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Alveolar Macrophage Polarization and Its Role in Common Lung Diseases

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Abstract: Pulmonary macrophages are a crucial component of the lung immune system. They exhibit high heterogeneity and plasticity: the heterogeneity of pulmonary macrophages is reflected in their diverse origins, which consist of multiple subpopulations identified by surface marker expression, location, and origin[1]: alveoli, interstitium, and recruited (monocyte-derived). Pulmonary macrophages can polarize into various phenotypes to respond to the local microenvironment. After sensing changes in the local tissue microenvironment, macrophages are regulated by multiple intracellular signaling molecules and pathways, leading to polarization into different phenotypes, and even mutual conversion between different phenotypes[2]. They are associated with the pathophysiology of various lung diseases, including acute lung injury (ALI), chronic obstructive pulmonary disease (COPD), and asthma. This article reviews the origin and phenotype of pulmonary macrophages, pulmonary macrophage polarization, and the role of macrophage polarization in lung diseases.

1. Introduction

In the lungs, macrophages constitute the most abundant immune cell population, accounting for about 70%. Pulmonary macrophages originate from circulating monocytes derived from bone marrow stem cells and can also come from primitive macrophages in the yolk sac of the embryo and the fetal liver[3]. Based on anatomical location, they are divided into two major subpopulations, alveolar macrophages(AMs) and interstitial macrophages (IMs)——where AMs further include tissue-resident alveolar macrophages (TR-AMs) and alveolar macrophages of monocyte origin (Mo-AMs), two distinct subgroups[4].

AMs are located in the alveolar space of the lungs. TR-AMs originate from fetal monocytes and differentiate into alveolar macrophages through paracrine signals from alveolar epithelial cells, playing a central role in maintaining pulmonary homeostasis. TR-AMs can independently

self-renew throughout life through proliferation. Therefore, when TR-AMs are not severely depleted, they can recover through their own proliferation. However, when severe infection or injury occurs, AMs are exhausted, leaving too few AMs to replenish them within a short period. In such cases, monocytes recruited from the bone marrow or circulation infiltrate the alveolar space and develop into Mo-AMs, helping to replenish the resident pulmonary macrophage population after inflammation or injury[5]. However, little is known about the differences in the functions and characteristics of IMs, so this article will not discuss them.

2. Alveolar macrophage polarization and phenotype

Macrophage polarization is a process that generates specific phenotypic and functional responses to different pathophysiological conditions and the surrounding microenvironment. Based on the surface markers and functions of polarized macrophages, they are primarily divided into two major phenotypes: M1 (classically activated) macrophages and M2 (alternatively activated) macrophages[6].

2.1 M1 macrophages

M1 macrophages, also known as "classically activated (pro-inflammatory) macrophages," are induced by Th1 cytokines such as interferon-γ (IFN-γ), tumor necrosis factor α (TNF-α), and microbial lipopolysaccharides (LPS), as well as granulocyte-macrophage colony-stimulating factor (GM-CSF)[7]. Polarized M1 macrophages are renowned for their ability to secrete inflammatory factors, chemokines, and other toxic molecules, including interleukin-6 (IL-6), interleukin-12 (IL-12), interleukin-23 (IL-23), interleukin-1β (IL-1β), TNF-α, and other inflammatory response molecules (such as reactive oxygen species ROS and nitric oxide NO). These molecules are associated with other pro-inflammatory functions of M1 macrophages, including enhanced antimicrobial activity and the recruitment of pulmonary immune cells[8]. Therefore, functionally, M1 macrophages play a pro-inflammatory role in the early stages of inflammation, possessing strong anti-infective, anti-tumor, and clearance capabilities for apoptotic cells and necrotic tissues. They can mediate Th1-type immune responses through T-cell antigen presentation to kill pathogens and protect the body. In normal tissues, the proportion of M1 macrophages is precisely regulated and increases during inflammation. In the early stages of an inflammatory response, M1 macrophages phagocytose exogenous pathogens and degrade bacteria and cellular debris. However, excessive secretion of pro-inflammatory cytokines can exacerbate the inflammatory response, leading to tissue damage and hindering wound healing.

