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Study on the polarization pathways of macrophages and related diseases

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Abstract: *Macrophage is a relatively stable heterogeneous immune cell isolated from monocytes in plasma, which plays a certain role in maintaining stable environment, host defense, phagocytosis and immune information transmission. Under the influence of different environmental factors, macrophages can be polarized into Ml and M2, and this process is reversible. The special phenotype of macrophage polarization can play a role in alleviating or curing the disease, and the polarization process is affected by the stimulation of different signaling pathways [1]. This chapter will review the classical types of macropage polarization, the most important information pathways and regulatory mechanisms, in an attempt to provide a basis for subsequent regulation and the occurrence and progression of lesions.*

Keywords: *Macrophage polarization, Classical activation, Vicarious activation, Signaling pathways*

1. Introduction

Macrophages originated from bone marrow are innate immune cells, differentiated from monocytes, and play roles in stabilizing the internal environment, host defense, phagocytosis and immune information transmission.Macrophages play an important role in atherosclerosis, heart infarction, liver cancer, systemic lupus erythematosus, pregnancy regulation, obesity and malignant inflammatory transformation of tumors.Macrophages live in a complex environment in vivo and can be transformed into M1 macrophages and M2 macrophages by different environmental stimuli.Among them, the polarization process of macrophages is affected by various environmental factors [1], such as different information pathways, complexity of transcription factors, genetic factors and so on.It is generally believed that Notch, JNK, JAK-STAT and PI3K/Akt are the main signaling pathways.Studying the polarization pathway of macrophages is helpful to understand the occurrence and outcome of diseases and provide new ideas for targeted prevention and treatment of related diseases.

2. Methodology

2.1. Types of macrophages

Macrophages are the main components of the human innate immune system, with extensive atypia and plasticity.Analysis results showed that the variation of macrophage performance was mainly affected by the microscopic environment [2].The plasticity of macrophages can adaptively respond to different kinds of signaling substances of pathogens, and corresponding substances are produced by activated lymphocytes.These developmental properties are usually referred to as macrophage polarization, and according to the differences in biological characteristics, reversibility includes M1 and M2 macrophages, tumor-associated macrophages (TAM) and other macrophage subgroups [3].

(1) M1 macrophages, also known as classically activated macrophages, are mediated by Th1 protein and are related to the production and progression of some diseases or pathological stages [4].Current scientific studies have proved that, under the influence of lipopolysaccharide (LPS) or IFN-ϒ factor, macrophages tend to polarize into Ml type, highly express IL-12 and IL-23 factors, and reduce the cellular characteristics of IL-1 factor, thereby producing reactive oxygen species (ROS), inducible nitric oxide synthase (iN0S), and a large amount of TNF-ɑ.Proinflammatory factors such as IL-6 and IL-1β.M1 macrophages can show strong bactericidal characteristics and participate in the early inflammatory

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reaction of the body, but their continued development helps to promote the continued destruction of tissues and aggravate some persistent inflammatory reactions.

(2) M2 macrophages, known as alternately activated macrophages, are characterized by high activation ability of inflammatory macrophages, such as IL-10, IL-13, transforming and proliferating mechanism (TGF-β) [5], etc. They have functions in cellular immunology such as inhibiting inflammatory reaction, removing cell debris, promoting tissue repair and stabilizing the microenvironment.M2 type macrophages were further divided into four types, namely M2a type, M2b type, M2c type and M2d type ① macrophages, which were stimulated by IL-4 and IL-13, and showed anti-inflammatory factors such as ARG-1, IL-10, TGF-β, FIZZl, Yml/2, CCL22 and CCL24, which were anti-inflammatory and pro-repairReplicating and clearing local infection with parasites [6];②M2b type produces a large amount of anti-inflammatory molecules such as CD86, IL-1, IL-6, TNF-α, which stimulates the immunity of Th2 type lymphocytes [7].③ The factors produced by M2c type include cDl63, CD206, IL-10, TGF-β, CXCLl3, MERTK and some extracellular matrix, which also have anti-inflammatory and pro-repair effects.(4) M2d type inhibits proinflammatory process, induces vasculogenesis process, and promotes tumorigenesis and metastasis in vivo [8].

