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Macrophages – silent enemies in juvenile idiopathic arthritis

Makrofagi – cichy przeciwnik w młodzieńczym idiopatycznym zapaleniu stawów

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Summary

The inflammatory response by secretion of cytokines and other mediators is postulated as one of the most significant factors in the pathophysiology of juvenile idiopathic arthritis (JIA).

The effect of macrophage action depends on the type of their activation. Classically activated macrophages (M1) are responsible for release of molecules crucial for joint inflammation. Alternatively activated macrophages (M2) may recognize self antigens by scavenger receptors and induce the immunological reaction leading to autoimmune diseases such as JIA.

Molecules essential for JIA pathophysiology include: TNF-α, the production of which precedes synovial inflammation in rheumatoid arthritis; IL-1 as a key mediator of synovial damage; chemotactic factors for macrophages IL-8 and MCP-1; IL6, the level of which correlates with the radiological joint damage; MIF, promoting the secretion of TNF-α and IL-6; CCL20 and HIF, significant for the hypoxic synovial environment in JIA; GM-CSF, stimulating the production of macrophages; and IL-18, crucial for NK cell functions.

Recognition of the role of macrophages creates the potential for a new therapeutic approach.

Keywords: ***macrophages • autoimmunology • arthritis • juvenile***

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Introduction

Juvenile idiopathic arthritis (JIA) is the most common childhood chronic rheumatic disease, defined as an arthritis of unknown origin with onset before the age of 16 years [72,74]. It is characterized by synovial joint inflammation, synovial tissue hyperplasia, progressive cartilage destruction, and bone erosion [74]. As JIA's pathogenesis remains unclear, it is crucial for the design of new targeted therapies to clarify the factors affecting the development of the disease. The most essential is the inflammatory response, which persists as a result of the ongoing leukocyte recruitment and retention within synovial tissue and synovial fluid [74]. Discovery of the abnormal secretion of several cytokines and inflammatory mediators was an important step in understanding their key roles during cell activation and its characterization [30,46,49].

M1 and M2 macrophages

Monocytic cells, and their tissue analogues macrophages, are significant in the pathophysiology of rheumatoid arthritis (juvenile and adult), as a major source of chemokines [38,46,55].

Macrophages are classified by the type of their activation (Fig. 1). Classically activated macrophages (M1) are stimulated by interferon (IFN)-γ or lipopolysaccharide (LPS) to release nitric oxide, important for killing intracellular pathogens. Alternatively activated macrophages (M2) are stimulated by interleukin (IL)-4 or IL-13 to produce IL-10, transforming growth factor (TGF)-β and arginase-1 (Arg1) [41,57]. There are some other suppressive or anti-inflammatory macrophages, including tumor-associated macrophages (TAM), "immature" monocyte-like (GR1/Ly6C+) or "mature" neutrophil-like (GR1/Ly6G+) myeloid-derived suppressor cells (MDSCs). IL-4 and IL-13 are not involved in the differentiation of TAM or MDSCs, and therefore these macrophage populations are not referred to as alternatively activated [57].

Although the hallmark of autoimmune diseases is the generation of autoantigen-specific T and B cell responses, macrophages and neutrophils are dominant in the infiltration during the peak of acute inflammation [31,85].

Classically activated macrophages (M1)

Classically activated macrophages are released as a response of stimulation by IFN-γ and LPS [58]. They are characterized by expression of MHC class II and CD86 and their ability to secrete proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α), IL-1β, IL-12, IL-18 and the chemokines CCL15, CCL20, CXCL8-11 and CXCL13 [57,58]. M1 effortlessly kill intracellular pathogens by endocytosis of bacteria and viruses, production of NO via IFN-γ-inducible NO synthase (iNOS), synthesis of reactive oxygen intermediates (ROI), and by restriction of iron and other nutrients required for bacterial growth and viral replication [58]. IFN-γ is produced by many cell types including $CD8^+$ cytotoxic T lymphocytes, natural killer (NK) and Th1 cells.

As cytokines produced by M1 are dominant in synovial inflammation, these macrophages apparently participate in JIA pathophysiology.

