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Review

Macrophages with regulatory functions, a possible new therapeutic perspective in autoimmune diseases

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ABSTRACT

Macrophages are pivotal cells involved in chronic inflammatory and autoimmune diseases. In fact, during these diseases, activated macrophages may play a critical role, promoting the inflammation as well as mediating the damage resolution. This dichotomy is referred to two end-stage phenotypes of macrophages, conventionally known as M1 and M2, playing a pro-inflammatory and anti-inflammatory role, respectively. The M1 macrophages are the mainly subset involved during inflammatory processes, producing pro-inflammatory mediators. Conversely, the M2 macrophages are proposed to contribute to the resolution phase of inflammation, when cells with pro-resolving property are recruited and activated. In fact, this subset of macrophages may activate regulatory T lymphocytes, which play a critical role in the maintenance of peripheral tolerance and preventing the occurrence of autoimmune diseases. On these bases, the polarization toward the M2 phenotype could play a therapeutic role for autoimmune diseases.

In this Review we discussed the characteristic of M1 and M2 macrophages, focusing on the immunoregulatory role of M2 cells and their potential ability to control the inflammation and to promote the immunological tolerance.

1. Introduction

Macrophages play a pivotal role in the innate immune system, controlling phagocytosis, bacterial killing, producing cytokines and presenting antigen(s) to naïve T cells for the development of adaptive immune response. Macrophages were identified for the first time by Metchnikoff in 1883, when phagocytic mononuclear cells were observed to be able to kill bacteria [1]. After that, the notion of macrophage activation was introduced by Mackaness [2] in the early 1960s, investigating the host response to Listeria infection. Subsequently, the macrophage activation was linked to T helper cells, type1 (Th1) phenotype, for the first time by Nathan [3], showing that, the exposition of macrophages to anti-microbial effect induces interferon-gamma (IFN-γ) production and Th1 response.

Tissue-resident macrophages exhibit specific transcriptional profiles and characteristics, depending on the specific tissue in which they reside [4], such as microglial cells in brain, Kupffer cells in liver, alveolar macrophages in lung, osteoclasts in the bone and red-pulp macrophages in spleen [5]. It is possible to recognize “prenatal” and “postnatal” established macrophages. The first ones, the primitive macrophages, appear in the yolk sac around embryonic day 7 and disseminate following the establishment of the blood circulation, throughout embryonic tissues. These macrophages are quantitatively maintained in adulthood through longevity and/or limited self-renewal. The “post-natal” established macrophages mainly derive from circulating monocytes, which may give rise to relatively short-lived, non-self-renewing tissue-resident macrophages in organs [6]. During inflammation, monocytes are recruited to inflamed sites and lymphoid tissues, where differentiate in macrophages [7], playing an important role during both beginning and resolution of inflammatory processes. In fact, although macrophages

Abbreviations: Th1, T helper cells, type1; IFN-γ, interferon-gamma; RA, Rheumatoid Arthritis; MPS, mononuclear phagocyte system (MPS); DCs, dendritic cells; CMPs, common myeloid progenitor cells; GM-CSF, granulocytes macrophages colony-stimulating factor; M-CSF, macrophage colony stimulating factor; IL-, interleukin-; APCs, antigen presenting cells; Tregs, regulatory T cells; MHC II, histocompatibility complex type II; LPS, lipopolysaccharide; TNF, tumor necrosis factor; TGF-β, transforming growth factor beta; VEGF, vascular endothelial growth factor; ILC2, group 2 innate lymphoid cells; Foxp3, forkhead box P3; CIA, collagen-induced arthritis

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were initially thought to only promote inflammation, it was later assessed that these cells play a role also to resolve the inflammation. Macrophages may secrete factors promoting survival, repair [8–10], proliferation of hepatocytes [11] as well as neurons, and skeletal muscle-regeneration [12,13]. On these bases, the paradigm of M1 and M2 has been proposed [14], suggesting the beneficial or the deleterious effects of macrophages, dependent upon their state of activation, which is, in turn, determined by the occupied tissue micro-environment. Of note, the failure of inflammation resolution could lead to chronic inflammatory autoimmune diseases, such as Rheumatoid Arthritis (RA), Colitis or Asthma, associated with irreversible tissue damage and significant morbidity [15–17]. In this context, the understanding of the molecular mechanisms that drive macrophages polarization toward an anti-inflammatory and/or possible immune-regulatory phenotype could open new perspectives and therapeutic strategies for autoimmune diseases. However, important questions persist regarding how to relate the macrophages plasticity in mediating inflammatory processes.

In this review, we aimed to describe the macrophages origin and function, their differentiation in different subsets and their possible role as regulatory cells, controlling the innate and adaptative immunity.

2. The medullar mononuclear phagocyte system

The mononuclear phagocyte system (MPS), originating from bone marrow progenitor cells, is composed by monocytes, macrophages, and dendritic cells (DCs); these cells are characterized by phenotypic and functional overlaps [18–20]. This system plays physiological and pathological roles, in which peripheral blood monocytes move to the tissues where they differentiate into mature macrophages or DCs. Monocytes arise from common bone marrow common myeloid progenitor cells (CMPs) [19,20]. The differentiation process of monocytes is driven by different cytokines, mainly granulocytes macrophages colony-stimulating factor (GM-CSF) and macrophage colony stimulating factor (M-CSF). The GM-CSF induces the differentiation of monocytes into DCs and, under the influence of M-CSF and GM-CSF, monocytes become macrophages [18,19].

3. Monocytes

The term monocyte identifies a blood cell of the MPS lineage. Previously known as agranulocytes, these cells are the largest sized cells in MPS, containing typical horseshoe-shaped nucleus in their cytoplasm. [21]. Monocytes correspond to 10% of leukocytes in human blood. Physiologically, monocytes circulate in the blood, bone marrow, and spleen [21,22]. In bone marrow, the monocytes derive from myelomonocytic stem cells, which give rise to more direct precursors like monoblasts and pro-monocytes. These cells may proliferate and differentiate toward monocyte subsets [23,24]. Monocytes are traditionally known as the second line of defence cells, after neutrophils, in the innate immune system. In early studies, they were identified based on glass adherence and morphology and, in clinical haematology, on physical properties of these cells, including light scatter [25]. In the spleen, the monocytes are characterized by specific markers, including $CD11b^{high}$ and (CD90, B220, CD49b, NK1.1, Ly-6G, F4/80, I-Ab, $CD11c)^{low}$. On these bases, human monocytes are traditionally divided into three phenotypically and functionally distinct populations according to differences in expression of CD14 and CD16 encoding for the lipopolysaccharide receptor and the low affinity FC gamma receptor (FCGR3), respectively. Classical ($CD14^{++}CD16^{-}$) monocytes account for 80–90% of human blood monocytes, intermediate ($CD14^{+}CD16^{+}$) monocytes comprise ~2–5% and the nonclassical ($CD14^{-}CD16^{++}$) monocytes account for the remaining 2–10% [26,27]. The Nomenclature Committee of the International Union of Immunologic Societies (Berlin, Germany) has recently approved a new nomenclature of monocytes in humans accordingly [28]. Classical and intermediate monocyte subsets display inflammatory properties, whereas the nonclassical monocyte subset demonstrates patrolling behaviour along blood vessel walls, responding to viral infection [28]. The number of circulating blood monocytes may strongly increase within minutes by stress or exercise followed by a rapid return to baseline levels. In inflammation, monocytes in response to proinflammatory stimuli move to inflamed sites and lymphoid tissues. Monocytes neutralize pathogens and toxic molecules, engulf dead, damaged, and exogenous cells, secrete cytokines and differentiate to macrophages and DCs [29,30].

4. Macrophages origin and definition

The macrophages are large cells present in all tissues. They may clear cellular debris and pathogens, present antigens to T cells, and produce cytokines to alert cells about ongoing damage and later promote tissue healing. Presently, we define macrophages by their function (phagocytosis, immunity), specific markers (F4/80, CD64, MertK), morphology (phagosome inclusions) and location in specific tissues. In addition, the macrophages are very plastic and dynamic cells. When activated, macrophages morphology and protein expression may rapidly change, and these cells may migrate to sites of inflammation [31–33]. Recent studies have shown that macrophages may develop from embryonic leukocyte precursors without the need for a monocyte intermediate, as illustrated for some tissue-resident macrophage pools [34]. Bone marrow-derived macrophages may infiltrate most tissues, contributing to the maintenance of the macrophage pool [35]. These cells may be effected by surrounding microenvironmental stimuli and signals responsible to their phenotype polarization [36,37].

