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Macrophage-Targeted Therapies for Rheumatoid Arthritis: Progress and Future Directions

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Abstract:

Considerable amounts of progress have been made to improve methods for treating RA within the past dozen of years. It is now clear that targeting macrophages in the development of RA is suitable for relieving symptoms or even for preventing them from developing. However, more research is to be done to promote the efficacy of current methods, as well as solving problems associated with frequent administration, sensitive reactions, and high doses. Treatment failures due to economical burdens are also problems to be solved. Macrophages are certainly linked with the progression of inflammation in the RA disease. In this article, we reviewed the role of macrophages and substances related to or secreted by them in the development of RA, and various treatments of RA targeting macrophages. Further research of macrophage behavior in inflamed joints with novel technologies may provide a better knowing of RA pathology, therefore helping develop RA therapies with less downsides.

Keywords: Macrophages; rheumatoid arthritis; cytokine inhibition.

1. Introduction

In 2019, there were 18 million patients with rheumatoid arthritis (RA) worldwide. In China, the incidence rate is 0.42%, and the total number of RA patients is 5 million. The peak incidence of this disease is between 40 and 70 years old, and the higher the age, the higher the incidence rate is. In 2009, the average annual total cost for RA patients in China was $3826, which was a heavy burden for both individuals and society. Among them, hospitalization expenses account for the largest share of direct costs, causing less than a quarter of RA patients to bear at least 43% and up to 75% of RA-related annual medical expenses.

Rheumatoid disease is a systemic autoimmune disease, affecting joints as the main symptom. The etiology of RA is still unclear. The early symptoms of RA include pain, swelling, stiffness, tiredness and weakness. Patients may as well develop constant low moods. As the condition progresses, joint symptoms can progress to joint abnormalities and muscle atrophy, leading to further loss of joint function. In early analyses, synovial macrophages (SMs) were considered to be wide-spreading, destructive, and

pro-inflammatory in the progression of RA. It is thought to be supporting the occurrence of acute disease. Therefore, deactivating the SMs selectively was thought to be an effective method to decrease inflammation and protect joints from being damaged. More modern analyses and ex vivo experiments have found that there are separate populations of SM in healthy and inflamed joints. These macrophages are found to be assuring protection in the synovial membranes and relieve symptoms of RA.

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Some macrophages exist as anti-inflammatory macrophages. They carry out efferocytosis, the phagocytosis of apoptotic cells, and produce growth factors for the cells that make up the surrounding tissue. This process promotes tissue repairment. Specific tissue resident macrophages (TRMs) play an essential role in preserving tissue homeostasis and, in the event that it is lost, aid in its recovery. TRMs also function as negative regulators of pro-inflammatory molecules, like IL-1RA, which helps to alleviate the symptoms of RA. By suppressing IL-1R, this reduces inflammation in the joints. Currently, the most widely approved Conventional synthetic disease-modifying antirheumatic drugs (scDMARDs), which has an impact on the damaged synovitis, macrophage components, and macrophage-associated metabolite levels.

This paper will provide an optimized processing direction for future research and a summary of some scientific frontiers of research progress, and provide some relevant information for patients to refer to. It is hoped that this article will be helpful to patients and doctors as well as future research.

2. Mechanism

The occurring of non-specific inflammation is considered to mark the start of the disease. Factors that may contribute to this inflammation include joint infection, intake of exogenous hormones, genetic factors, and environmental factors [1]. Women may have a higher risk of this, mainly due to pregnancy and other factors that may have an effect on one's hormone levels [2]. At the start of the disease, these factors interact with self-antigens and facilitate their citrullination. The immune system would then recognize the citrullinated self-antigens as invaders and promote an immune response. Antigen presenting cells (APCs) would display the antigens to T-helper cells, which release cytokines to stimulate the division of B-lymphocytes and activation of macrophages. After that, on one hand, cytokines secreted by macrophages would mediate the activation of osteoclasts and the apoptosis of chondrocytes, which lead to bone erosion and cartilage degradation in joints, respectively. On the other hand, the antibodies that are produced by plasma cells can also mediate lesions in other organs and tissues, such as lungs, eyes, and skin.

