




The role of lung macrophages in acute respiratory distress syndrome

Wenpei Dang^{1,2} · Yiming Tao^{1,2} · Xinxin Xu^{1,2} · Hui Zhao^{1,2} · Lijuan Zou^{1,2} · Yongsheng Li^{1,2} 

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Abstract

Acute respiratory distress syndrome (ARDS) is an acute and diffuse inflammatory lung injury in a short time, one of the common severe manifestations of the respiratory system that endangers human life and health. As an innate immune cell, macrophages play a key role in the inflammatory response. For a long time, the role of pulmonary macrophages in ARDS has tended to revolve around the polarization of M1/M2. However, with the development of single-cell RNA sequencing, fate mapping, metabolomics, and other new technologies, a deeper understanding of the development process, classification, and function of macrophages in the lung are acquired. Here, we discuss the function of pulmonary macrophages in ARDS from the two dimensions of anatomical location and cell origin and describe the effects of cell metabolism and intercellular interaction on the function of macrophages. Besides, we explore the treatments for targeting macrophages, such as enhancing macrophage phagocytosis, regulating macrophage recruitment, and macrophage death. Considering the differences in responsiveness of different research groups to these treatments and the tremendous dynamic changes in the gene expression of monocyte/macrophage, we discussed the possibility of characterizing the gene expression of monocyte/macrophage as the biomarkers. We hope that this review will provide new insight into pulmonary macrophage function and therapeutic targets of ARDS.

Keywords Acute respiratory distress syndrome · Alveolar macrophages · Monocyte-derived macrophages · Inflammation · Biomarker · Therapy

Introduction

Acute respiratory distress syndrome (ARDS) is a common and frequently fatal cause in intensive care units (ICUs), caused by various pulmonary and extrapulmonary factors, such as pneumonia; aspiration of gastric contents; non-pulmonary sepsis; trauma; acute pancreatitis; transfusion of fresh frozen plasma and so on [1]. The mortality rate of ARDS is as high as about 40. In the past two years, the Corona Virus Disease 2019 (COVID-19) epidemic has

severely affected people's lives and the global economy. And ARDS is one of the causes of its high mortality [3]. However, at present there is no specific pharmacotherapy for ARDS in clinical practice. The main therapies are supporting treatments such as liquid therapy, prone position ventilation, mechanical ventilation and extracorporeal membrane oxygenation (ECMO). These treatments have improved clinical outcomes in ARDS patients, but mortality remains high [4]. Therefore, it is necessary to find effective therapeutic targets.

The pathological features of ARDS include alveolar epithelial cells (AECs) injury, inflammatory response, and increased alveolar–capillary permeability. Whether ARDS is caused by direct factors with pulmonary inflammation as the first or ARDS is caused by indirect factors with vascular inflammation as the first, the inflammatory response is the central link [5]. Macrophages (MΦ) are innate immune cells that express pattern recognition receptors (PRR) to recognize pathogen-associated molecular patterns (PAMP) and damage-associated molecular patterns (DAMP). MΦ recruit neutrophils and other leukocytes to initiate innate immune

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✉ Yongsheng Li
zzyxyongshengli@163.com; 15893842053@163.com

¹ Department of Intensive Care Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Avenue, Wuhan 430030, Hubei, China

² Department of Emergency, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Avenue, Wuhan 430030, Hubei, China

responses by producing inflammatory cytokines. Moreover, they can remove cell debris, interact with alveolar epithelial cells and produce growth factors to regulate inflammation and promote tissue repair. Because M Φ have the characteristics of diversity and plasticity, they can obtain different phenotypes with the changes in the tissue environment.

For a long time, M Φ are divided into classically activated macrophages (M1) and alternatively activated macrophages (M2) according to different functions [6, 7]. Stimulated by lipopolysaccharide (LPS), tumor necrosis factor α (TNF- α) or interferon γ (IFN- γ), M Φ polarize to M1, producing TNF- α , interleukin (IL-1, IL-6), monocyte chemoattractant protein (MCP-1, MCP-2), macrophage inflammatory protein 2 (MIP-2), reactive oxygen species (ROS), cyclooxygenase 2 (COX-2) and so on, which are involved in the pathological processes of proinflammatory, chemotaxis, free radical formation, matrix degradation and antibacterial. Conversely, M2 are generated in response to cytokines such as IL-4, IL-13, IL-10, and TGF- β . This population produces chemokine CCL18, arginine enzyme 1 (Arg-1), IL-10, transforming growth factor- β (TGF- β), and Fizz1 (found in inflammatory zone 1), promoting inflammation resolution, angiogenesis, and tissue repair [8].