5. Macrophage function

During inflammation, the microenvironment is characterized by inflammatory mediators secreted by different population of infiltrated lymphocytes and tissue resident parenchymal cells. The interaction among these cells and the secreted molecules may induce a specific macrophage phenotype and, consequently, may influence their functions. Inflammation starts with a protective role, with the aim to remove the pathogens, to promote the tissue repair/wound healing and to establish memory, for a faster and specific future immune response. After arrival of polymorphonuclear neutrophils (PMNs), in the case of non-specific inflammation, or eosinophils, in response to allergens, macrophages eliminate microorganisms via intracellular and/or extra cellular killing mechanisms. During resolution phase, PMNs and eosinophils are replaced by phagocytosing macrophages. The major determinant of this shift, between PMNs and macrophages, is the interaction between interleukin- (IL-) 6 with its receptor. This interaction induces a chemokine shift, suppressing PMNs recruitments and promoting monocytes influx [38,39]. Furthermore, the macrophages may play an active role during the clearance of dead cells. Local cell death occurs in many ways including autophagy, excitotoxicity, pyroptosis, necrosis, necroptosis and caspase-mediated apoptosis [38–41]. Once the leucocytes are near to the end of its life, they release chemo-attractants, which signal their whereabouts to mononuclear phagocytes [42]. Apoptotic cells express or loss antigens that facilitate their rapid recognition and clearance by macrophages. In fact, apoptotic cells lose CD31 and CD47, which play a repellent role for phagocytes and upregulate phospholipids, nucleotides and phosphatidylserines, which promote the phagocytosis [38,43,44]. Macrophages play a central role also in both adaptative and innate immunity, due their ability as antigen presenting cells (APCs), that activate adaptive immunity, leading to priming of T and B cells. In addition, macrophages may control the effector T-cell behaviour and differentiation, inducing Th17, with proinflammatory function, or regulatory T cells (Tregs), with immune regulatory function, respectively [45].

6. Macrophage polarization

Different macrophages subsets are described, based on the production of specific molecules, expression of cell surface markers, and biologic activities [37,46,47]. Polarized macrophages may be classified in two main groups: classically activated macrophages (M1), which drive proinflammatory responses, and alternatively activated macrophages (M2), which control immune regulation and tissue remodelling. M2 macrophages may be further sub-classified in M2a, M2b, M2c and M2d based on resultant transcriptional changes after the exposure of different stimuli [36,37,46,48–50]. The stimulation-dependent polarization controls specific functions and phenotypes of macrophages: i. when exposed to the so-called M1 stimuli, macrophages acquire a pro-inflammatory phenotype, activating and producing proinflammatory molecules; ii. when exposed to M2 stimuli, macrophages acquire an anti-inflammatory phenotype, over-expressing mannose receptor, responsible to increase of clearance of mannosylated ligands, over-expression of histocompatibility complex type II (MHC II) and reduction of pro-inflammatory cytokines production [48,51,52]. On these bases, the M1/M2 macrophages paradigm was proposed, identifying two end-stage phenotypes with opposite functions. Recently, this paradigm has been revised, supporting the notion that, there is a continuum of intermediate phenotypes between these two apparent end-stage opposite ones [14,46,53–55] (Fig. 1).

7. Pro-inflammatory M1 macrophages

Macrophages differentiate into M1 type, when stimulated with M1 stimuli, which are grouped according to their ability to induce inflammatory response [48]. Three main M1 stimuli are recognized, including IFN-γ, major parts of the pathogens profile such as lipopolysaccharide (LPS), and GM-CSF. Recently, other stimuli have been proposed in inducing pro-inflammatory properties such as tumor necrosis factor (TNF), IL-1β and IL-6 [37]. Interestingly, although the consequent pro-inflammatory phenotype is the same, different sources, roles and signalling pathways of M1 stimuli are pointed out. In fact, IFN-γ controls cytokines receptor (CSF2RB, IL-15 receptor alpha, IL-2RA, and IL-6R), cell activation markers (CD36, CD38, CD69, and CD97), and cell adhesion molecules (intercellular adhesion molecule 1 [ICAM1], integrin alpha L [ITGAL], ITGA4, ITGbeta-7 [B7], mucin 1 [MUC1], and ST6 beta-galactosamide alpha-2,6-sialyltranferase 1 [SIAT1]) [48,56]. LPS activates the inflammasomes, by mechanisms, which are dependent or independent of toll-like receptor-4 (TLR-4) [57,58]. GM-CSF induces IL-6, IL-8, G-CSF, M-CSF, TNF, IL-1b, CD14, Fc fragment of IgG, high affinity Ia (FCgR1A) and nuclear receptor subfamily 1, group H, member 3 [NR1H3]) [59]. Classically, pro-inflammatory M1 macrophages secrete a number of cytokines, including TNF, IL-1β, IL-6, IL-12, IL-23 as well as of chemokines, including CCL5, CCL8, CXCL12, CXCL4 [18]. Furthermore, M1 macrophages produce nitric oxide (NO), via an increased synthesis of induced nitric oxide synthase (iNOS) [18]. M1 macrophages may also contribute to the tissue demolition and tumoricidal activity, promoting Th1 immune responses [60,61]. On these bases, an over-activation of M1 cells has been proposed to be involved in pathogenic mechanisms of several inflammatory, autoimmune and chronic diseases, including RA, Crohn's disease, Diabetes, Multiple Sclerosis, and Autoimmune Hepatitis [47,62–67].

8. Anti-inflammatory M2 macrophages

Macrophages differentiate into M2 type, when stimulated with M2 stimuli, which are grouped mainly due to their ability to antagonize inflammatory responses [48]. This group of stimuli includes very different molecules that span four levels of response and, in fact, M2 macrophages are sub-classified into 4 subtypes, including M2a, M2b, M2c and M2d. These cells are further identified based on expression markers: CD200R, CD206, CD163, arginase-1, STAT-3 and IL-10. The differentiation of M2a macrophages is a response to IL-4 and IL-13; their pivotal function is to inhibit M1 genes during tissue repair [68,69]. The M2b macrophages are polarized by combined immune