2.1 Inflammation Cytokines

In RA, cytokines are produced in excess amounts by macrophages. These cytokines promote the production of migrating immune cells, such as macrophages and neutrophils.

2.1.1 .IL-1

A major mediator in RA, IL-1 primarily mediates cartilage degradation and bone erosion. It increases levels of angiogenic factors and TNF-α and decreases osteoclast activity. Regulation of IL-1 and TNF-α is of crucial importance in the RA disease. The secretion and transcription of IL-1β in monocytes is stimulated by IL-1α. In sterile inflammation, IL-1β amplifies inflammation by recruitment of macrophages [3,4]. Studies have shown that the continuous overproduction of IL-1 compromises the host's immune system during the development of RA. IL-1 migrates immune cells which promotes inflammation toward the joints and synovium in RA patients. Joint breakdown is also promoted by IL-1, since it drives inflammatory leukocytes to the joints and activates synovial cells.

2.1.2 . IL-33

IL-33 belongs to the subfamily of the IL-1 family [5]. It has a major role in the development and exacerbation of RA and is markedly elevated in RA patients' serum and synovium [5]. Numerous cells, such as mast cells, T cells, macrophages, and even non-immune cells including chondrocytes, can interact with IL-33. Through the aforementioned cells, it can aid in the immune response as well as inflammatory and allergic reactions. NF-κB signaling downstream and IL-33R together activate the IL-33 molecule [6]. IL-33 stimulates the release of MHC class I and II molecules, such as TNF-α, IL-1β, and IL-6, when it interacts with macrophages. Through influencing the expression of costimulatory molecules and the cross-presentation of antigens in dendritic cells, IL-33 encourages T-cells to take part in the immune response [5]. Additionally, it stimulates the release of several cytokines

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from mast cells, which aids in some allergic reactions and inflammation of the joints. By stimulating chondrocytes, IL-33 will intensify joint inflammation and angiogenesis, aiding in the development of synovitis.

2.2 Macrophages

Macrophages and other immune cells are constantly being stimulated throughout the course of RA. They are the key cause of bone erosion and cartilage destruction. SMs can act as APCs, and therefore stimulating the action of pathogenic T-cells. Macrophages additionally promote the hypervascularization during the development of RA by producing angiogenic factors TNF-α, transforming growth factor (TGF) α/β, and vascular endothelial growth factor (VEGF) [5]. RANKL is the main mediator of bone resorption. Its expression is indirectly impacted by macrophages through other synovial cells. Macrophages can also differentiate in osteoclasts, which contributes to the breaking down of bone tissue by secreting acid, collagenase, hydrolytic enzymes and cathepsin K. Inorganic components are first dissolved, followed by the digestion of organic components by the creation of an acidic environment.

Macrophages are also found to have beneficial effects in RA. Anti-inflammatory macrophages carry out efferocytosis, the phagocytosis of apoptotic cells, and produce growth factors for the cells that make up the surrounding tissue, promoting tissue repairment [7]. TRMs express high amounts of anti-inflammatory mediators, for example IL-1RA. IL-1RA is a competitive inhibitor of IL-1 receptor. Once IL-1RA binds to an IL-1 receptor, the receptor would not be able to transmit signals to the cell. IL-1RA is able to counteract the effect of IL-1α and IL-1β, and is currently used to treat RA.

Currently, the treatment choices for inflammatory arthritis encompass oral medications, local or intra-articular anti-inflammatory drugs, surgical interventions, and physical therapy. However, developing new alternative treatments for inflammatory arthritis remains difficult due to the substantial economic impact and minimal improvements in treatment results.

