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Research Progress of M2 Macrophage

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Abstract: *M2 macrophages are polarized by macrophages under a variety of stimuli, including cytokines, micro-RNA and tissue microenvironment. M2 macrophages play a positive role in promoting wound healing, tissue recovery and immunosuppression, but they are also closely related to tissue and organ fibrosis and tumor occurrence and development. This article will review the research status of M2 macrophages from the aspects of the phenotype of M2 macrophages, the reasons for promoting M2 polarization of macrophages, and the significance and function of M2 macrophages.*

Keywords*: M2 macrophages, polarization, micro-RNA, cytokines, tissue microenvironment*

1. Introduction

Macrophages are an important part of the innate immune system of the human body and play an important role in the occurrence and development of inflammation and host defense. In response to various environmental factors (e.g., microbial products, damaged cells, activated lymphocytes) or under different pathophysiological conditions, macrophages are transformed into different functional phenotypes, namely classical activated macrophages (M1) and alternative activated macrophages (M2) [1].

2. Phenotypes and characteristics of M2 macrophages

M2 macrophages are mainly activated by macrophage colony-stimulating factor (MCSF), interleukin-4(IL-4), interleukin-13(IL-13) and other factors. M2 macrophages secrete anti-inflammatory cytokines such as interleukin 10(IL-10), transforming growth factor-β(TGF-β), interleukin 1 receptor antagonist (IL-1ra), chemokine CCL18, expression of arginase 1(Arg1), foundininflammatoryzone1 (Fizz1) and other products, which inhibit the proliferation and activation of T cells and regulate Th2 immune response. It is helpful to tissue remodeling and wound healing. In addition, M2 macrophages can be divided into M2a, M2b, M2C and M2d 4 subtypes according to the different stimuli of differentiation.

2.1. M2a macrophages

M2a macrophages are induced by IL-4 or IL-13 and express mannose receptor, macrophage cytosol clearance receptor 1, Arg1, Fizz1 and major tissue compatible complex II (MHC II). Secrete IL-12, IL-1ra, IL-8 and IL-10, which can promote Th2 immune response, participate in allergic reaction and kill phagocytic parasites.

2.2. M2b macrophages

M2b macrophages are induced by IL-1 β or immune complex, express CD163, CD86, MHC II, secrete IL-10 and chemokine CCL1, and mainly participate in immune regulation.

2.3. M2c macrophages

M2c macrophages are induced by IL-10 and glucocorticoids, secrete a large number of anti-inflammatory cytokines (IL-10, TGF- β, IL-1ra), mainly participate in tissue remodeling and matrix deposition. 4M2d macrophages are induced by Toll-like receptor (TLR) and adenosine A2a receptor

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agonist, and secrete IL-10 and vascular endothelial growth factor, which is mainly related to the promotion of angiogenesis and tumor growth.

3. Related hormones that promote M2 polarization of macrophages

3.1. Micro-RNA

MicroRNAs (miRNAs) is a kind of non-coding nucleotides with a length of about 20,25 nucleotides, which can regulate gene expression at the translation level, and it can regulate the expression of hundreds of genes in epigenetics. therefore, more and more studies have begun to focus on the regulatory role of miRNAs in macrophage polarization. MiRNAs has been shown to be involved in macrophage polarization by regulating the expression of various proteins and transcription factors. The change of miRNAs level in macrophages should affect the phenotypic transition between M1 and M2. Such as miR-124, miR-223, let-7c, miR-132, miR-146a, miR-125a-5p have been proved to induce macrophages to M2 polarization [3].

MiRNAs can not only promote the M2 polarization of macrophages, but some miRNAs can inhibit the M2 polarization of macrophages. For example, MicroRNA-720 can inhibit M2 polarization of macrophages by targeting GATA3[4], and exocrine microRNA-34a secreted by adipocytes can inhibit M2 polarization of macrophages [5]. In addition to promoting and inhibiting M2 polarization of macrophages, some studies have found that individual miRNAs synthesis can also regulate the polarization of macrophages. LncRNA-MM2P is a specific regulator of M2 polarization, which plays a role through STAT6 signal pathway [6].