Alternatively activated macrophages (M2)

The activation of M2 is labeled "alternative" as they are induced mainly by IL-4 and IL-13 instead of IFN-γ as the classical stimulator [4]. Monocytes differentiate into M2 as a response to IL-4, IL-13, IL-10, and TGF-β [58]. Differentiation may also be stimulated by LPS along with M1 and/or IL-1β secreted by M1 [63]. In general, M2 are distinguished from other macrophage populations by several markers including IL-4R, mannose receptor (MR/CD206), Arg1, Fizz1 (found in the inflammatory zone), PPARγ (peroxisome proliferator-activated receptor) and Ym1/2 (eosinophilic protein from the chitinase family) [57]. M2 are typically associated with Th2 responses and tissue repair, where they are thought to increase fibrosis by expressing profibrotic factors such as fibronectin, matrix metalloproteinases (MMPs), IL-1β and TGF-β. However, a precise role for M2 in mediating fibrosis has not yet been established *in vivo* [58]. IL-10 and TGF-β released from M2 have been found to inhibit LPS/TLR4-mediated production of TNF-α and IL-1β by M1 [3] and down-regulate Th1 responses by increasing $CD4^+Foxp3^+$ regulatory T cells (Treg) [9]. M2 are characterized by producing Arg1 rather than iNOS/NO, which makes them highly effective at fighting parasitic helminth infections but significantly compromises their ability to kill intracellular pathogens [5,41,80]. The mannose receptor (MR) is upregulated on M2 by IL-4 and IL-13 and down-regulated by proinflammatory cytokines [25]. MR signaling inhibits Th1 responses by interfering with TLR/IL-1R-mediated signaling by upregulating IL-1R type II (a decoy receptor) and by secretion of the IL-1R antagonist (IL-1Ra) and IL-10 [57,81]. Importantly, expression of scavenger receptors and C-type lectins such as the MR and DC-SIGN on M2 serve not only as pattern recognition receptors for pathogen binding and uptake during infection, but also bind self tissues such as apoptotic cells and oxidized LDL as a part of natural homeostasis and tissue repair [15,66,83]. Thus, M2 are increased in response to many infections, particularly those associated with Th2 responses, and are important in mediating wound healing following tissue damage.

M2 pathogenesis of autoimmune diseases

There are few studies specifically examining the role of M2 or MDSCs in the development of autoimmune diseases (AD). Most experimental models of AD are considered to be Th1 and/or Th17-mediated [43,52]. However, IL-4 and IL-13-induced Th2 responses are necessary for the development of several ADs usually considered to be