It is widely recognized that M1 macrophage polarization primarily relies on various signaling molecules and transcription factors, including nuclear factor κB light chain enhancer (NF-κB)[9] , interferon regulatory factor (IRF) 5 , signal transducer and activator of transcription (STAT) 1, and cytokine receptor suppressor (SOCS) 1/3. Pro-fibrinogen inhibitor inhibits M1 macrophage polarization in a NF-κB/mitogen-activated protein kinase (MAPK)-dependent manner (Liu et al., 2020)[10]. According to a recent study, physiological extreme D re-polarizes M1 macrophages into the M2 phenotype by inhibiting STAT1 activation and nuclear translocation (Ding et al., 2019)[11]. Conversely, introducing short hairpin RNA (shRNA) targeting SOCS1 to downregulate SOCS1 expression promotes the M1 phenotype by enhancing the STAT1 pathway (Liang et al., 2017)[12]. Additionally, Chen et al.'s latest research highlights that the activation of protease-activated receptor

2 (PAR2) promotes M1 macrophage polarization through a forkhead box protein O1 (FOXO1)-dependent signaling pathway (Chen et al., 2019)[13]. In addition, it has recently been found that the extranuclear network of neutrophils can promote the polarization of M1 alveolar macrophages in acute lung injury in mice, significantly increasing the production of cytokines such as IL-6, TNF-α and IL-1β[14].

2.2 M2 macrophages

Also known as selectively activated macrophages or alternatively activated macrophages. Th2 cytokines such as interleukin 4 (IL-4), interleukin 13 (IL-13), interleukin 10 (IL-10), and transforming growth factor-β (TGF-β) can induce the production of alternatively activated M2 macrophages[15]. M2 macrophages primarily participate in immune responses by releasing anti-inflammatory factors, including IL-1, IL-10, TGF-β, and chemokines CCL18 and CCL22. Additionally, M2 macrophages are highly expressed on the surface of CD163, CD206, CD209, scavenger receptor A (SR-A), SR-B1, CCR2, CXCR1, and CXCR2, which help suppress inflammatory responses and regulate immune balance[16]. The polarization of M2 macrophages is mainly regulated by STAT3/6, IRF4, and peroxisome proliferator-activated receptor (PPAR)-γ/δ[17]. To date, the STAT6 signaling pathway represents the primary route for activating M2 macrophages[18]. Recently, Wang et al. demonstrated that myristate ester conjugates (MCTR1) in tissue regeneration 1 enhance the polarization of resident M2 alveolar macrophages in LPS-induced lung injury in mice through a STAT6-dependent pathway (Wang et al., 2020)[19]. In terms of function, M2 macrophages can mediate anti-inflammatory responses and Th2-type immune responses, playing roles in inflammation suppression, parasite clearance, tolerance development, elimination, angiogenesis, and tissue repair. Additionally, M2 macrophages exhibit certain antimicrobial activity, but compared to M1 macrophages, their anti-inflammatory and immunomodulatory functions are more pronounced. Targeting macrophages to inhibit M1 or promote M2-like macrophage polarization is a potential approach for treating inflammatory diseases.

When induced by different stimuli, M2 macrophages also have different phenotypes. For example, when stimulated by IL-4/IL-13, immune complex and lipopolysaccharide/IL-1 receptor, IL-10 and Toll-like receptor respectively, M2 macrophages can be subdivided into M2a, M2b, M2c and M2d subgroups[20].

(1) M2a macrophages: produced and matured by IL-4 or IL-13 stimulation, mainly involved in anti-inflammatory and tissue repair processes, promoting angiogenesis and matrix reconstruction, helping to maintain the integrity of tissues, can also remove residual extracellular matrix (ECM), thus promoting wound healing and tissue regeneration[20].