2.2. Signaling pathways and regulatory mechanisms of macrophage polarization

In recent years, with the continuous in-depth discussion on the polarization of macrophages, it is believed that the relatively perfect pathway is mainly through JAK/STAT signal channel, P13K/Akt signal channel, JNK signal channel, Notch signal channel.This chapter mainly introduces four well-studied information pathways and related regulatory mechanisms.2.1Notch Signaling pathway Notch signaling pathway has been shown to promote inflammation and enhance M1 polarization of macrophages [9].Bai et al. [10] found that lipopolysaccharide (LPS) can enhance the expression of macrophage Notch-1 and induce the activation of downstream Hes1 and Deltex gene expression. If RBP-J leading factor is knocked down and stimulated by LPS again, macrophages can no longer polarize to M1 type, but to M2 type [11]

(1) The relevant regulatory mechanism of Notch pathway has been found that NF leading B/Hmgbl/lincRNA/Tnfaip3 complex in macrophages can activate and regulate NF- leading B inflammation genes after LPS stimulation [12]. After LPS stimulation, the SWI/SNF complex and LincrNA-CoX2 factor are recruited to the promoter/enhancer region of Saa3 and Ccl5 genes, thereby promoting the binding of RelA and P50 subunit at the SWI/SNF complex, promoting the methylation of H3 histones, and finally initiates its transcription process [12].

JanusKinases (JAK) -message transducers and gene activators (STAT) pathways are the main channels of message transduction in bacteria, which regulate and participate in the inflammatory response of the body.It is closely related to the occurrence and outcome of lung cancer, ulcerative colitis and other diseases [13]

(2) Regulation mechanism of JAK/STAT signaling pathway JAK/STAT signaling pathway realizes and controls cytohormone signaling through negative feedback regulation, which is generally regulated by cytohormone delivery control factors (SOCS), protein tyrosine phosphatases (PTPs) and activated STAT gene activity control genes (PI)AS).SOCSl is an endogenous inhibitor of STATl pathway. If JAK/STAT signaling channel is opened, KIR and SH-2 domains should be used to promote the polarization of M2 macrophages.SOCS3 is a negative feedback regulator of STAT3, and its expression rate is negatively correlated with the polarization of M2 high type [14].The combination of PIAS with activated STATl and STAT inhibits the STAT transcriptome process and negatively regulates this pathway.Recent studies have found that a kind of lncrNA-MAC0ris (Mac0RIS) can promote the phosphorylation of both JAK2 and STATl induced by IFN- ⌴ factor, and eventually polarize macrophages toward M1 [15].

(3) P13K/Akt information pathway, which can lead to various diseases such as tumors, type II diabetes and heart disease if disturbed [16]. P13K converts phosphatidylinositol 4,5-2 phosphate (PIP2) to phosphatidylinositol 3,4, 5-triphosphate (PIP3).The fusion of PIP3 and the PH domain of Akt promotes the translocation of Akt to the plasma membrane and phosphorylation of Akt to stimulate the activation of Thr308 and Ser473 factors. Activated Akt controls cell activities by controlling the transcriptional function of downstream target genes [17].

Regulation Mechanism of P13K/AKt signaling pathway At present, many feasibility has been proposed for P13K, AKt and MTOR control agents and cell targeted therapies using P13K/MTOR