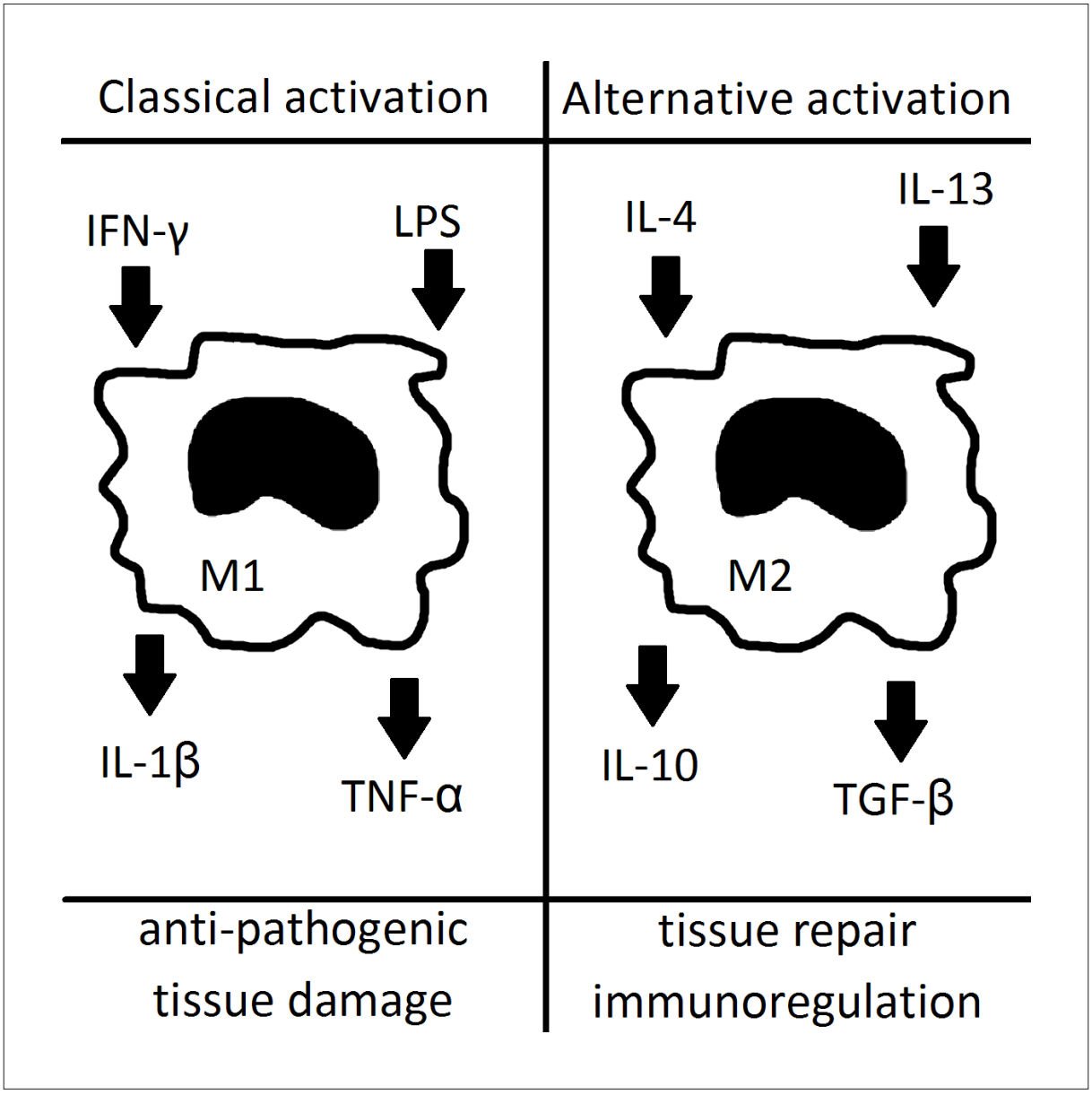

Fig. 1. Activation of M1 and M2 macrophages – full description in the text

mediated by Th1 or Th17 responses [2,27,28,48,71]. Many pattern recognition receptors (PRRs) that are present on M2 and MDSCs are able to recognize both foreign and self antigens, suggesting a possible role for alternatively activated macrophages in the pathogenesis of AD [1].

Recent findings in animal models suggest that M2 and/or MDSCs exacerbate autoimmune disease by presenting self antigens taken up by scavenger receptors in response to tissue damage and by contributing to fibrosis and immune complex-mediated pathology. Evidence is beginning to emerge that M2 may also be pathogenic in arthritis. However, few studies of AD have specifically examined the role of M2 or MDSCs in the pathogenesis of disease. Realizing that proinflammatory receptors such as TLR4 and IL-1R drive M2 differentiation indicates that an evaluation of the role of M1 vs. M2 macrophages in the pathogenesis of autoimmune disease is needed [8,56,79,83].

Macrophage effector molecules in juvenile idiopathic arthritis

TNF-α

TNF-α is a pleiotropic cytokine that increases the expression of cytokines, adhesion molecules, prostaglandin E_2, collagenase and collagen by synovial cells [20]. It is mostly produced by macrophages in the synovial membrane and at junctions [29] and is believed to be a proximal cytokine in the inflammatory cascade. The importance of TNF-α and its potential role in JIA pathogenesis is evidenced by several experimental and clinical

observations: lymph node TNF-α production precedes clinical synovitis in experimental arthritides [62,76]; neutralization of TNF-α suppresses collagen-induced arthritis and reduces inflammation in human/murine severe combined immunodeficiency arthritis [75]; TNF-α, in combination with IL-1, is a potent inducer of synovitis [39]; transgenic, deregulated expression of TNF-α causes development of chronic arthritis [73]; the TNF-α levels in the synovial fluid correlate with the number of lining macrophages and with the degree of radiologically assessed bone erosion [64]; serum TNF-α and soluble TNF receptors 1 and 2 are increased in active, systemic juvenile idiopathic arthritis (sJIA), including some cases of macrophage activation syndrome [21].

Interleukin-1

IL-1 gene expression is found predominantly in $CD14^+$ macrophages [86], which includes both M1 and M2 populations. IL-1 levels in the synovial fluid significantly correlate with joint inflammatory activity [6]. This cytokine, which is believed to act in sequence after TNF-α [29], appears to mediate most of the articular damage in arthritis, because it induces proteoglycan degradation and inhibition of proteoglycan synthesis [53]. Also, IL-1 induces the production of the metalloproteases, stromelysin and collagenase [5], and enhances bone resorption. In rheumatoid processes, the balance between IL-1 and its physiological inhibitor IL-1Ra is shifted in favor of IL-1, indicating a dysregulation that may be crucial in promoting chronicity.