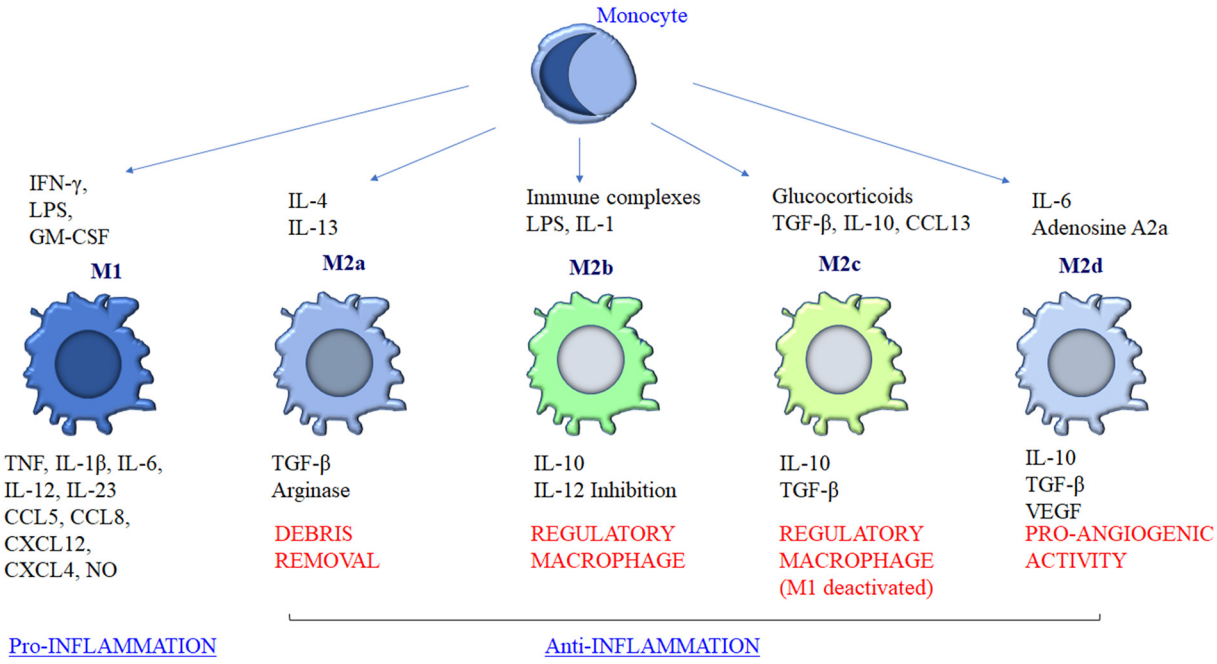

Fig. 1. Macrophage classification and polarization. Monocytes undergo polarization depending on received stimuli. M1 stimuli include IFN-γ, LPS and GM-CSF, which induce pro-inflammatory M1 macrophages differentiation. The anti-inflammatory M2 macrophages are classified in M2a, M2b, M2c, M2d depending on received stimuli. IL-4 and IL-13 induce M2a macrophages, their pivotal function is to inhibit M1 genes and to remove of debris during tissue repair. Immunocomplex, LPS and IL-1 promote M2b macrophages, that play a regulatory ability. Glucocorticoids, TGF-β, IL-10 and CCL13 induce the deactivation of M1 macrophages, which consequently acquire a regulatory activity, probably by TGF-β production. Finally, IL-6 and adenosine A2a promote M2d macrophages, playing a pro-angiogenic activity.

complexes that comprehend TLR and/or IL-1 receptor agonist [70,71]; they may play an immunoregulatory activity, although M2b polarization could promote the persistence of infection [36,72–74]. M2c macrophages are induced by glucocorticoids and transforming growth factor beta (TGF-β), these are referred as deactivated macrophages; they release large amounts of IL-10 and pro-fibrotic TGF-β, playing an efficient phagocytosis of apoptotic cells [75,76]. M2d macrophages are activated in response to IL-6 and A2 adenosine receptor (A2R) agonist [75,77–79]; they are characterized by high IL-10, TGF-β and vascular endothelial growth factor (VEGF) as well as by low IL-12, TNF and IL-1β production [73,78–80].

Taking together all these observations, the M2 macrophages generally play an anti-inflammatory and immune regulatory role and their activation is induced by parasites, fungal cells, immune complex, complements, apoptotic cells and allergic reaction [72,81]. They are characterized by high phagocytosis capacity, secreting extracellular matrix (ECM) components, angiogenic and chemotactic factors [82, 83, 84] and promoting the wound healing [85,86]. M2 macrophages are also characterized by the production of anti-inflammatory and regulatory cytokines, such as IL-4, IL-33 [87], IL-10, IL-1 receptor antagonist (IL-1RA) and TGF-β [88,89]. Interestingly, the TGF-β production is one of the most important function for M2 phenotype development and its activity, arresting NO production [53,90] and promoting Treg cells differentiation [91], through the TGF-β/SMAD signalling pathway [92–94].

9. M2 macrophages with regulatory activity

Inflammation is characterized by an induction phase, with strong immune activation and a resolution phase, in which the damage is eliminated, and the tissue integrity is restored. During resolution phase, the macrophages phenotype switches in pro-resolving, in M2 one [60]. This switch toward M2 macrophage function, may be supported by different cells, such as eosinophils [15,95] and tissue resident group 2 innate lymphoid cells (ILC2), which have been implicated in host type 2 immune responses. It has been shown that ILC2 cells promote the maintenance of alternatively activated M2 macrophages, producing IL-4 and IL-13. Under combined exposure to TLR agonists and/or IL-1R agonists, M2 subtype may acquire regulatory function, changing in M2b phenotype, that express CCL1, TNF, CD86 and IL-6, high levels of IL10 and low levels of IL-12 [36,46,49,96–98] (Fig. 2). Several further factors, such as posttranscriptional regulators, signalling molecules and transcriptional factors, have been found to play pivotal roles in the control of M2b macrophages polarization [36]. miRNAs, which are short noncoding RNAs playing a key role in immune and inflammatory responses, are modulated in M2b macrophages. In fact, it has been shown that the radiations may induce miR-222 [99] and its upregulation may promote M2b polarization by increasing the expression of CCL1. Furthermore, many studies showed that M2b macrophages are crucial players in immune tolerance, in fact, these cells may secrete IL-10, and inhibit IL-12 that stimulates M1 phenotype [37,46,100,101].

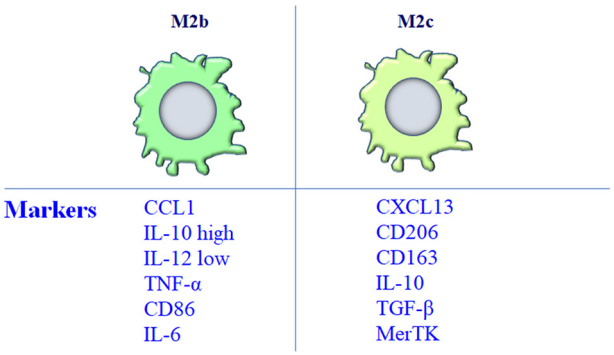

Fig. 2. Markers of M2 macrophages with regulatory function. M2 subtype may acquire regulatory functions, changing in M2b phenotype, that express CCL1, TNF, CD86 and IL-6, high levels of IL-10 and low levels of IL-12. Another subset of M2 macrophages with possible regulatory function could be M2c macrophages, which express CXCL13, CD206, CD163, IL-10, TGF-β and MerTK.

Another subset of M2 macrophages with possible regulatory function could be M2c macrophages, which express CXCL13, CD206, CD163, IL-10, TGF-β and MerTK [48–50,75] (Fig. 2). The M2c macrophages produce TGF-β and IL-10. In fact, TGF-β may play an immunoregulatory role, promoting Treg cells, playing a crucial role in maintaining peripheral tolerance [45,102]. While the role of M1 and M2 macrophages, during the development of Th1 and Th2 responses, is well characterized, the M2 macrophages role in the modulation of Treg cells remains to be defined [91], especially which subset of M2 macrophages interact with Treg cells. However, concerning their function role, it has been shown that M2 macrophages, in the cancer environment, could promote the differentiation of CD4+ CD25- T cells into activated Treg cells. In turn, these generated Treg cells skew the differentiation of monocytes toward M2 macrophages, through the IL-10 and TGF-β pathways [103], forming a positive-feedback loop. In fact, Tregs cells may direct monocytes differentiation toward an M2 subsets, promoting the increased expression of the mannose receptor CD206 and the hemoglobin scavenger receptor CD163, the increased production of CCL18 and IL-1Ra, and the reduced production of proinflammatory cytokines/chemokines [104]. Taking together, the consequent M2 macrophages-Treg cells loop contribute to immunosuppression, by release of molecules and/or through a cell-cell mechanism [105].

In this context, conflicting results are reported about the expression of Forkhead box P3 (Foxp3) [106,107], a well-recognized specific transcription factor for regulatory cells, in M2 macrophages. Recently, it has been reported that the TGF-β, VEGF and TLR ligands stimulations could promote the expression of FoxP3 in F4/80+ cells, a lineage of macrophages [108,109]. In the same work, the Authors also reported that FoxP3+ macrophages could play an immune regulatory role, by the production of soluble factors, such as PGE2, arginase-2, Arg-2, IL-1α and could stimulate the cells death by increasing the expression of TRAIL, CD200r, LAG3 [109]. Although this report of macrophage expression of Foxp3 raised a lot of interest in the scientific community, this report was subsequently retracted by the same institute [109]. After that, another paper investigated the role of Foxp3+ macrophages in the pathogenesis of atherosclerosis using experimental mouse model. However, the Authors were unable to replicate the presence of CD11b + F4/80+ macrophages expressing Foxp3 and noted that the Foxp3 positive staining was most likely an artefact, attributable to autofluorescence [110]. Recently, it has been shown that Foxp3 may be expressed in kidney tumor-associated macrophages, and the depletion of Foxp3+ cells reduced the frequency of M2 macrophages. Although functional and mechanistic insight needs to be performed, to reveal whether macrophages-expressed Foxp3 have immunosuppressive activity, these cells could be an interesting candidate to improve therapies for tumors containing M2 infiltrating macrophages [111].