Morrell et al. performed genome-wide transcriptional profiling of AMs purified from BALF (bronchoalveolar lavage fluid) collected from patients with ARDS. They found that the enrichment of M1-like genes on the first day was related to survival/extubation_{Day28}. On days 4 and 8, enrichment of M2-like genes was associated with 28-day survival, while enrichment of M1-like genes was associated with death/intubation_{Day28} [9]. Likewise, several studies have found that the proportion of M1 in BALF increased in LPS-induced or CLP-induced ALI/ARDS (acute lung injury and acute respiratory distress syndrome) mice, while promoting M2 polarization by some interventions can reduce inflammatory lung injury [10–13]. In the bleomycin-induced pulmonary fibrosis model, the polarization of M2 promotes pulmonary fibrosis [14, 15].

The above studies have proved the correlation between lung inflammation and the M1/M2 phenotype. Although as an experimental research method, M1–M2 dichotomy greatly reduces the research complexity caused by the diversity of macrophages. Various subpopulations of macrophages can both express markers of M1 and M2: nitric oxide synthase2 (NOS2) and Arg1, because the M1/M2 phenotype is proposed based on different arginine metabolic processes in cells [16, 17]. Then, there is a question of whether the M1/M2 ratio changes are caused by reprogramming single macrophages or simply increasing or decreasing the number of these two types of cells in vivo during acute lung injury.

With the development of single-cell sequencing, fate mapping, and other new technologies, the researcher has

found that the aggregate expression of M1 and M2 genes is closely related to cell origin. Compared with resident alveolar macrophages (RAMs), recruited alveolar macrophages (RecAMs) highly expressed M1 markers. The expression of M1 marker increased at the peak of inflammation. It returned to the baseline level after the inflammation subsided, consistent with the dynamic changes of monocyte-derived macrophages in the lung. In contrast, M2 markers are most expressed in homeostasis, mainly in RAMs. In addition, a cluster of cells was found to be mononuclear macrophages, the main secreting growth factor. These cells are associated with the function of M2 macrophages but do not express M2 markers [18]. The above results indicate that in the course of ARDS, the change in M1/M2 ratio may be related to the shift in cell ratio of different subgroups. The M1/M2 paradigm is so simple that it cannot describe the multidimensional, complex, and dynamic changes of macrophages in detail.

Therefore, it is necessary to understand the origin, distribution, molecular markers, functions of different macrophages, and the relationship with other cells. This review is meant to explain the role of pulmonary macrophages from the aspects mentioned above and the prospective therapeutic targets in ALI/ARDS.

Dynamic changes of pulmonary macrophages in ALI/ARDS

When pathogens or other stimuli invade, TLR (toll-like receptors) on RAMs and alveolar type II epithelial cells (ATII) are activated to induce chemokine secretion, thereby recruiting circulating immune cells into the airspace, such as monocytes, neutrophils, platelets, etc. These immune cells further release inflammatory factors and promote the damage of alveolar epithelial cells and endothelial cells, thereby increasing vascular permeability and liquid extravasation, leading to pulmonary edema [19, 20] (Fig. 1).

Among them, circulating monocytes are recruited to the lungs in a CCL2/CCR2 axis-dependent manner and differentiate into macrophages, known as RecAMs [21]. Self-maintenance and renewal of RecAMs are regulated by macrophage colony-stimulating factor (M-CSF) produced by its autocrine epithelial cells and activated fibroblasts [22]. As is known, circulating monocytes are divided into classical monocytes (CD14⁺CD16⁻), intermediate monocytes (CD14⁺CD16⁺), and nonclassical monocytes (CD14^{lo}CD16⁺). One vitro study found that all human monocyte subsets could differentiate into macrophages [23]. Recently, Evren et al. used the humanized mouse model to dissect the development process of circulating monocytes differentiating into pulmonary macrophages. They reported that CD14^{lo}CD16⁺ monocytes differentiated into pulmonary vascular macrophages, while HLA-DR^{hi} (human leukocyte