Macrophages are essential to the pathophysiology of RA. Research has demonstrated that FLIP is required for macrophage survival and/or differentiation. Additionally, FLIP was discovered to be substantially expressed in RA synovial macrophages. The study aims to determine whether the reduction of FLIP in mouse macrophages 4 will decrease synovial tissue macrophages and improve serum metastatic arthritis. The researchers used Flipf/f LysMC/+mice with missing Flip in their myeloid cells and littermates as controls. Abdominal injection of K/BxN serum produces arthritis. Examine the ankle joint thickness changes and clinical scoring to determine the extent of the disease. You can also perform an immunohistochemical and histological examination of the joints. Based on the disease stage, the final observation results suggest that decreasing FLIP in macrophages by an increase in anti-inflammatory macrophages could be a useful treatment for reducing inflammation. The purpose of a different investigation is to investigate the pharmacological mechanism and effectiveness of naringin in the management of collagen-induced arthritis (CIA) [8]. Naringin was found to have an effect on RA by using a DBA/1 mice CIA model and giving various doses of the drug orally. Naringin has been demonstrated in experiments to exhibit its therapeutic impact in the CIA model through the reduction of inflammation, regulation of cytokine levels, and enhancement of antioxidant capacity. Furthermore, AMPK/ULK1 signaling pathway-mediated autophagy activation in macrophages appears to be a major factor in naringin‘s anti-inflammatory actions. Potential guidelines for the development of naringin-based anti-rheumatic medications are provided by this study [9].

According to certain research, several inhibitors that macrophages designed to understand the pathophysiology of RA have demonstrated significant therapeutic potential and efficacy in the management of RA. Macrophage migration inhibitory factor (MIF) is a multifunctional inflammatory cytokine that is associated with the etiology of autoimmune disorders, such as RA. It functions as an upstream regulator of both innate and adaptive immunity. Clinical research and development are underway for a number of MIF inhibitors. Through experiments on humans and animals, the researchers proved that MIF inhibition is an effective treatment for RA. Patients with high expression of MIF gene variants benefit most from mif-oriented therapy. Patients with RA who have high expression levels of MIF alleles may benefit from targeted suppression of MIF as a precise and efficient treatment [10].

TLR7-mediated immune metabolism in fibroblasts (FLS), RA macrophages (MΦs), and experimental arthritis was described by the researchers. The study discovered that TLR7-enhanced metabolic rewiring in RA MΦs and FLS is caused by GLUT1, HIF1α, cMYC, LDHA, and lactate. Additionally, TLR7-driven hypermetabolism, non-oxidizing PPP (CARKL), and oxidative phosphorylation (PPARγ) are narrowly dysregulated in TLR7-activated RA MΦs and FLS and can be reversed by IRAK4i. Treatment with IRAK4i interfered with the function of miR-Let7b/TLR7 in arthritis while causing damage to a variety of glycolytic intermediates, including GLUT1, HIF1α, cMYC, HK2, PFKFB3, PKM2, PDK1, and RAPTOR. TLR7-induced inflammatory markers of RA MΦs and

FLS were lessened by inhibition of the mutually elevated glycolytic metabolites HIF1α and cMYC. In line with IRAK4i, TLR7-enhanced IRF5 and IRF7 in RA MΦs were intercepted by HIF1i and cMYCi therapy, and IRAK4i was in line with HIF1i to counteract TLR7-induced CARKL.

Phylloprotein I (PPI) is one of the main components of phylloprotein nodules in Paris, and shows selective inhibition on various tumor cells [11]. The researchers studied the effects and mechanisms of PPI on the anti-rheumatoid arthritis of macrophages in vivo and in vitro. In vitro, primary bone marro-derived macrophages (BMMs) and peritoneal articulator macrophages (PEMs) were stimulated with lipopolysaccharide (LPS) and interferon (IFN-γ) and then treated with PPI. In vivo, PPI (1 mg/kg) was administered once daily in the stomach for 7 weeks starting on day 42 after the first collagen immunization in a mouse model of collagen-induced arthritis (CIA). PPI reduced the production of inflammatory cytokines in PEM stimulated by LPS/IFN-γ, inhibited the phosphorylation of IKKα/β and p65, and prevented p65 nuclear localization [12].

