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Review

Is macrophage polarization important in rheumatoid arthritis?

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ABSTRACT

Macrophages are myeloid immune cells which are strategically positioned throughout the body, where they engulf and degrade debris, dead cells, and foreign substances, and coordinating the inflammatory processes. Macrophages can be divided into two extreme subsets, classical activation (M1), and alternatively activation (M2). The symptoms and signs of rheumatoid arthritis (RA) would exacerbate with the increase in pro-inflammatory cytokines, whereas anti-inflammatory cytokines will alleviate the symptoms and signs of RA. This review, mainly discusses the effects of Notch, JNK and ERK signaling pathways on the regulation of macrophage polarization, and the effects of pro-inflammatory factors and/or anti-inflammatory cytokines produced by polarized macrophages in RA. Also, we will make an attempt to find out the importance of macrophage polarization in RA treatment as a drug target.

1. Introduction

Rheumatoid arthritis (RA) is a common chronic autoimmune disease with unknown etiology so far. The main pathological process of RA is the abnormal activation of the immune system, monocytes and other immune cells enter RA synovial tissue leading to synovitis and synovial hyperplasia. This is an important reason for RA induction and enhancement [1]. Glucocorticoids and non-steroidal anti-inflammatory drugs (NSAIDs) are currently widely used in the treatment of acute joint swelling and pain; disease-modifying drugs: such as methotrexate (MTX) and biologics (like TNF-α inhibitors) are widely used in the treatment of RA patients [2–4]. However, complete remedy has not been realized, thus it is urgent to develop new effective drugs and/or to clarify the pathogenesis.

In recent years, the role of macrophages in inflammation was studied gradually. In general, when a pathogen enters the body, mature DCs present antigens to Th cells, naive T cells, macrophages get activated, and perform specific immune responses, then macrophages detect and engulf exogenous foreign body [5]. At the same time, macrophages can secrete inflammatory factors, destroy pathogens, and secrete anti-inflammatory factors to protect organs, this property is caused by macrophages in accordance with the local environmental specific differentiation. Two different polarization states of macrophages have been identified: M1 macrophages mainly secreted several proinflammatory cytokines such as TNF-α and IL-1, which are responsible for joint destruction; the antiinflammatory cytokines IL-10, TGF-β primarily secreted by M2 macrophages which always be used to the treatment of RA [6–8]. Different phenotype of macrophages has very different effects on RA. In this review, we provide an overview of different types of macrophages with important roles in RA pathogenesis and how drugs affect macrophage polarization to improve RA signs and symptoms.

2. The origin of the macrophages study in mice

In the 1960s, Van Furth put forward the famous mononuclear phagocyte system (MPS) theory that all macrophages originate from the monocyte, which has been a common perception in the past 40 years, despite the evidence suggests that macrophage tissue is independent of circulating monocytes [9–12]. During the infection phase, monocytes differentiate into macrophages or dendritic cells during peripheral blood migration. The migration and differentiation of these tissues into inflammatory DC and macrophages may be identified by inflammatory disorders and pattern recognition receptors [13]. Investigative results show that under the stimulation of granulocyte-macrophage colony stimulating factor (GM-CSF) and IL-4, the monocytes of human and mice differentiate into DC [13]. In the role of transforming growth factor (TGF-β), can induce cells similar to Langerhans cell phenotype, macrophage colony-stimulating factor (M-CSF) can induce monocytes to differentiate into macrophages, eventually under the action of the body-related signals, through the capillary wall into the different local tissue, transformed into tissue-resident macrophages [14,15]. However,

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in the past few years, a series of more authoritative publications have greatly changed our understanding of the origin of macrophages by demonstrating that several macrophages are actually established during embryonic development independently and continue to enter the stable state of adult blood mononuclear cells [16–22]. In the early stages of pregnancy (embryonic day 6.5 ([E6.5]–E8.5), macrophages first appear in the yolk sac, the yolk sac only produces macrophages and erythrocytes, macrophages are the only "white blood cells" at this stage [16]. Subsequently (E8.5–E10.5), definitive hematopoietic stem cells (HSCs) from the aorta-gonad-mesonephros caused all immune lineages. Starting at E10.5, HSCs migrate to fetal liver, then, as the main hematopoietic organ in the remainder of embryonic development, only in perinatal period, the traditional bone marrow hematopoietic stem cells become an important part of hematopoiesis system, and generate a complete immune lineage [23]. Therefore, it can be concluded that macrophages mainly come from two aspects: the first is that precursor of mononuclear cells derived from bone marrow, into tissues or organs in the blood under the action of the formation of tissue resident macrophages or inflammatory macrophages; another widely held theory is that macrophages are derived from yolk sac and fetal liver, and then transferred to the body. Myb is an important regulator of hematopoietic stem cell differentiation, but has no effect on yolk sac hematopoiesis [24]. In Myb null homozygous mice, the yolk sac macrophages of the embryo develop normally, but due to lack of hematopoietic stem cells, the bone marrow cells of CD45. 1; $Myb^{+/+}$ mice were injected into the CD45. 2; $Myb^{-/-}$ mice treated with myeloablative pretreatment, macrophages from peripheral tissues of mice expressed the phenotype of donor hematopoietic cells CD45.1, nevertheless, the liver, epidermis and brain macrophages still retain the phenotype of CD45.2 derived from the hematopoietic cell of the mice, this suggests that macrophages from the liver, epidermis, and brain originate from the yolk sac, but not the hematopoietic stem cell [21]. In a follow-up study, the researchers found the brain (microglia) almost from Yolk sac; and liver [Kupffer cells (KCs)], epidermis [Langerhans cells (LCs)], most come from fetal liver and monocytes small part comes from Yolk sac; other macrophages such as red pulp macrophages, alveolar macrophages and peritoneal macrophages primarily come from fetal liver and monocytes; while, in the gastrointestinal tract, a large number of tissue intrinsic macrophages are derived from monocyte differentiation [16,25,26]. The generation processes of macrophages in different tissues are different (Fig. 1).