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complex as P13K/AKt channel, and the purpose of prevention and treatment has been achieved by interfering with these channels, but specific studies on many molecules have not been carried out.BAO et al. [18] believed that miR32 guided the polarization of macrophages toward M2 by down-regulating PTEN-stimulated P13K/AKT signaling channels.OHASHI et al. [19] suggested that glycogen synthase kinase 3β(GSK-3β) could act as an anti-inflammatory feedback regulator of P13k/Akt signaling channels.LIU[20] et al. believed that silencing signal regulator 1(Sirt1) improved macrophage phenotype through this pathway, while controlling the P13K/Akt pathway could partially control the anti-inflammatory function of Sirt1 and STAT6 translocation. In Sirt1+/- mice,IL-18 and InosmRNA levels were significantly increased, and STAT6 andArg1 expression was significantly decreased, while activation of Sirt1 increased the phosphorylation of STAT6.2.4JNK signaling pathway C-Jun N-terminal active kinase (JNK) is a mitogen-activated protein kinase (MAPK). The main composition of MAPK channel is a 3-level kinase pattern, including MAPK kinase kinase (MKKK),MAPK kinase (MKK) and MAPK3 kinases activated sequentially. JNK pathway regulates cellsProliferation and apoptosis, the inflammatory process of related lesions, and the pathological process of diseases such as heart disease all play a major function [21]. This pathway can be stimulated by many endogenous factors and environment, such as ROS, biological antigens and related inflammatory factors such as interleukin-4 (IL-4) [22].Il-4 can increase the expression of down-cursors c-MYc factor and reduce the migration of macrophages to M2 type by controlling JNK signaling channels. The conclusion indicates that JNK pathway regulates macrophage immune response in human body by increasing the polarization of M2 phenotype and secreting anti-inflammatory factors.

(4) Mechanism of JNK signal channel regulation There are two main mechanisms of JNK signal channel regulation. One is the recognition of MKKK and MKK, MKK and MAPK sequences, and the other is the formation of a complex between level 3 kinase pattern and scaffold protein.MAPK binds specifically to MKK through the common docking domain and glutamate and aspartic acid domains, which promote substrate identification, orientation, information transfer specificity and protein complex assembly [23].Certain molecules, such as JNK inhibitors, compete with or inhibit the processes that regulate JNK channel activation.Scaffold proteins can promote normal subcellular localization, thereby mediating the conduction of different information and supporting the generation of more protein complexes. Scaffold proteins themselves do not have catalytic function, and can change the localization site of MAPK signaling pathway by fusing with some special domains and proteins.

3. The relationship between macrophage polarization and different inflammatory diseases

In the early stage of inflammation, macrophages first transform into M1 phenotype to promote inflammatory response. At this time, inflammatory macrophages are beneficial to the body and promote cell phagocytosis.As the disease progresses to the later stage of inflammation, macrophages gradually transform into M2-high type and produce a large amount of anti-inflammatory factors such as IL-10 and IL-6, which inhibit the progression of inflammation, promote the remodeling of injured tissues, angiogenesis and maintain the balance and stability of the microenvironment [24].This process is dynamically reversible, that is, with the change of microenvironmental conditions,M1 and M2 types can be converted to each other [25].The polarization of macrophages, the emergence of two polarization states in succession throughout the whole process of the disease, is the necessary stage to terminate inflammation.The study of macrophage polarization is very important for the diagnosis and treatment of macrophage-mediated diseases.

3.1. Macrophage polarization and inflammatory bowel disease (innammatoryboweldisease, IBD)

IBD in clinical performance as the main manifestation of crohn's disease, IBD etiology has not been clear at present, among them, the intestinal M1 / M2 macrophages imbalance is considered to be one of IBD pathogenesis factors [26]. Cytological detection in the colon of IBD patients showed that a large number of M1 and a small number of M2 macrophages co-existed [27], which provided a new idea for the study of curing IBD.

Some studies have shown that increasing the local M1/M2 type ratio leads to progression of IBD.QUALLS et al. [28] demonstrated that depletion of mononuclear phagocytes leads to a decrease in M2-type macrophages and a significant decrease in IL-10 levels, while the levels of proinflammatory cytokines such as IFN γ and TNF-α are not affected, thus making mice more susceptible to DSS-induced colitis.Il-10 is a key factor in maintaining intestinal homeostasis. Studies have found that mice with IL-10 knockout will develop spontaneous IBD[29], and patients with IL-10 receptor (IL10R) deficiency will