Interleukin-8 and MCP-1

Several studies have documented the existence of positive feedback between the macrophage-derived TNF-α and IL-1 and chemotactic factors for monocytes, IL-8 and MCP-1 [53]. These factors are produced by synovial macrophages in an autocrine manner. Significantly, IL-8 derived from synovial macrophages is a powerful promoter of angiogenesis, thus providing a link between macrophage activation and the prominent neovascularization of the rheumatoid synovium [45].

Interleukin-6

IL-6 is the most strikingly elevated cytokine, especially in the synovial fluid during acute disease [40]. The acute rise is consistent with the role of IL-6 in acute-phase responses. Although IL-6 levels in the synovial fluid correlate with the degree of radiological joint damage, IL-6 and its soluble receptors promote the generation of osteoclasts [47]. IL-6 is mostly produced by synovial fibroblasts and only partially by macrophages [87]. Two findings suggest that the striking IL-6 rise is a prominent outcome of macrophage activation: the morphological vicinity of IL-6-expressing fibroblasts with $CD14^+$ macrophages in the rheumatoid arthritis (RA) synovial tissue [87]; and the *in vitro* and coculture studies [16] that showed that IL-1 stimulates IL-6 production.

MIF

Among the cytokines involved in pathogenesis of autoimmune diseases is macrophage migration inhibitory factor (MIF), which appears to be an important mediator of inflammatory responses following its secretion from T lymphocytes, macrophages, endothelial cells (ECs), and other inflammatory cells [44]. Besides its original ability to prevent the random migration of macrophages in culture, MIF shows a broad range of immunostimulatory and proinflammatory activities [11]. Recent data suggest that MIF is involved in the pathogenesis of arthritis. In rat adjuvant arthritis, elevated levels of MIF are present both in serum and in synovium, and anti-MIF treatment reduces arthritis severity as well as macrophage and T cell accumulation in the joints [51]. Similarly, in murine collagen-induced arthritis, anti-MIF treatment before immunization with collagen results in delayed onset and reduced incidence of arthritis [60]. In humans, high levels of MIF are present in the serum and synovial fluid of adult patients with RA [50]. Serum MIF levels are also increased in patients with active JIA, with the highest serum levels of MIF present in sJIA [59]. Treatment with glucocorticosteroids affects in vitro MIF production in a bimodal way, being able at low doses to stimulate MIF production and at high doses to inhibit it [13]. Therefore, increased MIF levels in patients with sJIA do not appear to be a consequence of oral glucocorticosteroid treatment. Serum MIF levels were associated with the persistence of systemic features and with the number of active joints, supporting the conclusion that serum MIF levels are related to disease severity in sJIA [59]. Since macrophages and T cells have been shown to contain significant amounts of preformed MIF [11,13], the observation of increased MIF production by peripheral blood mononuclear cells (PBMCs) suggests that T cells and/or monocytes represent the source of circulating MIF in sJIA. sJIA is characterized by increased levels of the macrophage inflammatory cytokines TNF-α and IL-6 compared with those in patients with poly- or oligo-onset JIA. Since MIF promotes the production of inflammatory cytokines by macrophage cell lines and mouse peritoneal macrophages [14] and counteracts the GC-induced inhibition of TNF and IL-6 production [13], increased MIF production may play a role in the pathogenesis of sJIA, being at least one of the factors responsible for the increased production of inflammatory cytokines.

Serum and synovial fluid (SF) levels of MIF, as well as *in vitro* MIF production by PBMCs, in patients with JIA are elevated. In particular, both serum and SF levels of MIF are markedly elevated in patients with sJIA, who also show increased *in vitro* MIF production by PBMCs.

Macrophage inflammatory protein 3/CCL20 and HIF

Macrophage inflammatory protein 3 (MIP-3)/CCL20, a chemokine implicated in RA pathogenesis [77], was recently identified as a hypoxia-inducible gene in pri-