3.2. Tissue microenvironment

Many studies have found that tissue microenvironment is also one of the stimulating factors to stimulate the polarization of macrophages. The polarization trend of macrophages is different in different tissue microenvironments. For example, in tumor microenvironment, it has been proved that chemical stimulation in tumor tissue can change the behavior of macrophages, and tumor-associated macrophages (TAMs) are also considered to be one of the phenotypes of M2 macrophages, promoting tumor progression and representing poor prognosis [7]. In addition, interstitial fluid flow (IF) in tumor microenvironment can polarize macrophages to M2-like phenotype [8], and THP-1-derived macrophages can also polarize to M2-like macrophages when suffering from chronic iron overload [9].

In addition, in the tissue microenvironment, the molecular arrangement and structure of substances can also affect the M2 polarization of macrophages. For example, on the surface of nanofibers, the arrangement of nanofibers greatly stimulates macrophages to extend along the nanofibers and, more importantly, induces the development of macrophage phenotypes (M2) that promote healing [10]. At the same time, the change of surface roughness of titanium coating can also affect the polarization of human macrophages into different phenotypes. The rough titanium coated surface decreased the initial adhesion ability of macrophages, and only a few rough surfaces (Ra=0.51~ 1.36 μ m; Sa=0.66~ 2.91 μ m) tended to polarize macrophages to M2 phenotype [11].

3.3. Cytokines

Many studies have confirmed that cytokines promote the polarization of macrophages. Because M2 macrophages can be further divided into four phenotypes: M2a, M2b, M2C and M2d, these four phenotypes have different stimulating factors. Among them, macrophages stimulated by IL-4 and IL-13 showed M2a phenotype, macrophages triggered by TGF- β and glucocorticoid showed M2c phenotype, and IL-6 induced M2d macrophages characterized by CD80, CD86, MHC-II and IL-15 [12-14]. In addition, transcription factor MafB also plays a key role in regulating macrophage polarization. MafB can enhance the expression of anti-inflammatory M2 polarization marker gene and inhibit the expression of pro-inflammatory M1 marker gene in macrophages, thus promoting M2 polarization of macrophages [15]. According to WheelerKC et al, VEGF may contribute to the recruitment and M2 polarization of decidual macrophages [16].

3.4. Other factors

The M2 polarization of macrophages is stimulated by many factors. After research, some natural

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compounds can also promote M2 polarization of macrophages. For example, natural compounds such as luteolin, saffron and ginsenoside Rb1 have been found to promote M2 polarization of macrophages [17-18], curcumin can prevent macrophages from polarization to pro-inflammatory M1, and promote the transfer of macrophages and polarized M1 macrophages to anti-inflammatory M2 [19].

In addition, some biometabolites can also promote M2 polarization of macrophages. For example, butyrate, a microbial metabolite, promotes the polarization of macrophages toward M2 [20]. 5Pentamethoxyflavone can not only promote M2 polarization of macrophages, but also inhibit M1 polarization of macrophages [21]. In addition, exocrine MALAT1 from endothelial cells treated with oxidized low density lipoprotein can also promote M2 macrophage polarization [22]. Even cellular metabolites in some pathological environments can promote M2 polarization of macrophages, for example, pancreatic cancer-related fibroblasts promote M2 polarization of pancreatic ductal adenocarcinoma macrophages [23]. In addition, it has been found that many compounds can also promote M2 polarization of macrophages. D series hemolysin 2 (RvD2), phenylenediamine compounds FC-99, α-linolenic acid (ALA), 22 carbon hexaenoic acid, 1,25-dihydroxyvitamin D3, ω-alkyne peanut tetraenoic acid and other compounds can promote M2 polarization of macrophages [24-29].