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also develop severe childhood IBD[31].HUNTER et al. [30] believed that YAP could effectively reduce the polarization of type M2 macrophages induced by IL-4/IL-13, and promote the activation of type M1 macrophages by lipoextracellular polysaccharide /IFN- to form IL-6, and confirmed that YAP could induce inflammatory bowel disease by regulating the polarization of type M1/M2 macrophages [31].It was recently found that in DSS-induced mice treated with genistein, the reduction of M1 macrophages and the increase of M2 macrophages ameliorated experimental colitis [32].In addition, Lactobacillus lactis EJ-1 can inhibit NF- B signaling and polarize to M1 macrophages, which can alleviate colitis.TANG et al. [33] showed that oxytocin reduced the sensitivity of macrophages to LPS stimulation and the expression of inflammatory cytokines IL-1β, IL-6 and TNF-α, but enhanced the sensitivity of macrophages to IL-4 stimulation and increased the expression of anti-inflammatory factors Arg1, CD206 and chitinase-like 3(ChI3).In addition, many Chinese herbs such as small alfan can control M1 polarization of macrophages by AKT1/SOCS1/NF- B signaling pathway, thereby antagonizing DSS-induced colitis [34].Baicalin can also promote the transformation of M1 to M2 macrophages by upregulating the expression of IRF-4 protein, thus effectively alleviating the symptoms of colitis in mice [35].Arctiin can up-regulate IL-10 level by inhibiting the expression of IL1-β, TNF-α and IL-6, and treat TNBS-induced colitis [36].It provides a new idea for the treatment of IBD by combining traditional Chinese and western medicine.

3.2. Macrophage polarization and autoimmunehepatitis (AIH)

AIH is a substantial chronic inflammatory disease of the liver. The mechanism of AIH is not fully understood, but it can develop into liver fibrosis, cirrhosis, and liver failure in severe cases. At present, there are no reliable large-scale epidemiological studies in China. Polarization of immune cells, especially macrophages, is involved in the pathogenesis of autoimmune hepatitis [37].Using the ConA-induced hepatitis model, LIU et al. [38] found for the first time that the expression of IL-34 in the liver of CONA-treated WT mice was lower than that of negative control mice, suggesting that IL-34 may play a protective role in ConA-induced liver injury. They concluded that IL-34 may inhibit inflammation by driving macrophages to M2 phenotype polarization in AIHDisease to prevent liver damage.

Similarly, regulating the transformation of inflammatory macrophages to anti-inflammatory phenotype is also an effective method for the treatment of AIH. Recently, some researchers have pointed out that the alcohol extract of the juglaceae plant Maupen can reduce the contents of serum IL-6 and TNF-α, and thus effectively resist AIH caused by ConA, which may be related to the inhibition of STAT3 phosphorylation [37].

However, it is interesting that IL-6 and TNF-α both belong to the proinflammatory factors secreted by M1 macrophages. Whether the mechanism of the effect of the alcohol extract of maple is also related to the polarization of macrophages deserves further investigation. At present, there is no effective treatment for AIH1, so in-depth study of its pathogenesis has profound guiding significance for clinical practice. Macrophage polarization has also become a popular cutting point for the treatment of AIH in recent years.

3.3. Macrophage polarization and asthma (AA)

AA is a chronic inflammatory disease characterized by airway hyperresponsiveness. The disorder of lung macrophage phenotype regulation is also one of the mechanisms of AA infection. It is widely believed that M2 macrophages contribute to the repair of tissue repair and the repair of lung tissue microenvironment homeostasis. However, excessive number of M2 macrophages can accelerate cell recruitment and mucus secretion, resulting in airway hyperresponsiveness. MOREIRA et al. [39] transferred M2 phenotype macrophages into the lungs of fungus-induced AA mice and found that the inflammatory response was enhanced, accelerating the pathological process of AA [40].Recent studies have confirmed that ATP/P2X7R activates P2X7R to induce the polarization of M2 lung macrophages and inhibit the polarization of M1 lung macrophages, which is involved in the pathogenesis of AA. This finding further confirmed the leading role of M2 macrophages in the pathogenesis of AA.