3. Macrophage polarization and classification

Cumulative evidences show that macrophages undergo reprogramming in the microenvironment and become classical activation (M1) and alternative activation (M2) phenotype [6–8]. M1 phenotype activated by Th-1 cytokine interferon-γ (IFN-γ) or lipopolysaccharide (LPS) [27,28], plays an important role in the initiation and development of inflammation by producing a large number of pro-inflammatory factors, such as IL-6, IL-1β, TNF [29], as well as IL-23, IL-12 [30]. The M1 phenotype highly expressed toll-like receptor 4 (TLR4), cluster of differentiation 86 (CD86), major histocompatibility complex class II (MHC-II), inducible nitric oxide synthase (iNOS/NOS2), and IL-1β, furthermore, chemokine (C-C motif) ligand 2 (CCL2) and chemokine (C-C motif) ligand 5 (CCL5) are associated with the M1 phenotype, M1 phenotype also promote the recruitment of Th1 and natural killer cells (NK), which play a crucial role in killing intracellular pathogens [31–34]. The initiation of the NK cell response is thought to arise from signals provided by the specialized pathogen sensing system, which is mainly composed of dendritic cells (DC) [35–37]. Also, the direct activation of NK cells may also occur through NK cell expression of pathogen recognition receptors [38,39]. The cross-talk between DC and NK activates NK, after that, their mode of operation depend on the detection of specific molecules causing viral infection in cells by expression of receptors on NK cell surface. In a way, the identification of NK cells by infected cells relies on the detection of the missing self, that is, the lack of expression of the major histocompatibility complex class I on the surface of infected cells. Finally, the balance between NK cell suppression and activation of receptor signaling controls the response of NK cells to infection [40], subsequently, NK cells are involved in cytokine secretion, release of infected cells in the cytotoxic particles, induced apoptosis. These mechanisms have led to the removal of intracellular pathogens. Although these inductions are beneficial after acute infection, chronic induction of M1 macrophage activation can cause tissue damage and impede wound healing, especially under aseptic inflammatory condition. On the contrary, the M2 phenotype are usually induced by the Th-2 cytokines IL-4, IL-10 and IL-13, which showed high levels of cluster of differentiation 206 (CD206) and cluster of differentiation 163 (CD163), chemokine (C-C motif) ligand 17 (CCL17) and chemokine (C-C motif) ligand 22 (CCL22). Also Arginase 1 (arg1) and chitinase 3-like 3 (Ym-1) are M2 markers [36–38]. Recently, M2 has been divided into M2a, M2b, M2c and M2d four subtypes. IL-4

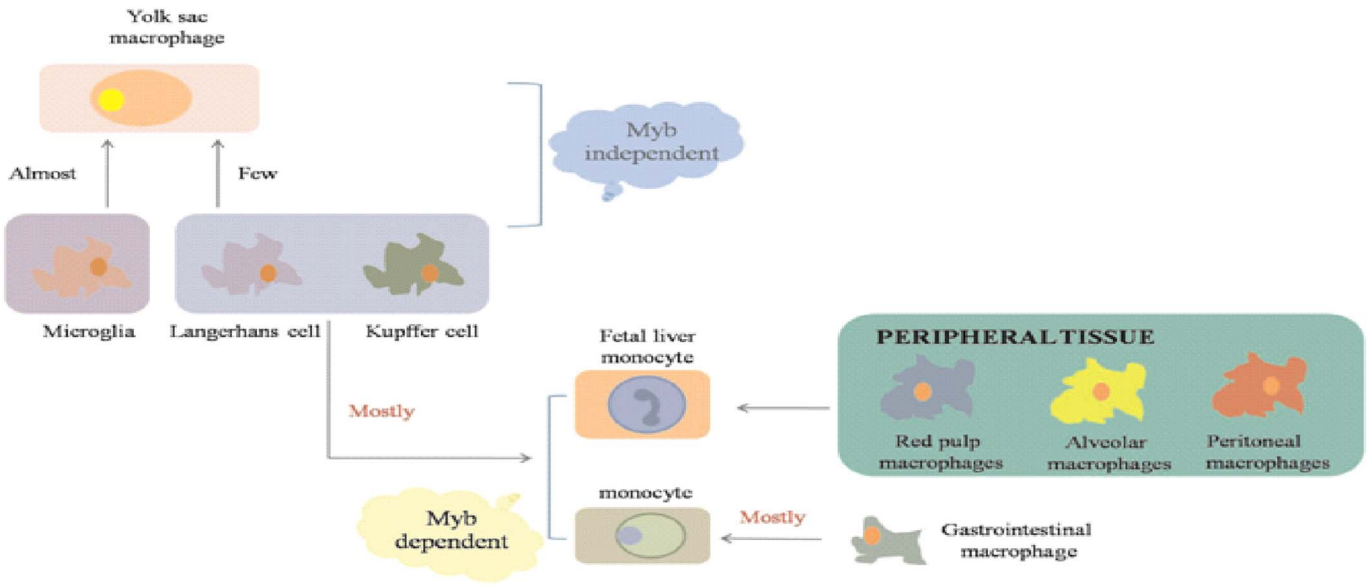

Fig. 1. The origin of different tissue-resident macrophage: microglia almost comes from Yolk sac; and Kupffer cells, Langerhans cells small part comes from Yolk sac mostly from fetal liver and monocyte; while the macrophages in the gastrointestinal tract are mainly derived from monocyte.