According to the study, M2 polarization of macrophages can even be realized by physical methods. LeeCH et al found that bivalent cations on the implanted surface of nanostructured titanium modulate the bioactive ion chemistry of macrophages polarized J774 and regulate the morphology of adherent macrophages, which significantly changes the phenotype of macrophages from inflammatory M1 macrophages to tissue healing M2 macrophages [30].

4. The role of M2 macrophages

4.1. Positive effect

First of all, M2 macrophages are involved in inflammation regression and wound healing. According to the research of KasuyaA et al, M2 macrophages play an important role in hair growth and wound healing [31]. The results of SuzukiK et al show that M2 macrophages can be a new therapeutic target for the treatment of allergic contact dermatitis [32]. Secondly, M2 macrophages have a protective effect on nerves. M2 macrophage adoptive transfer reduces neuropathic pain through opioid peptides[33]. Galectin-3 in M2 macrophages plays a protective role in neuropathology of brain parasite infection by regulating the conversion of neutrophils [34]. In addition, M2 macrophages play an important role in regulating tumor initiation, growth, metastasis, angiogenesis, immunosuppression and so on. M2 macrophages have a profound inhibitory effect, suggesting that M2 macrophages play a key role in preventing the expansion of small aneurysms [35].

The most important role of M2 macrophages is to promote osteogenesis and angiogenesis. M2 polarization of macrophages can induce preosteoblast differentiation and increase bone mineralization [36]. According to the study of periodontal stem cells by LiuJ et al, the transition of macrophages to M2 polarization in the early stage of tissue repair contributes to the enhancement of periodontal regeneration after stem cell transplantation [37]. In addition, M2 macrophages can also cooperate with other cells to promote osteogenesis. Liu J et al.'s results show that adipose stem cells and M2 macrophages cooperate to promote the repair of bone injury [38].

4.2. Negative effect

Many studies have shown that M2 macrophages play a positive role in inflammatory healing, osteogenic angiogenesis and so on. However, M2 macrophages can also have some negative effects on the body. Among them, M2 macrophages promote the myofibroblast differentiation of rat mesenchymal stem cells and are related to lung fiber formation [39]. According to deSouzaAWS et al., M2 macrophages are also the main phenotype of airway inflammation in patients with granuloma complicated with polyvasculitis [40]. The latter can promote the occurrence and metastasis of tumor cells, inhibit T cell-mediated anti-tumor immune response, promote tumor angiogenesis, and lead to tumor progression [41].

5. Conclusion

Macrophages are a kind of cells with strong heterogeneity and plasticity, but they have different effects on the polarization of macrophages in different microenvironments, and they play an important

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role in the processes of pathogen clearance, wound healing, tissue remodeling and immune regulation. Macrophage polarization participates in the process of infection, metabolism and immunity, as well as the occurrence, development and prognosis of tumors and other diseases. In-depth study of the regulation mechanism of macrophage polarization will provide new clues for the study of the occurrence and development mechanism of related diseases, and may also become a new target and method for the prevention and treatment of a variety of diseases. Among them, M2 macrophages have a variety of functions, including promoting the growth of blood vessels and bone, reducing pain and even inhibiting tumor progression, as well as neuroprotective effects. Although M1 macrophages are necessary for bone healing, continuous M1 activation will hinder healing. At the same time, many studies have shown that M2 macrophages play an active role in extracellular matrix remodeling and wound stabilization. In addition, people have gradually found the factors that promote the M2 polarization of macrophages, which shows that researchers can regulate M2 macrophages through a variety of ways, so as to make full use of the positive role of M2 macrophages, and try to avoid its negative effects. Therefore, M2 macrophage is the current research hotspot, especially its function of promoting osteogenesis and angiogenesis provides a new idea for the study of tissue defect repair and biological combination of external implanted materials.

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