotype [49]. Fucosylation is a posttranslational modification catalysed by the enzyme fucosyltransferases (FUTs). This modification is required for the commitment as well as maintenance of M1 macrophages. Inhibition of fucosylation by the use of 2-deoxy-D-galactose skewes the M1 macrophages to M2 phenotype in collagen-induced arthritis model [89]. Another drug, Withaferin-A (a steroidal lactone with mannosylated liposome incorporation) has shown the ability to get internalized in isolated synovial macrophages and convert them to M2 phenotype. Following this, the converted macrophages increase osteoprotegerin production and reduce RANKL release, thus inhibiting osteoclastogenesis and reducing inflammation [90]. Silibinin, a natural flavonoid with anti-oxidant and anti-inflammatory properties, was shown to induce the polarization of macrophages towards

M2 phenotype and suppress M1 cytokines, viz., TNF-αand iNOS in RAW264.7 cells (murine-macrophage like cell line). This can be used as a therapeutic drug in RA treatment [91].

Dexamethasone has shown anti-inflammatory effect on OA synovium by suppressing the M1 and enhancing the M2 macrophage phenotype. Pravastatin also enhanced M2 macrophages, but does not cause reduction in M1 macrophages [54]. Triamcinolone acetonide inhibits osteophyte formation in osteoarthritic rats by inducing monocyte differentiation towards $CD163^+$ (M2) macrophages [92].

A natural flavanol called Morin has shown the ability to impair MSU crystal mediated inflammation in macrophages via reduction of reactive oxygen species in acute gouty arthritis in vitro model [93].

Protein/histone deacetylase SIRT1 promotes phosphorylation of acetyl CoA carboxylase or adenosine monophosphate activated protein kinase α in response to IL-4, thus enhancing expression of M2 genes, e.g., MDC, IL-10, and MRC1. This treatment led to reduction in the histological signs of arthritis in mice [94].

Macrophages co-cultured with adipose-derived stromal cells under low serum condition develop into M2 phenotype and protect rat model of anti-glomerular basement membrane (anti-GBM) disease from renal disease. This can be used as a therapeutic strategy for crescentic GM [95].

Transplantation of M2 macrophages in the ALD-DNA-induced SLE mouse model has been shown to reduce the severity of the disease [96]. Another study on the same mouse model has shown that macrophage polarization towards M2 phenotype is induced via TNF-α-induced protein 8 (TIPE) overexpression which contributes to resolution of the disease [97].

We apparently have many promising leads, though more work is needed to be done before they can be tried in patients.

Conclusion

Although a lot of headway has been made towards understanding the function of alternatively activated or M2 macrophages in rheumatic diseases, much yet needs to be unravelled. Their antigen presentation capability killing mechanisms and signals which determine the spectrum of differentiation of macrophages to M2 phenotype need to be understood. Finally, the role of these macrophages in other rheumatic diseases needs to be studied. This information along with animal data on strategies to increase M2 macrophages can provide us with newer therapeutic strategies for treatment of chronic rheumatic disorders.

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