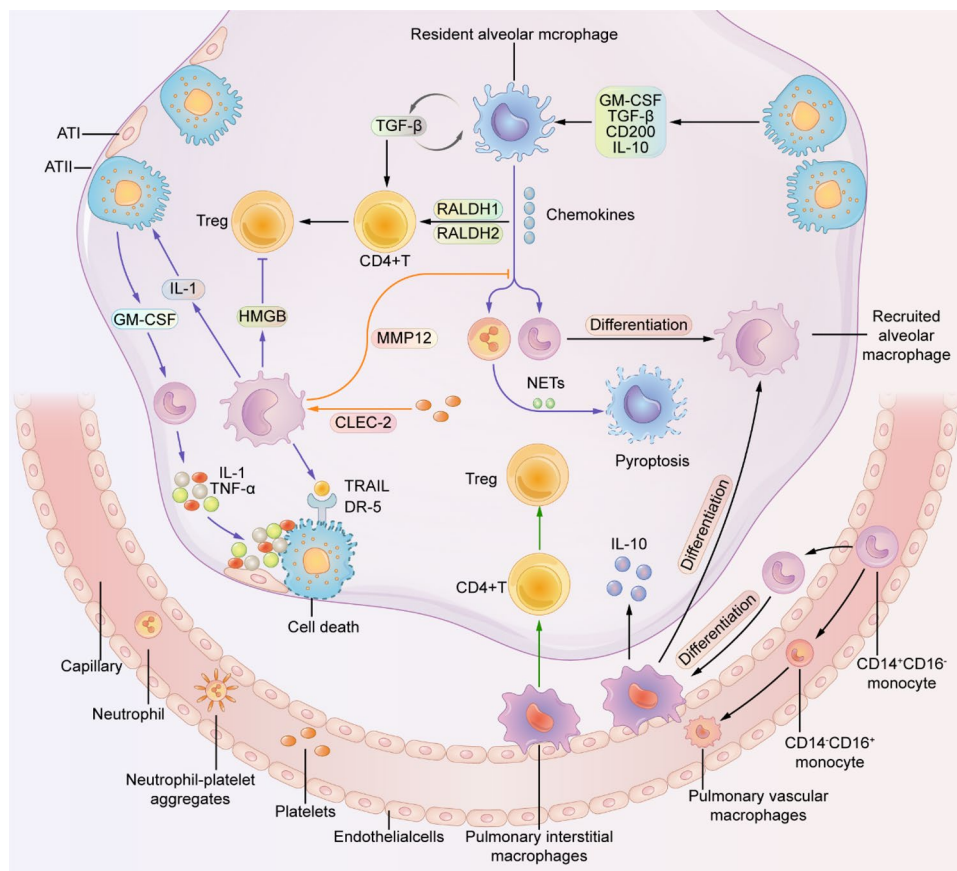


Fig. 1 The function of pulmonary macrophages and their interactions with other cells. At steady state, resident alveolar macrophages (RAMs) maintain the hyporesponsive state affected by various cytokines and promote the differentiation of CD4⁺ T cells into Treg cells through secreting transforming growth factor- β (TGF- β) and retinal dehydrogenase (RALDH). Likewise, interstitial macrophages can facilitate the differentiation of CD4⁺ T cells into Treg cells. In inflammation, RAMs secrete chemokines to recruit neutrophils and monocytes. Neutrophil extracellular traps (NETs) can lead to the pyroptosis of AMs. Monocytes can differentiate into pulmonary vas-

cular macrophages, interstitial macrophages and RECAMs. Recruited alveolar macrophages (RECAMs) secrete inflammatory factors leading to alveolar epithelial cell apoptosis and inhibiting the differentiation of Treg cells. C-type lectin-like 2 (CLEC-2) expressed by platelets interacted with RECAMs to inhibit the activities of chemokines. ATI alveolar type I cell, ATII alveolar type II cell, GM-CSF granulocyte-macrophage colony stimulating factor, L-10 interleukin-10, IL-1 interleukin-1, Treg regulatory T cells, HMGB1 high mobility group protein-1, MMP12 matrix metalloproteinase-12, TRAIL tumor necrosis factor related apoptosis-inducing ligand, DR-5 death receptor-5

antigen DR) monocytes derived from CD14⁺CD16⁻ monocytes migrated to lung tissue and then differentiated into alveolar macrophages and interstitial macrophages [24]. In addition, some studies found that PIMs derived from monocytes could also differentiate into RecAMs through transcriptome data analysis [25–27].