10. M2 regulatory activity in autoimmune diseases, the model of RA

A growing body of evidence suggests the pathogenic involvement of macrophages in autoimmune diseases, showing an imbalance in M1/M2 ratio. In fact, a reduced frequency of anti-inflammatory M2 macrophages or a prolonged activation of M1 macrophages could lead to inflammation and autoimmunity development [67,112]. However, conflicting results are available in literature concerning this topic [17,113,114], suggesting further studies.

RA is a common autoimmune disease, exhibiting a remarkable level of inflammatory chronicity [15]. It is characterized by synovial inflammation, joint damage and systemic features [16,115–119]. The pannus formation and synovial hyperplasia are the main aspects of RA,

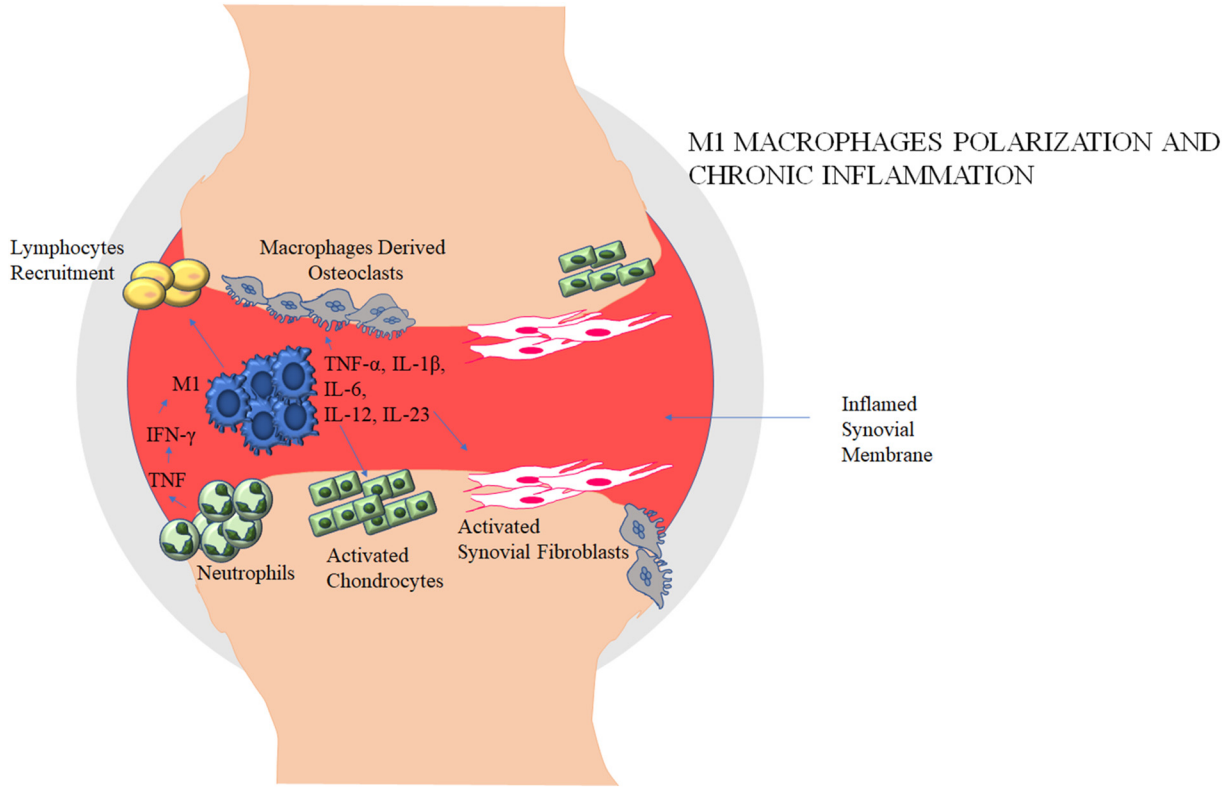

Fig. 3. M1 macrophages polarization during RA. Neutrophils are the first effector cells at site of inflammation. They release TNF and IFN-γ responsible to monocytes differentiation toward M1 cells. The latter promotes leucocytes recruitment to the inflamed joint. Furthermore, M1 macrophages produce TNF, IL-1β, IL-6, IL-12 and IL-23, promoting synovial fibroblasts proliferation, osteoclast and chondrocytes activation, leading to joint destruction.

due an inflammatory cellular infiltrate of several cell types (neutrophils, macrophages, fibroblasts, T-cells, and dendritic cells) in the synovial tissue [60]. In this context, neutrophils are the first effector cells, that facilitate the inflammatory process and macrophages, resident in synovial tissue, may promote osteoclastogenesis [120]. It has been reported that the 68% of macrophages like synoviocytes from synovial fluid of RA patients are M1 macrophages [121], playing a pro-inflammatory role (Fig. 3).

M2 macrophages, producing anti-inflammatory cytokines, promoting tissue remodelling and playing an immunoregulatory function, may improve the RA. In fact, some studies have used M2 polarizing cytokines, like IL-10, as therapeutic target, showing that IL-10-treated animals exhibited a reduced development of joint inflammation [122,123]. Furthermore, IL-10 gene therapy, targeted to macrophages, reprogrammed the macrophages phenotype from a predominantly M1 (pro-inflammatory) to M2 (anti-inflammatory) phenotype, preventing the joint damage associated with adjuvant-induced arthritis [124]. In this context, it has been proposed that a M2c polarization, induced by both M-CSF and IL-10, would be a desirable condition to counteract the autoimmune diseases, as suggested by the possible therapeutic utility of M-CSF and IL-10 [76]. Different additional strategies are currently exploring the possibility to increase M2 macrophages, to control inflammation during autoimmune diseases, mostly in animal models of RA, such as mesenchymal stem cells (MSCs), IL-9, IL-35 and Sema-3A (Fig. 4). Interestingly among the M2 stimuli, MSCs have been suggested. The immuno-regulatory properties of these cells were linked to their ability to polarize M1 macrophages toward an M2 phenotype, in collagen-induced arthritis (CIA) mice [125]. Furthermore, it has been shown that IL-9 may be a cytokine involved in arthritis resolution [126]. IL-9 could act as an autocrine growth factor for ILC2s, cells with pro-resolving properties, by promotion of M2 macrophages differentiation and Treg cells activation [127]. IL-35, produced by Treg cells, was also proposed in promoting the conversion of M1 to M2 macrophages [128] and in attenuating collagen induced arthritis in mice [129]. Of note, Teng et al., using in vitro culture of macrophages with Sema3A recombinant protein, showed that Sema3A inhibited LPS/IFN-γ induced M1 polarization of macrophages, whereas promoted IL-4 induced M2 polarization. This finding suggested the possibility that Sema3A could be used as a macrophages editor for the therapeutic purpose of RA [130], although further in vivo experiments are necessary. In this context, a growing body of data suggested that semaphorins are involved in the regulation of the immune system, the so called “immune semaphorins”, being involved in all phases of both normal and pathological immune responses [131,132]. Interestingly, Sema3A is of importance for its regulatory properties, thus downregulating the over-activity of both T and B cell autoimmunity [133].

Taking together these observations, new strategies targeting macrophages and their polarization could open the way for new therapeutic perspectives for the management of autoimmune diseases.

11. Conclusion

In conclusion, macrophages are pivotal cells of innate immunity and are also indispensable players in organ development, tissue turnover, and regeneration [134]. The naïve macrophages may polarize to differentiate toward either M1 or M2 macrophages, the balance of activation and inhibition of different M1 and M2 phenotypes may contribute to the development of many autoimmune diseases. In this context, the immune-modulatory role of M2 macrophages is still matter of debate. Probably, M2 macrophages could promote and activate Treg cells, after release of cytokines and growth factors, thus resolving the inflammatory process. On these bases, a better understanding of pathobiology of M2 macrophages may suggest new therapeutic perspective, to improve the management of autoimmune diseases.