(2) M2b macrophages: They are typically activated by immune complexes or LPS (bacterial endotoxin). M2b macrophages play a crucial role in immune regulation, inhibiting the progression of inflammatory responses. By secreting suppressive factors such as IL-10 and TGF-β, they prevent the activation of Th1 and Th17 cells, reducing excessive inflammation and thus maintaining the balance of the immune system to avoid excessive damage to self-tissue.

(3) M2c macrophages: generated by stimulation with IL-10, TGF-β, or glucocorticoids (GC). M2c macrophages primarily participate in the later stages of immune response regulation, reducing the release of inflammatory factors to promote tissue repair and modulate immune responses.

Additionally, they facilitate the development of tolerance and have an inhibitory effect on autoimmune diseases and transplant rejection.

(4) M2d macrophages: Not a typical category of macrophages, but rather a relatively new and less common concept, often used to describe a subtype of macrophages found under specific research conditions. M2d macrophages are frequently mentioned in certain tumor studies and are therefore also known as tumor-associated macrophages (TAMs). Their characteristics and functions differ from other M2-type macrophages (such as M2a, M2b, and M2c). The formation of M2d macrophages is typically influenced by specific factors in the tumor microenvironment, such as certain factors secreted by tumor cells. These factors may include cytokines or growth factors, such as adenosine A2 receptor (A2AR), leukemia inhibitory factor (LIF), and IL-6. They primarily suppress inflammatory responses, promote angiogenesis, and support the growth and spread of tumor cells[21].

Overall, M2 macrophages play a crucial role in immune regulation. They exhibit diverse phenotypes and functions, capable of adjusting their activity according to different stimuli and environmental factors. This enables them to maintain immune balance, promote tissue repair, and prevent excessive inflammatory responses. As such, M2 macrophages have become an important target in immunological research and clinical therapy.

3. The role of lung macrophage polarization in pulmonary diseases

3.1 Macrophage polarization and acute lung injury

Acute lung injury (ALI) is a common and critical condition caused by various direct or indirect factors. ALI often leads to acute respiratory distress syndrome (ARDS). The hallmark of ALI/ARDS is an excessive and uncontrolled inflammatory response to lung damage, resulting in epithelial and endothelial barrier disruption, alveolar capillary membrane dysfunction, increased vascular permeability, alveolar hemorrhage, and diffuse alveolar injury. Studies have shown that macrophage polarization plays a significant role in the three distinct pathological stages of ALI/ARDS, with AMs being particularly prominent as key immune cells involved at all stages of ALI/ARDS[22].

(1) During the acute phase of ALI/ARDS, also known as the exudative phase, a large amount of inflammatory mediators and inflammatory cells accumulate in the lungs during ALI exudation, causing diffuse alveolar injury and increased pulmonary capillary permeability. M1 macrophages play a crucial role in the development of ALI exudation. In this process, TLRs or other recognition receptors are induced and activated, leading to alveolar macrophage polarization towards M1 macrophages, which release various inflammatory factors such as IL-1β, IL-6, IL-12, MCP-1, MIP-2, TNF-α, and ROS[23]. These pro-inflammatory factors then recruit neutrophils from the vascular space, crossing endothelial and epithelial cells, and finally enter the lung and alveolar spaces. The excessive accumulation of pro-inflammatory factors and neutrophils ultimately leads to diffuse alveolar injury. Macrophages polarize towards the M1 phenotype by activating the classical JAK/STAT1 signaling pathway, where IFN-γ binds to IFN-γR on the macrophage surface, activating signaling molecules such as JAK1, JAK2, and STAT1[24]. This promotes the release of inflammatory cytokines, leading to macrophage polarization to M1. SOCS, primarily SOCS1 and SOCS3, negatively regulate the JAK/STAT1 pathway. Studies have shown that some naturally

derived or synthetic materials can improve the prognosis of ALI in animal models by inhibiting AM M1 polarization[25]. Therefore, M1 macrophages act as initiators in the process of lung tissue damage during ALI/ARDS. However, recent studies have shown that M1 macrophages can protect lps-induced ALI and ventilator-induced lung injury by enhancing amphireglin expression, inhibiting the gene expression of pro-inflammatory cytokines, and protecting the epithelial barrier[26].