Osteoblasts, chondrocytes, and fat cells are just a few of the many cell types that mesenchymal stem cells (MSCS) can transform into. Apart from their ancestry, MSCs possess distinct immunomodulatory attributes that present novel prospects for addressing autoimmune disorders and could function as a propitious instrument in stem cell therapy. Accordingly, newly studied MSC-based treatments are thought to be a viable strategy for treating RA [13].

The traditional dosage forms of RA treatment have the drawbacks of high dose, frequent administration, sensitive reactivity, low reaction, high cost, and major side effects. They also have poor efficacy. An important area of concern is the development of stimulus-responsive drug delivery systems using nanomaterials with switching potential for biomedical applications, given the low bioavailability of non-targeted systemic cytotoxicity and pharmacological treatments. In order to effectively treat rheumatoid arthritis, researchers are also working on creating a range of nanoformulations that contain anti-inflammatory medications that can target inflamed areas either actively or passively. The pharmacological efficacy of nanoformulations is enhanced by changes in their surface area and nanoscale size, which result in advantageous physical and chemical properties. These medication-containing nanoformulations have the ability to target, enhance bioavailability, increase solubility of weakly water-soluble medicines, and maybe enhance therapeutic action [14].

3. Conclusion:

In the past few decades, significant progress has been made in the treatment of rheumatoid arthritis. Current research indicates that targeting macrophages has a good effect on alleviating RA symptoms and may even prevent further disease progression to some extent. This discovery brings new hope. However, in order to achieve more effective treatment, further research is needed to optimize existing treatment methods, particularly addressing issues of frequent dosing, drug sensitivity, and high-dose use. In addition, economic burden is also a challenge that cannot be ignored, as it may lead to treatment failure, therefore urgent measures need to be taken to address this issue. In rheumatoid arthritis, macrophages produce excessive cytokines, leading to inflammation and joint damage. Key cytokines include IL-1 and IL-33. IL-1 is pivotal in RA by mediating bone erosion and cartilage destruction, increasing angiogenic factors, and promoting inflammation through recruitment of immune cells. IL-33, elevated in RA patients, interacts with various cells to enhance immune responses and inflammation, contributing to joint inflammation and angiogenesis. Macrophages play a dual role; they drive bone erosion and cartilage destruction by acting as antigen-presenting cells and promoting hypervascularization through factors like TNF-α and VEGF, while also supporting tissue repair by performing efferocytosis and producing growth factors. Additionally, anti-inflammatory macrophages express IL-1RA, which inhibits IL-1 signaling and is used therapeutically in RA. Among many treatment methods, some technologies based on macrophages to find breakthrough points show special advantages in the treatment of RA. The researchers summarized some of these treatments and techniques, hoping to contribute to future research and treatment. FLIP is essential for macrophage function and exhibits high expression levels in RA synovial macrophages. Modulating FLIP levels in macrophages may attenuate inflammation and ameliorate RA symptoms. Naringin holds promise as a therapeutic agent for RA by mitigating inflammation and enhancing antioxidant capacity through autophagy. Inhibitors targeting MIF also demonstrate potential, particularly for patients with elevated MIF gene expression. IRAK4 inhibitors can disrupt TLR7-mediated metabolic alterations in RA macrophages and fibroblasts, thereby restoring metabolic balance and alleviating inflammatory dysfunction in RA.

PPI, a key component of phylloprotein nodules in Paris, selectively inhibits various tumor cells. Research shows that PPI reduces inflammatory cytokines in macrophages, inhibits NF-κB signaling, and alleviates symptoms of CIA in mice. PPI's effects include reduced bone erosion, syno-

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vitis, and immune cell infiltration, suggesting it has significant therapeutic potential for treating arthritis by targeting the NF-κB pathway. These treatments have some side effects, which should be corrected. summary, this article introduces the influence of macrophages on the course of RA disease, and introduces some inhibitors and other therapeutic methods based on macrophages for RA treatment and the other aspects are not deeply discussed and studied. In The researchers sincerely hope that the information in this article will help inspire future studies and doctors to develop better treatments for RA.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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