In patients with more severe forms of AA, especially those resistant to glucocorticoids, macrophages mainly exhibit M1 phenotype, and thus form a large number of pro-inflammatory mediators, such as TNF-α, IL-1, IL-1β and NO, which aggravate lung damage and promote bronchiolar remodeling [41].For example, in a mouse model of allergen-induced airway disease, NO produced by the M1 phenotype leads to oxidative DNA damage and inflammation, increases mucus production, and amplifies the lung injury mouth.In cockroach extract (cockroachextract, CRE) found that AA mice model of the induction of MSC

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can be triggered by aromatic hydrocarbon receptor (AHR aromatichydmcarbonreceptor,) signal from macrophages proinflammatory M1 phenotypic pole into anti-inflammatory M2 phenotypes [42].In addition, hydrogen inhalation can promote the phagocytosis of alveolar macrophages induced by Ovalbumin (OVA) in AA mice, which may be related to the antioxidant effect of hydrogen and the activation of Nrf2 pathway [43].It is still controversial which type of lung macrophages is dominant in the pathogenesis of AA, but macrophages are undoubtedly a key link to explore its pathogenesis, so regulating the polarization balance of macrophages is also an important way to solve AA clinically.

3.4. Macrophage polarization is the same metabolic dysregulation as obesity

Which can eventually lead to insulin resistance, glucose intolerance, hyperlipidemia and hypertension. Existing data, points out that obesity is a low inflammatory disease [44], associated with the activity of macrophages, when the obese body macrophages to secrete a variety of inflammatory medium, such as chemokines, tumor necrosis factor and free fatty acids that macrophage activation, activation of macrophages after secretion of proinflammatory factor can block insulin action and ultimately lead to glucose intolerance[45].Therefore, the etiology of obesity may be related to the imbalance of macrophage polarization. Recent studies have shown that glucose-regulatedprotein94 (GRP94), as a new regulator, is highly related to the polarization of M1 macrophages, insulin resistance, and the occurrence and development of inflammation [46]

As one of the ways to treat obesity, adjusting the proportion of macrophage M2 has gradually become a new treatment hotspot. Recent studies have found that Spexin(SPX), as a novel adipokine, has been confirmed by GAMBARO et al. [47] that SPX can reduce the polarization ratio of M1 macrophages through the induction of mature adipocytes, thereby improving obesity [47].In addition,M1/M2 macrophage transformation is also an effective treatment for obesity. Previous studies have confirmed that the loss of inhibitory transcripts of inflammatory cytokines in macrophages in obese patients can eventually lead to the imbalance of the proportion of M1 macrophages and the disorder of metabolic system [48].Above all, the study of macrophage polarization plays an important role in the treatment of obesity.

4. Discussion

Macrophages not only play an important role in inflammatory diseases, but also participate in the pathological process of many metabolic diseases, infection, atherosclerosis, sepsis, cancer and other diseases. The treatment strategy centered on regulating the polarization balance of macrophages has been increasingly paid attention to and adopted by researchers at home and abroad. Various kinds of macrophages have distinct functions in the activation, protection, mitigation, diagnosis and immune regulation of inflammation. In various types of inflammatory environments, macrophages can be polarized into M1 and M2 types of macrophages, and the polarization inhomogeneity and mutual transfer of M1/M2 macrophages point out the research direction for further diagnosis of inflammatory diseases. Although in recent years, the study of macrophage polarization has been greatly improved, but there are still many areas need to be researched: (1) macrophage polarization is a kind of dynamic change, the current monitoring only stay at some point the fixed environment, and in the future to be thinking about how to take the initiative to monitor and more effective to the observation of the change trend; Macrophages (2) people and animals have huge difference, not an introduction to, there is uncertainty, while the current experiment results in the future, but should also study through the homologous experimental studies in mice, as far as possible to reduce because of macrophages in the difference caused by different acquisition of the source, to the study of macrophage polarization effect in various cancers of higher solution;(3) people because of the complexity of the research structure of various kinds of macrophage, and the complexity of the information channel transduction and regulation, information channel and a variety of bacteria complex network connection, makes the research of macrophage phenotype transformation process has huge uncertainty, so must be studying the information of the macrophage polarization way and regulation mechanism to carry out in-depth study.

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