In the late stage of inflammation, most of the RecAMs apoptosis, while the number of RAMs has no significant change. A study suggests that RecAMs apoptosis is due to its high expression of the death receptor Fas [28]. When RAMs are severely depleted, and alveolar niches are accessible and available, RecAMs can infiltrate the alveolar and replenish the macrophage population [29, 30]. Over time, the transcript profile and phenotype of RecAMs gradually become similar to resident macrophages under the influence of the tissue microenvironment [31–34].

Notable, compared the bleomycin-induced fibrosis model with the LPS-induced acute lung injury model, there are time differences in the dynamic changes in the number of monocyte-derived macrophages (MDMs). In the former, the number of C11b^{hi}M Φ began to increase on Day7 and reached its peak on Day14 [35]. In the latter, the recruitment of MDMs peaked on Day3 and Day 6 and returned to baseline levels on Day 30 and Day 12, respectively, depending on the dose of LPS (200 or 20 μ g) [28].

Table 1 Classification, markers and functions of macrophages

Subset	Origin	Biomarker	Functions
AMs			
RAMs	Fetal liver monocytes [36, 37]	F4/80 Siglec-F CD11c ⁺ CD11b ⁻ CD206 ⁺ CD169 ⁺ CD64 ⁺	Detective microenvironment changes Phagocytosis and cell proliferation Inflammation initiation [16, 18, 59]
RECAMs	CD14 ⁺ CD16 ⁻ Monocytes [24]	F4/80 CD11c ⁻ CD11b ⁺ CD14 ⁺	Pro-inflammatory Tissue repair [16, 18]
PIMs	Yolk sac-derived F4/80 lineage MΦ [36]; CD14 ⁺ CD16 ⁻ Monocytes [24]		
Vascular-associated IMs		Lyve1 ^{hi} MHCII ^{lo} CD206 ⁺	Secretion of IL-10 Maintenance of vascular permeability Preventing inflammatory cells infiltration Inhibiting fibrosis [43, 45]
Nerve-associated IMs		Lyve1 ^{lo} MHCII ^{hi} CD206 ⁻	Antigen presentation Regulation of T cell activity [43, 45]
PVMs	CD14 ⁻ CD16 ⁺ Monocytes [24]	CD68 ⁺ [52]	Secretion of pro-inflammatory factors Recruitment of platelets and Neutrophils [54]

AMs alveolar macrophages, RAMs resident alveolar macrophages, RECAMs recruited alveolar macrophages, PIMs pulmonary interstitial macrophages, IMs interstitial macrophages, MΦ macrophages, PVMs pulmonary vascular macrophages

The role of pulmonary macrophages from different anatomical positions

Pulmonary macrophages can be divided into alveolar macrophages (AMs), pulmonary interstitial macrophages (PIMs) and pulmonary vascular macrophages (PVMs) according to the anatomical location (Table 1).

Alveolar macrophages

Alveolar macrophages (AMs) are located in the alveolar cavity, with the highest content in pulmonary macrophages. AMs are mainly derived from fetal liver monocytes [36, 37]. Self-sustainment and renewal of AMs require granulocyte-macrophage colony-stimulating factor (GM-CSF) and TGF-β secreted by alveolar type II epithelial cells [38–40]. At steady state, AMs can be regarded as a cell sensor to identify various changes in microenvironment, phagocytose inhaled stimulants and cell debris, and coordinate immune responses. AMs can also maintain the balance of alveolar surface protein. Its deficiency or dysfunction can lead to pulmonary alveolar proteinosis [41]. The study has shown that

AMs maintain the hyporesponsive state and lung homeostasis under the action of TGF-β, IL-10, and CD200 in alveolar microenvironment [42].