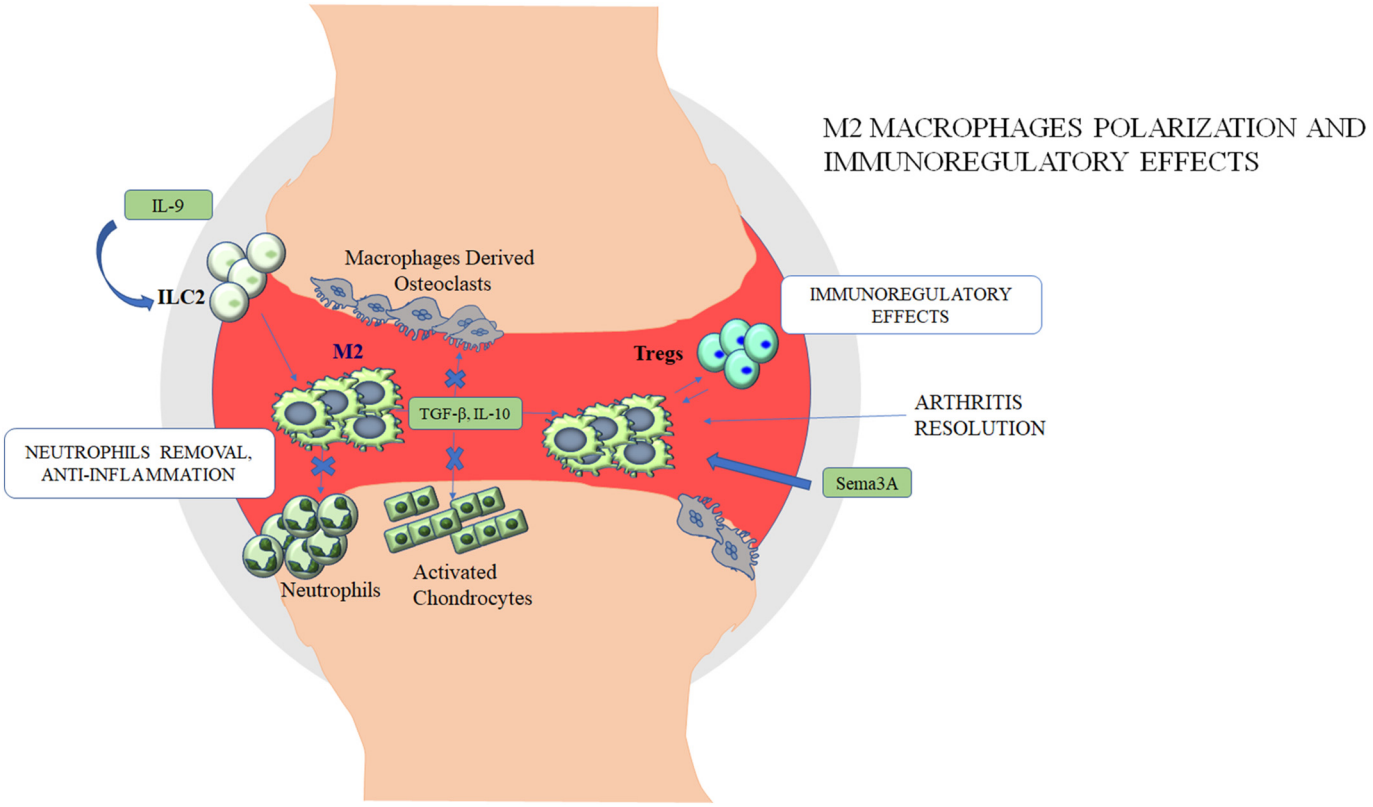

Fig. 4. Therapeutic perspective and M2 polarization during RA. M2 macrophages may play a therapeutic role during RA, promoting an anti-inflammatory and immuno-regulatory activity. In experimental models of RA, it has been shown that IL-9 overexpression may play an anti-inflammatory role, promoting ILC2 cells, responsible to M2 macrophages differentiation. The latter plays an anti-inflammatory activity promoting the neutrophils removal. Furthermore, M2 macrophages release TGF-β, that may induce Treg cells recruitment. Another molecule, with potential therapeutic role for RA, is Sema3A, contributing to M2 macrophages differentiation.

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Declaration of Competing Interest

No conflicting interests (including but not limited to commercial, personal, political, intellectual, or religious interests) to declare.

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References

[1] Metchnikoff E. On the present state of the question of immunity in infectious diseases. Scand J Immunol 1989;4:387–98.
[2] Mackaness GB. Cellular resistance to infection. J Exp Med 1962;116:381–406.
[3] Nathan CF, Murray HW, Wiebe ME, Rubin BY. Identification of interferon-gamma as the lymphokine that activates human macrophage oxidative metabolism and antimicrobial activity. J Exp Med 1983;158:670–89.
[4] Gautier EL, Shay T, Miller J, Greter M, Jakubzick C, Ivanov S, et al. Randolph GJ, Immunological Genome Consortium. Gene-expression profiles and transcriptional regulatory pathways that underlie the identity and diversity of mouse tissue macrophages. Nat Immunol 2012;13:1118–28.
[5] Epelman S, Lavine KJ, Randolph GJ. Origin and functions of tissue macrophages. Immunity 2014;41:21–35.
[6] Varol C, Mildner A, Jung S. Macrophages: development and tissue specialization. Annu Rev Immunol 2015;33:643–75.
[7] Davies LC, Jenkins SJ, Allen JE, Taylor PR. Tissue-resident macrophages. Nat Immunol 2013;14:986–95.
[8] Hikawa N, Takenaka T. Myelin-stimulated macrophages release neurotrophic factors for adult dorsal root ganglion neurons in culture. Cell Mol Neurobiol 1996;16:517–28.
[9] Rapalino O, Lazarov-Spiegler O, Agranov E, Velan GJ, Yoles E, Fraidakis M, et al. Implantation of stimulated homologous macrophages results in partial recovery of paraplegic rats. Nat Med 1998;4:814–21.
[10] Luk HW, Noble LJ, Werb Z. Macrophages contribute to the maintenance of stable regenerating neurites following peripheral nerve injury. J Neurosci Res 2003;73:644–58.
[11] Shiratori Y, Hongo S, Hikiba Y, Ohmura K, Nagura Y, Okano K, et al. Role of macrophagesin regeneration of liver. Dig Dis Sci 1996;41:1939–46.
[12] Arnold L, Henry A, Poron F, Baba-Amer Y, van Rooijen N, Plonquet A, et al. Inflammatory monocytes recruited after skeletal muscle injury switch into anti-inflammatory macrophages to support myogenesis. J Exp Med 2007;204:1057–69.
[13] Zhang L, Ran L, Garcia GE, Wang XH, Han S, Du J, et al. Chemokine CXCL16 regulates neutrophil and macrophage infiltration into injuredmuscle, promoting muscle regeneration. Am J Pathol 2009;175:2518–27.
[14] Stein M, Keshav S, Harris N, Gordon S. Interleukin 4 potently enhances murine macrophage mannose receptor activity: a marker of alternative immunologic macrophage activation. J Exp Med 1992;176:287–92.
[15] Schett G, Elewaut D, McInnes IB, Dayer JM, Neurath MF. How cytokine networks fuel inflammation: toward a cytokine-based disease taxonomy. Nat Med 2013;19:822–4.
[16] McInnes IB, Schett G. Pathogenetic insights from the treatment of rheumatoid arthritis. Lancet 2017;389:2328–37.
[17] Nielsen OH, Ainsworth MA. Tumor necrosis factor inhibitors for inflammatory bowel disease. N Engl J Med 2013;369:754–62.
[18] Juhas U, Ryba-Stanisławowska M, Szargiej P, Myśliwska J. Different pathways of macrophage activation and polarization. Postepy Hig Med Dosw (Online) 2015;69:496–502.
[19] Alikhan MA, Ricardo SD. Mononuclear phagocyte system in kidney disease and repair. Nephrology 2013;18:81–91.
[20] Lawrence T, Natoli G. Transcriptional regulation of macrophage polarization: enabling diversity with identity. Nat Rev Immunol 2011;11:750–61.
[21] Rana AK, Li Y, Dang Q, Yang F. Monocytes in rheumatoid arthritis: Circulating precursors of macrophages and osteoclasts and, their heterogeneity and plasticity role in RA pathogenesis. Int Immunopharmacol 2018;65:348–59.
[22] Auffray C, Sieweke MH, Geissmann F. Blood monocytes: development, heterogeneity, and relationship with dendritic cells. Annu Rev Immunol 2009;27:669–92.
[23] Ziegler-Heitbrock L. Blood monocytes and their subsets: established features and open questions. Front Immunol 2015;6:423.
[24] Hettinger J, Richards DM, Hansson J, Barra MM, Joschko AC, Krijgsveld J, et al.