(2) ALI/ARDS Recovery Phase: After the exudation phase, the second stage of ALI/ARDS is the recovery phase. During this recovery phase, pathogenic factors are eliminated, resident and recruited macrophages are then converted from M1 to M2 phenotype[26]. The phagocytosis of apoptotic neutrophils by macrophages is one of the driving factors promoting the M2 phenotype. In this stage, a new extracellular matrix is produced in the alveoli, accompanied by new blood vessels, which facilitates the repair of damaged lung tissue. M2 macrophages play a crucial role in the regulation of ALI recovery and tissue repair. These macrophages enhance the expression of IL-10, fibronectin 1, TTGF-β-induced matrix-associated protein BIG-H3, and insulin-like growth factor 1, while inhibiting the expression of pro-inflammatory cytokines[23]. This promotes host tissue repair, reduces alveolar epithelial cell injury, and enhances post-inflammatory lung barrier function, making it possible to promote lung tissue repair. Additionally, M2 macrophages can activate anti-inflammatory signals, terminate pro-inflammatory responses, and ultimately promote lung injury recovery by clearing apoptotic neutrophils from inflamed sites. A large number of M2 macrophages phagocytose apoptotic neutrophils, further releasing anti-inflammatory factors such as IL-4 and IL-10, thereby suppressing inflammation and promoting lung injury recovery. Studies have shown that the transition of macrophages from M1 to M2 during ALI recovery is also regulated by several pathways, including JAK/STAT and IRF signaling[27]. In addition, Tu et al. found that methylprednisolone can reduce LPS-induced ALI by increasing the number of M2 macrophages and inducing M2 polarization[28]. These results suggest that M2 macrophages are key coordinators regulating lung injury and tissue repair during the recovery phase of ALI/ARDS.

(3) Pulmonary fibrosis is the late stage of ALI pathology: characterized by fibroblast proliferation and extracellular matrix (ECM) deposition. At this stage, after basement membrane disruption, M1 and M2 macrophages are recruited to the site of lung tissue injury to regulate the fibrotic process. M1 macrophages play a crucial role in matrix degradation by directly and indirectly producing matrix metalloproteinases (MMPs) and various anti-fibrotic cytokines. The production of MMPs is particularly important for ECM remodeling, helping to reduce pathological fibrosis observed in the late stages of ALI[29]. Compared to M1 macrophages expressing MMPs, M2 macrophages express high levels of anti-inflammatory cytokines and tissue inhibitor metalloproteinases, promoting ECM deposition in lung tissue, thereby facilitating fibrosis. Additionally, studies have shown that co-culturing M2 macrophages with myofibroblasts can induce complex ECM deposition[30]. Arg-1 is an important M2 macrophage-associated molecule that degrades L-arginine into L-proline. It can be used to produce collagen by myofibroblasts. Long-term effects of IL-13 and IL-4 on AM promote the presence of M2 macrophages, ultimately leading to excessive fibrosis. Therefore, M2 macrophages are generally considered to more effectively promote a fibrotic microenvironment. However, some studies have proposed conflicting results: IL-4 polarized M2 macrophages can inhibit fibrosis by expressing Arg-1 and resistin-like α genes (surface markers of the M2 phenotype)[31]. (Wakayama et al.) Using an early PF model established with bleomycin, found that depletion of M2 is beneficial for PF[32]. Overall, macrophages paradoxically participate in the process of pulmonary fibrosis, indicating that an

imbalance between M1 and M2 plays a significant role in the development of PF. Therefore, maintaining an appropriate balance between M1 and M2 macrophages in vivo provides a target for the treatment of ALI/ARDS.