mary PBMCs [22]. Hypoxia is a characteristic of the inflamed rheumatoid synovium [32]. Expression of hypoxia-inducible factor 1 (HIF-1) and HIF-2, key regulators of the hypoxia transcriptional response [78], was observed in the synovium of RA and osteoarthritis (OA) patients, and the involvement of hypoxia in the pathogenesis and progression of these arthropathies was suggested [10,32]. The same pattern is observed in production of CCL20 in SF of JIA patients; the hypoxic synovial environment induces CCL20 expression in infiltrating monocytic cells [24]. HIF-1 and HIF-2 are expressed constitutively in the JIA synovium in areas characterized by high monocytic cell infiltration, suggesting that local hypoxia stimulates HIF expression in recruited monocytic cells. These data extend the results of previous observations showing expression of HIF-1 in monocytic cells from RA synovial specimens [24] and of both subunits in monocytic cells from OA synovial specimens [32]. The demonstration that fresh SF monocytic cells, but not matched PBMCs, constitutively expressed HIF-1 supports the possibility that HIF-1 is induced in monocytic cells after migration to the hypoxic synovium. Induction of CCL20 in SF monocytic cells by intraarticular hypoxia is of pathologic relevance, given the chemokine's role in the recruitment of immature dendritic cells, effector/memory T lymphocytes, and naive B cells [77]. This represents a potential mechanism of control of the kinetics and composition of cellular infiltration in the synovial microenvironment, which may contribute to the chronicity of inflammation in JIA [74].

Granulocyte-macrophage colony-stimulating factor

GM-CSF is similarly important in mouse models of arthritis and is found in high concentrations in the synovial fluid (SF) of patients with rheumatoid arthritis and JIA [18,19,33]. It has widespread effects, promoting granulopoiesis and activating neutrophils, monocytes, and macrophages that contribute to joint inflammation and damage [17,26,61]. Although GM-CSF is widely expressed in both stromal and hematopoietic compartments, recent murine studies suggest that GM-CSF from the hematopoietic compartment, particularly $CD4^+$ T cells, is essential for disease [17,26]. GM-CSF has long been recognized as an inflammatory mediator in the joints of patients with inflammatory arthritis. Although this has been extensively studied during the last 2 decades [19], recent data from murine models of autoimmunity have led to a reappraisal of the role of T cell-derived GM-CSF and its importance in arthritis. These data, together with the emergence of biologic agents targeting this cytokine, make the study of T cell GM-CSF expression and its regulation in human arthritis both timely and important. GM-CSF-expressing T cells in human autoimmune disease have a phenotype associated with ex-Th17 cells, coexpressing CD161 and IFN [70]. It has previously been shown that Th17 clones secrete GM-CSF [68], and also there is a role of IL-12 in driving Th17 plasticity toward a GM-CSF phenotype, and its possible role in arthritis [70]. The development of therapeutic antibodies targeting the GM-CSF receptor chain offers a valuable opportunity to test the importance of GM-CSF in JIA pathology, and early reports from rheumatoid arthritis studies are encouraging [12]. Irrespective of the cellular source, receptor blockade would abrogate the downstream actions of GM-CSF and may be a viable therapeutic option in treatment-resistant JIA.

Interleukin-18

Massive hypercytokinemia is strongly associated with the pathogenesis of macrophage activation syndrome [82] in JIA; however, the kinetics of cytokine release in patients with MAS are still unclear.

IL-18 was originally described as an IFN-γ-inducing factor mainly produced by activated macrophage lineage cells [42]. IL-18 stimulates a variety of inflammatory responses, enhances proliferation and activity of T cells and NK cells, and shifts the Th cell balance towards the Th1 response [34,35,67]. Some reports have recently shown that serum concentrations of IL-18 are highly elevated in patients with sJIA [54,65,69]. Abnormal production of IL-18 appears to be highly specific for sJIA. However, it is still unknown what causes the induction of extremely high IL-18 concentrations in the serum of patients with sJIA. IL-18 is the most effective at regulating NK cell activity, and it has been reported that decreased NK cell function is found in sJIA [36,37,84]. Recently, it was reported that the mechanism of the impaired NK cell function in sJIA involves a defect in IL-18 receptor β phosphorylation [23]. Further study will be required, but the non-functional IL-18/NK cell axis might be associated with the pathogenesis of sJIA.

Conclusion

Although it is uncommon to consider macrophages as the initiators of the pathogenetic cascade in rheumatoid processes, it is believed that these cells magnify local and systemic inflammation. At a local level, macrophages are involved in acquiring and activating inflammatory cells, cell contact, or cytokine-mediated activation and differentiation of neighboring cells, secretion of matrix-degrading enzymes, and neovascularization. At a systemic level, macrophages exaggerate disease through the acute phase response network, production of TNF-α and chronic activation of circulating monocytes.

Identifying the pathophysiology of rheumatoid diseases, such as juvenile idiopathic arthritis, merits further investigation. Trials involving reducing the numbers of activated macrophages, inhibiting the activation signal and their specific receptors, and counteracting the macrophage products raise the hope of optimizing the therapeutic success in suppression of joint inflammation and prevention of irreversible joint damage.

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