Origin of monocytes and macrophages in a committed progenitor. Nat Immunol 2013;14:821–30.
[25] Van Furth R, Cohn ZA. The origin and kinetics of mononuclear phagocytes. J Exp Med 1968;128:415–35.
[26] Das A, Sinha M, Datta S, Abas M, Chaffee S, Sen CK, et al. Monocyte and macrophage plasticity in tissue repair and regeneration. Am J Pathol 2015;185:2596–606.
[27] Wong KL, Yeap WH, Tai JJ, Ong SM, Dang TM, Wong SC. The three human monocyte subsets: implications for health and disease. Immunol Res 2012;53:41–5.
[28] Italiani P. Boraschi D: From monocytes to M1/M2 macrophages: phenotypical vs. functional differentiation. Front Immunol 2014;5:514.
[29] Manzella L, Conte E, Cocchiaro G, Guarniera E, Sciacca B, Bonaiuto C, et al. Role of interferon regulatory factor 1 in monocyte/macrophage differentiation. A. Eur J Immunol 1999;29:3009–16.
[30] Woollard KJ, Geissmann F. Monocytes in atherosclerosis: subsets and functions. Nat Rev Cardiol 2010;7:77–86.
[31] Frodermann V, Nahrendorf M. Macrophages and cardiovascular health. Physiol Rev 2018;98:2523–69.
[32] Wynn TA, Chawla A, Pollard JW. Origins and hallmarks of macrophages: development, homeostasis, and disease. Nature 2013;496:445–55.
[33] Tay TL, Mai D, Dautzenberg J, Fernández-Klett F, Lin G, Sagar. A new fate mapping system reveals context-dependent random or clonal expansion of microglia. Nat Neurosci 2017;20:793–803.
[34] Hume DA. The Many Alternative Faces of Macrophage Activation. Front Immunol 2015;22:370.
[35] Pollard JW. Trophic macrophages in development and disease. Nat Rev Immunol 2009;9:259–70.
[36] Wang LX, Zhang SX, Wu HJ, Rong XL, Guo J. M2b macrophage polarization and its roles in diseases. J Leukoc Biol 2018;21.
[37] Mantovani AA, Sica S, Sozzani P, et al. The chemokine system in diverse forms of macrophage activation and polarization. Trends Immunol 2004;25:677–86.
[38] Motwani MP, Gilroy DW. Macrophage development and polarization in chronic inflammation. Semin Immunol 2015;27:257–66.
[39] McLoughlin RM, Witowski J, Robson RL, Wilkinson TS, Hurst SM, Williams AS, et al. Interplay between IFN-gamma and IL-6 signaling governs neutrophil trafficking and apoptosis during acute inflammation. J Clin Invest 2003;112:598–607.
[40] Vanden Berghe T, Linkermann A, Jouan-Lanhouet S, Walczak H, Vandenabeele P. Regulated necrosis: the expanding network of non-apoptoticcell death pathways. Nat Rev Mol Cell Biol 2014;15:135–47.
[41] Remijsen Q, Kuijpers TW, Wirawan E, Lippens S, Vandenabeele P, Vanden Berghe T. Dying for a cause: NETosis, mechanisms behind anantimicrobial cell death modality. Cell Death Differ 2011;18:581–8.
[42] Horino K, Nishiura H, Ohsako T, Shibuya Y, Hiraoka T, Kitamura N, et al. A monocyte chemotactic factor S19 ribosomal protein dimer, inphagocytic clearance of apoptotic cells. Lab Invest 1998;78:603–17.
[43] Brown S, Heinisch I, Ross E, Shaw K, Buckley CD, Savill J. Apoptosis disables CD31-mediated cell detachment from phagocytes promoting binding and engulfment. Nature 2002;418:200–3.
[44] Gardai SJ, McPhillips KA, Frasch SC, Janssen WJ, Starefeldt A, Murphy-Ullrich JE, et al. Cell-surface calreticulin initiates clearance of viable or apoptotic cellsthrough trans-activation of LRP on the phagocyte. Cell 2005;123:321–34.
[45] Kleinewietfeld M, Hafler DA. The plasticity of human Treg and Th17 cells and its role in autoimmunity. Semin Immunol 2013;25:305–12.
[46] Mosser DM, Edwards JP. Exploring the full spectrum of macrophage activation. Nat Rev Immunol 2008;8:958–69.
[47] Chinetti-Gbaguidi G, Colin S, Staels B. Macrophage subsets in atherosclerosis. Nat Rev Cardiol 2015;12:10–7.
[48] Martinez FO, Sica A, Mantovani A, Locati M. Macrophage activation and polarization. Front Biosci 2008;13:453–61.
[49] Gensel JC, Zhang B. Macrophage activation and its role in repair and pathology after spinal cord injury. Brain Res 1619;2015:1–11.
[50] Graff JW, Dickson AM, Clay G, McCaffrey AP, Wilson ME. Identifying functional microRNAs in macrophages with polarized phenotypes. J Biol Chem 2012;287:21816–25.
[51] Sunderkotter C, Nikolic T, Dillon MJ, Van Rooijen N, Stehling M, Drevets DA, et al. Leenen PJ. Subpopulations of mouse blood monocytes differ inmaturation stage and inflammatory response. J Immunol 2004;172:4410–7.
[52] Auffray C, Fogg D, Garfa M, Elain G, Join-Lambert O, Kayal S, et al. Monitoring of blood vessels and tissuesby a population of monocytes with patrolling behaviour. Science 2007;317:666–70.
[53] Funes SC, Rios M, Escobar-Vera J, Kalergis AM. Implications of macrophage polarization in autoimmunity. Immunology 2018;154:186–95.
[54] Murray Peter J, Allen Judith E, Biswas Subhra K, Fisher Edward A, Gilroy Derek W, Goerdt S, et al. Macrophage activation and polarization: nomenclature and experimental guidelines. Immunity 2014;41:14–20.
[55] Mantovani A, Sica A, Locati M. Macrophage polarization comes of age. Immunity 2005;23:344–6.
[56] Chistiakov DA, Myasoedova VA, Revin VV, Orekhov AN, Bobryshev YV. The impact of interferon-regulatory factors to macrophage differentiation and polarization into M1 and M2. Immunobiology 2018;223:101–11.
[57] Kayagaki N, Wong MT, Stowe IB, Ramani SR, Gonzalez LC, Akashi-Takamura S, et al. Noncanonical inflammasome activation by intracellular LPS independent of TLR4. Science 2013;341:1246–9.
[58] Hagar JA, Powell DA, Aachoui Y, Ernst RK, Miao EA. Cytoplasmic LPS activates caspase-11: implications in TLR4-independent endotoxic shock. Science 2013;341:1250–3.
[59] Lehtonen A, Ahlfors H, Veckman V, Miettinen M, Lahesmaa R, Julkunen I. Gene expression profiling during differentiation of human monocytes to macrophages or dendritic cells. J Leukoc Biol 2007;82:710–20.
[60] Navegantes KC, de Souza Gomes R, Pereira PAT, Czaikoski PG, Azevedo CHM, Monteiro MC. Immune modulation of some autoimmune diseases: the critical role of macrophages and neutrophils in the innate and adaptive immunity. J Transl Med 2017;15:36.
[61] Wynn TA, Chawla A, Pollard JW. Macrophage biology in development, homeostasis and disease. Nature 2013;496:445–55.
[62] Ruscitti P, Cipriani P, Di Benedetto P, Liakouli V, Berardicurti O, Carubbi F. Monocytes from patients with rheumatoid arthritis and type 2 diabetes mellitus display an increased production of interleukin (IL)-1β via the nucleotide-binding domain and leucine-rich repeat containing family pyrin 3(NLRP3)-inflammasome activation: a possible implication for therapeutic decision in these patients. Clin Exp Immunol 2015;182:35–44.
[63] Liu YC, Zou XB, Chai YF, Yao YM. Macrophage polarization in inflammatory diseases. Int J Biol 2014;10:520–9.
[64] Jansen A, Homo-Delarche F, Hooijkaas H, Leenen PJ, Dardenne M, Drexhage HA. Immunohistochemical characterization of monocytes-macrophages and dendritic cells involved in the initiation of the insulitis and beta-cell destruction in NOD mice. Diabetes 1994;43:667–75.
[65] Furlan R, Cuomo C, Martino G. Animal models of multiple sclerosis. Methods Mol Biol 2009;549:157–73.
[66] Murphy CA, Langrish CL, Chen Y, Blumenschein W, McClanahan T, Kastelein RA, et al. Divergent pro- and antiinflammatory roles for IL-23 and IL-12 in joint autoimmune inflammation. J Exp Med 2003;198:1951–7.
[67] Smith AM, Rahman FZ, Hayee B, Graham SJ, Marks DJB, Sewell GW, et al. Disordered macrophage cytokine secretion underlies impaired acute inflammation and bacterial clearance in Crohn's disease. J Exp Med 2009;206:1883–97.
[68] Gordon S, Martinez FO. Alternative activation of macrophages: mechanism and functions. Immunity 2015;32:593–604.
[69] Gordon S, Taylor PR. Monocyte and macrophage heterogeneity. Nat Rev Immunol 2005;5:953–64.
[70] Guilliams M, Ginhoux F, Jakubzick C, Naik SH, Onai N, Schraml BU, et al. Dendritic cells, monocytes and macrophages: a unified nomenclature based on ontogeny. Nat Rev Immunol 2014;14:571–8.
[71] Junttila IS, Mizukami K, Dickensheets H, Meier-Schellersheim M, Yamane H, Donnelly RP, et al. Tuning sensitivity to IL-4 and IL-13: differential expression of IL-4Ralpha, IL-13Ralpha1, and gammac regulates relative cytokine sensitivity. J Exp Med 2008;205:2595–608.
[72] Filardy AA, Pires DR, Nunes MP, et al. Proinflammatory clearance of apoptotic neutrophils induces an IL-12(low)IL-10(high) regulatory phenotype in-macrophages. J Immunol 2010;185:2044–50.
[73] Atri C, Guerfali FZ, Laouini D. Role of human macrophage polarization in inflammation during infectious diseases. Int J Mol Sci 2018;19:E1801.
[74] MacParland SA, Tsoi KM, Ouyang B, et al. Phenotype determines nanoparticle uptake by human macrophages from liver and blood. ACS Nano 2017;11:2428–43.
[75] Shapouri-Moghaddam A, Mohammadian S, Vazini H, et al. Macrophage plasticity, polarization, and function in health and disease. J Cell Physiol 2018;233:6425–40.
[76] Zizzo G, Hilliard BA, Monestier M, Cohen PL. Efficient clearance of early apoptotic cells by human macrophages requires M2c polarization andMerTK induction. J Immunol 2012;189:3508–20.
[77] Novak ML, Koh TJ. Macrophage phenotypes during tissue repair. J Leukoc Biol 2013;93:875–81.
[78] Duluc D, Delneste Y, Tan F, et al. Tumor-associated leukemia inhibitory factor and IL-6 skew monocyte differentiation into tumorassociated macrophage-like cells. Blood 2007;110:4319–30.
[79] Wang Q, Ni H, Lan L, et al. Fra-1 protooncogene regulates IL-6 expression in macrophages and promotes the generation of M2d macrophages. Cell Res 2010;20:701–12.
[80] Ferrante CJ, Leibovich SJ. Regulation ofmacrophage polarization and wound healing. AdvWound Care (New Rochelle) 2012;1:10–6.
[81] Banerjee S, Cui H, Xie N, Tan Z, Yang S, Icyuz M, et al. miR-125a-5p regulates differential activa¬tion of macrophages and inflammation. J Biol Chem 2013;288:35428–36.
[82] Espinoza-Jiménez A, Peón AN, Terrazas LI. Alternatively ac¬tivated macrophages in types 1 and 2 diabetes. Mediators Inflamm 2012;2012:815953.
[83] Fuentes L, Roszer T, Ricote M. Inflammatory mediators and insulin resistance in obesity: role of nuclear receptor signaling inmacrophages. Mediators Inflamm 2010;2012:2010–30.
[84] Bohlson SS, O'Conner SD, Hulsebus HJ, Ho MM, Fraser DA. Complement, C1q, and C1q-related molecules regulate macrophage polarization. Front Immunol 2014;5:402.
[85] Sica A, Mantovani A. Macrophage plasticity and polarization: in vivo veritas. J Clin Invest 2012;122:787–95.
[86] Ferrante CJ, Leibovich SJ. Regulation of macrophage polarization and wound healing. Adv Wound Care 2012;1:10–6.
[87] Locati M, Mantovani A, Sica A. Macrophage activation and polarization as an adaptive component of innate immunity. Adv Immunol 2013;120:163–84.
[88] Wang XF, Wang HS, Zhang F, Guo Q, Wang H, Wang KF, et al. Nodal promotes the generation of M2-like macrophage and downregulates the expression of IL-12. Eur J Immunol 2014;44:173–83.
[89] Giacomelli R, Ruscitti P, Alvaro S, Ciccia F, Liakouli V, Di Benedetto P, et al. IL-1β at the crossroad between rheumatoid arthritis and type 2 diabetes: may we kill two birds with one stone? Expert Rev Clin Immunol 2016;12:849–55.