3.2 Macrophage polarization and COPD

COPD is an inflammatory lung disease affecting the lung parenchyma and airways, leading to narrowed airways and emphysema obstruction. In the early stages of COPD, M1 macrophages release pro-inflammatory mediators such as IL-1, TNF-α, NO, ROS, CCL2, and CXCL1, stimulating adaptive immune responses to remove exogenous irritants. In the middle and late stages, M2 macrophages dominate, suppressing excessive inflammation and maintaining dynamic balance[33]. Additionally, M2 macrophages have tissue repair functions and can secrete various anti-inflammatory factors in the lung tissue of COPD patients. Macrophages play a crucial role in maintaining immune function. M2 macrophages are the primary cells responsible for phagocytosis and clearance in COPD lungs. Studies show that the reduced phagocytic capacity of lung macrophages in COPD patients is associated with decreased key markers of M2 macrophages, such as CD206 and CD163, highlighting the importance of M2 macrophages in phagocytosis[34]. Furthermore, as COPD progresses, the number of M2 macrophages decreases, reducing their ability to engulf early disease accumulations, leading to weaker phagocytic activity in M2 macrophages during the middle and late stages of COPD. Overall, macrophage polarization plays a critical role in the pathogenesis and pathophysiology of COPD. A deeper understanding of the polarization state of macrophages and its regulatory mechanisms may provide new insights and targets for the treatment of COPD. However, further research is needed to elucidate the specific relationship between COPD and macrophage polarization.

3.3 Macrophage polarization and bronchial asthma

Asthma is a heterogeneous chronic lung disease characterized by airway inflammation, reversible airflow obstruction, airway remodeling, and bronchial hyperresponsiveness. Regardless of the type of asthma, it features increased immune cell infiltration, release of inflammatory cytokines, and airway remodeling. Pulmonary macrophages play a crucial role in recruiting immune cells (such as eosinophils, neutrophils, and monocytes), which enhance allergic inflammation and initiate T helper cell responses. Persistent pulmonary remodeling, including excessive mucus secretion, airway smooth muscle mass reduction, and airway fibrosis, contributes to progressive pulmonary function decline that is insensitive to current asthma treatments. Macrophages secrete inflammatory mediators, inducing airway inflammation and remodeling. Additionally, pulmonary macrophages help protect against pathogens and play a key role in returning to dynamic equilibrium after inflammation subsides. Recent studies have shown that macrophages, particularly M2 macrophages, play a significant role in the pathogenesis of asthma, such as bronchial hyperactivity, airway inflammation, and remodeling[35]. Although disturbances in macrophage homeostasis are associated with the pathogenesis of asthma, the underlying mechanisms remain elusive. Studies have shown that HDAC10 expression is highly upregulated in macrophages, promoting M2 macrophage activation and airway inflammation in both asthma patients and mice. Hdac10 deficiency significantly reduces M2 macrophage polarization after allergen exposure[36]. Overall, macrophage polarization plays a regulatory role in the development and progression of asthma.

However, further research is needed to elucidate the detailed relationship between asthma and macrophage polarization.

4. Summary and outlook

Lung macrophages are a critical component of the lung immune system, playing a significant role in the initial defense against pathogens. They exhibit high heterogeneity and plasticity. Heterogeneity is characterized by diverse origins, comprising multiple subpopulations such as alveolar, interstitial, and recruited (monocyte-derived) cells, which can be identified through surface markers, location, and origin. Plasticity is demonstrated by their ability to polarize into various phenotypes based on the local microenvironment, regulated by multiple intracellular signaling molecules and pathways, allowing for mutual conversion between different phenotypes. Lung macrophages are associated with the pathophysiology of various pulmonary diseases, including acute lung injury, chronic obstructive pulmonary disease, and asthma. This review discusses the origin, phenotype, polarization, regulation of polarization, and their role in pulmonary diseases, aiming to gain a deeper understanding of their functions and immunomodulatory properties. Based on the exploration of lung macrophages, regulating their M1/M2 phenotype polarization to achieve immune homeostasis holds potential as a new therapeutic strategy for pulmonary diseases. Further research into the regulatory mechanisms and application effects could advance the development of treatments for pulmonary diseases.

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