[90] Vodovotz Y, Bogdan C, Paik J, Xie Q, Nathan C. Mechanisms of suppression of macrophage nitric oxide release by transforming growth factor b. J Exp Med 1993;178:605–13.

[91] Sun SW, Chen L, Zhou M, Wu JH, Meng ZJ. Han HL BAMBI regulates macrophages inducing the differentiation of Treg through the TGF-β pathway in chronic obstructive pulmonary disease. Respir Res 2019;20:26.

[92] Di Benedetto P, Liakouli V, Ruscitti P, Berardicurti O, Carubbi F, Panzera N, et al. Blocking CD248 molecules in perivascular stromal cells of patients with systemic sclerosis strongly inhibits their differentiation toward myofibroblasts and proliferation: a new potential target for antifibrotic therapy. Arthritis Res Ther 2018;20:223.

[93] Cipriani P, Di Benedetto P, Ruscitti P, Verzella D, Fischietti M, Zazzeroni F, et al. Macitentan inhibits the transforming growth factor-β profibrotic action, blocking the signaling mediated by the ETR/TβRI complex in systemic sclerosis dermal fibroblasts. Arthritis Res Ther 2015;17:247.

[94] Cipriani P, Di Benedetto P, Ruscitti P, Liakouli V, Berardicurti O, Carubbi F, et al. Perivascular cells in diffuse cutaneous systemic sclerosis overexpress activated ADAM12 and are involved in myofibroblast transdifferentiation and development of fibrosis. J Rheumatol 2016;43:1340–9.

[95] Chen Z, Andreev D, Oeser K, Krljanac B, Hueber A, Kleyer A, et al. Th2 and eosinophil responses suppress inflammatory arthritis. Nat Commun 2016;7:11596.

[96] Ito I, Bhopale KK, Nishiguchi T, Lee JO, Herndon DN, Suzuki S, et al. The polarization of M2b monocytes in cultures of burn patient peripheral CD14+ cells treated with a selected human CCL1 antisense Oligodeoxynucleotide. Nucleic Acid Ther 2016;26:269–76.

[97] Giat E, Ehrenfeld M, Shoenfeld Y. Cancer and autoimmune diseases. Autoimmun Rev 2017;16:1049–57.

[98] Ruscitti P, Cipriani P, Di Benedetto P, Liakouli V, Carubbi F, Berardicurti O, et al. Advances in immunopathogenesis of macrophage activation syndrome during rheumatic inflammatory diseases: toward new therapeutic targets? Expert Rev Clin Immunol 2017;13:1041–7.

[99] Suzuki F, Loucas BD, Ito I, Asai A, Suzuki S, Kobayashi M. Survival of mice with gastrointestinal acute radiation syndrome through control of bacterial translocation. J Immunol 2018;201:77–86.

[100] Mantovani A, Sozzani S, Locati M, Allavena P, Sica A. Macrophage polarization: tumor-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes. Trends Immunol 2002;23:549–55.

[101] Mantovani A, Locati M. Tumor-associated macrophages as a paradigm of macrophage plasticity, diversity, and polarization: lessons and open questions. Arterioscler Thromb Vasc Biol 2013;33:1478–83.

[102] Cipriani P, Di Benedetto P, Liakouli V, Del Papa B, Di Padova M, Di Ianni M, et al. Mesenchymal stem cells (MSCs) from scleroderma patients (SSc) preserve their immunomodulatory properties although senescent and normally induce T regulatory cells (Tregs) with a functional phenotype: implications for cellular-based therapy. Clin Exp Immunol 2013;173:195–206.

[103] Liu G, Ma H, Qiu L, Li L, Cao Y, Ma J, et al. Phenotypic and functional switch of macrophages induced by regulatory CD4+CD25+ T cells in mice. Immunol Cell Biol 2011;89:130–42.

[104] Tiemessen MM, Jagger AL, Evans HG, van Herwijnen MJ, John S, Taams LS. CD4+CD25+Foxp3+ regulatory T cells induce alternative activation of human monocytes/macrophages. Proc Natl Acad Sci U S A 2007;104:19446–51.

[105] Schmidt A, Zhang XM, Joshi RN, Iqbal S, Wahlund C, Gabrielsson S, et al. Human macrophages induce CD4(+)Foxp3(+) regulatory T cells via binding and re-release of TGF-beta. Immunol Cell Biol 2016;94:747–62.

[106] Miyao T, Floess S, Setoguchi R, Luche H, Fehling HJ, Waldmann H, et al. Plasticity of Foxp3(+) T cells reflects promiscuous Foxp3 expression in conventional T cells but not reprogramming of regulatory T cells. Immunity 2012;36:262–75.

[107] Vadasz Z, Toubi E. FoxP3 expression in macrophages, Cancer, and B cells-is it real? Clin Rev Allergy Immunol 2017;52:364–72.

[108] Cassetta L, Cassol E, Poli G. Macrophage polarization in health and disease. Scientific World Journal 2011;11:2391–402.

[109] Manrique SZ, Correa MA, Hoelzinger DB, Dominguez AL, Mirza N, Lin HH, et al. Foxp3-positive macrophages display immunosuppressive properties and promote tumor growth. J Exp Med 2011;208:1485–99. (RETRACTED ARTICLE).

[110] Li F, Yang M, Wang La, Williamson I, Tian F, Qin M, et al. Autofluorescence contributes to false-positive intracellular Foxp3 staining in macrophages: a lesson learned from flow cytometry. J Immunol Methods 2012;386:101–7.

[111] Devaud C, Yong CSM, John LB, Westwood JA, Duong CPM, House CM, et al. Foxp3 Expression in Macrophages Associated with RENCA Tumors in Mice. PLoS One 2014;9:e108670.

[112] Giacomelli R, Afeltra A, Alunno A, Baldini C, Bartoloni-Bocci E, Berardicurti O, et al. International consensus: what else can we do to improve diagnosis and therapeutic strategies in patients affected by autoimmune rheumatic diseases (rheumatoid arthritis, spondyloarthritides, systemic sclerosis, systemic lupus erythematosus, antiphospholipid syndrome and Sjogren'ssyndrome)?: the unmet needs and the clinical grey zone in autoimmune disease management. Autoimmun Rev 2017;16:911–24.

[113] Zhu W, Yu J, Nie Y, Shi X, Liu Y, Li F, et al. Disequilibrium of M1 and M2 macrophages correlates with the development of experimental inflammatory bowel diseases. Immunol Invest 2014;43:638–52.

[114] Gagliani N, Amezcua Vesely MC, Iseppon A, Brockmann L, Xu H, Palm NW. Th17 cells transdifferentiate into regulatory T cells during resolution of inflammation. Nature 2015;523:221–5.

[115] Ruscitti P, Di Benedetto P, Berardicurti O, Liakouli V, Carubbi F, Cipriani P, et al. Adipocytokines in rheumatoid arthritis: the hidden link between inflammation and cardiometabolic comorbidities. J Immunol Res 2018;2018:8410182.

[116] Giacomelli R, Afeltra A, Alunno A, Bartoloni-Bocci E, Berardicurti O, Bombardieri M, et al. Guidelines for biomarkers in autoimmune rheumatic diseases - evidence based analysis. Autoimmun Rev 2019;18:93–106.

[117] Pingiotti E, Cipriani P, Marrelli A, Liakouli V, Fratini S, Penco M, et al. Surface expression of fractalkine receptor (CX3CR1) on CD4+/CD28 T cells in RA patients and correlation with atherosclerotic damage. Ann N Y Acad Sci 2007;1107:32–41.

[118] Ruscitti P, Cipriani P, Masedu F, Romano S, Berardicurti O, Liakouli V, et al. Increased cardiovascular events and subclinical atherosclerosis in rheumatoid arthritis patients: 1 year prospective single centre study. PLoS One 2017;12:e0170108.

[119] Burmester GR, Pope JE. Novel treatment strategies in rheumatoid arthritis. Lancet 2017;389:2338–48.

[120] Bhattacharya S, Aggarwal A. M2 macrophages and their role in rheumatic diseases. Rheumatol Int 2018;9.

[121] Mottonen M, Isomaki P, Saario R, Toivanen P, Punnonen J, Lassila O. Interleukin-10 inhibits the capacity of synovial macrophages to function as antigen-presenting cells. Br J Rheumatol 1998;37:1207–14.

[122] Vandooren B, Noordenbos T, Ambarus C, Krausz S, Cantaert T, Yeremenko N, et al. Absence of a classically activated macrophage cytokine signature in peripheral spondylarthritis, including psoriatic arthritis. Arthritis Rheum 2009;60:966–75.

[123] Whalen JD, Lechman EL, Carlos CA, Weiss K, Kovesdi I, Glorioso JC, et al. Adenoviral transfer of the viral IL-10 gene periarticularly to mouse paws suppresses development of collagen-induced arthritis in both injected and uninjected paws. J Immunol 1999;162:3625–32.

[124] Jain S, Tran TH, Amiji M. Macrophage repolarization with targeted alginate nanoparticles containing IL-10 plasmid DNA for the treatment of experimental arthritis. Biomaterials 2015;61:162–77.

[125] Shin TH, Kim HS, Kang TW, Lee BC, Lee HY, Kim YJ, et al. Human umbilical cord blood-stem cells direct macrophage polarization and block inflammasome activation to alleviate rheumatoid arthritis. Cell Death Dis 2016;7:e2524.

[126] Ciccia F, Guggino G, Ferrante A, Raimondo S, Bignone R, Rodolico V, et al. Interleukin-9 overexpression and Th9 polarization characterize the inflamed gut, the synovial tissue, and the peripheral blood of patients with psoriatic arthritis. Arthritis Rheumatol 2016;68:1922–31.

[127] Gerlach K, Hwang Y, Nikolaev A, Atreya R, Dornhoff H, Steiner S, et al. TH9 cells that express the transcription factor PU.1 drive T cell-mediated colitis via IL-9 receptor signaling in intestinal epithelial cells. Nat Immunol 2014;15:676–86.

[128] Zhang X, Zhang X, Zhuang L, Xu C, Li T, Zhang G, et al. Decreased regulatory T-cell frequency and interleukin-35 levels in patients with rheumatoid arthritis. Exp Ther Med 2018;16:5366–72.

[129] Shen P, Roch T, Lampropoulou V, O'Connor RA, Stervbo U, Hilgenberg E, et al. IL 35 producing B cells are critical regulators of immunity during autoimmune and infectious diseases. Nature 2014;507:366–70.

[130] Teng Y, Yin Z, Li J, Li K, Li X, Zhang Y. Adenovirus-mediated delivery of Sema3A alleviates rheumatoid arthritis in a serum-transfer induced mouse model. Oncotarget 2017;8:66270–80.

[131] Vadasz Z, Toubi E. Semaphorin3A: a potential therapeutic tool in immune-mediated diseases. Eur J Rheumatol 2018;5:58–61.

[132] Chapoval SP, Vadasz Z, Chapoval AI, Toubi E. Semaphorins 4A and 4D in chronic inflammatory diseases. Inflamm Res 2017;66:111–7.

[133] Vadasz Z, Toubi E. Semaphorins: their dual role in regulating immune-mediated diseases. Clin Rev Allergy Immunol 2014;47:17–25.

[134] Rőszer T. Understanding the mysterious M2 macrophage through activation markers and effector mechanisms. Mediators Inflamm 2015;2015:816460.