Pulmonary interstitial macrophages

Pulmonary interstitial macrophages (PIMs) are located in bronchial interstitial and alveolar interstitial, accounting for 30–40% of pulmonary macrophages. Although researchers found that PIMs were only located in bronchial stroma by fluorescence microscopy, but compared with the results obtained by confocal microscopy, such result is doubtful [43, 44]. PIMs were initially derived from yolk sac-derived embryonic F4/80 macrophages and then replenished by circulating progenitor cells [36]. At present, studies have found that PIMs are divided into two groups, vascular-associated IMs distributed around blood vessels and peripheral nerve-associated IMs distributed around nerves. The two cells both express high-level IL-10 gene and promote the proliferation of CD4⁺ T cells and the differentiation of Treg cells. But the functions of the two cells have a different emphasis. Vascular-associated IMs play a key role in maintaining vascular

permeability, preventing inflammatory cell infiltration, and inhibiting tissue inflammation and fibrosis. Nerve-associated IMs play an important role in antigen presentation and regulation of T cell activity [43, 45]. Basak et al. treated CD169DTR, AM-DTR, NAM-DTR, and IL-10—GFP mice with influenza virus PR8 and the ligand Poly (I:C) of TLR3, respectively. They found that PIMs were the main secretor of IL-10, which may be the potential mechanism of PIMs regulating lung inflammation. When PIMs were depleted, pro-inflammatory factors (IL-6), chemokines (CCL2, CCL3 and CCL5) and the recruitment of monocytes increased in the alveolar lavage fluid, thereby enhancing the inflammatory response. While in the absence of AMs, the viral load was significantly increased and the mortality of mice was increased. And confocal analysis revealed that AMs but not NAMs could engulf the influenza virus. This indicates that alveolar macrophages mainly play the role of phagocytosing viruses, while pulmonary interstitial macrophages are involved in immune regulation and inflammatory response [46–48].

Pulmonary vascular macrophages

For a long time, it has been believed that pulmonary macrophages only contain AMs and PIMs, because there are no constitutive pulmonary vascular macrophages (PVMs) in humans, mice, and rats. But in the condition of liver dysfunction and bile duct ligation, PVMs appear in the lungs of humans and rats. In the mouse model of acute pancreatitis induced by L-arginine, PVMs (CD68⁺) are recruited to the lung in an MCP-1-dependent manner. It has been reported PVMs are not only associated with ARDS caused by acute pancreatitis but also may increase the incidence rate and mortality of ALI/ARDS [49–53]. Taking swine as the research object, the researcher found the mechanism of PVMs participating in ALI/ARDS may be related to the activation of NF-κB, the secretion of pro-inflammatory factors (TNF-α, IL-1β, IL-6, IL-8, COX-2) and the recruitment of platelets and neutrophils [54]. Apoptosis of PVMs can attenuate inflammation [50, 55]. Recently, researchers found PVMs in the lungs of humanized mice. Utilizing gene sequencing technology, the researcher found this subgroup expressed genes related to leukocyte adhesion to endothelium and participated in erythrocyte turnover and iron metabolism. It was also found the existence and maintenance of PVMs depended on CD14^{lo}CD16⁺ monocytes. SPIC is a candidate transcription factor driving the development of human PVMs [24]. Notably, PVMs were found in humanized mice without stimulation. Does this mean that humanized mice have changed the structural composition of pulmonary macrophages to some extent? It needs further research and discussion. But in any way, the presence of

PVMs provides a research direction for ARDS caused by extrapulmonary factors.

The role of pulmonary macrophages from different origins

Depending on the origins, pulmonary macrophages can be divided into tissue-resident and recruited macrophages. The function of RAMs is mainly to detect and respond to microenvironment changes, phagocyte debris, cell proliferation, and anti-inflammatory, while RecAMs show a strong pro-inflammatory effect in inflammation and promoting fibrosis after inflammation regression [25, 27, 35, 56–58]. Through single-cell sequencing technology, the researcher found enriched genes in RAMs are related to PPAR signaling, lipid metabolism, cell cycle, proteasome function, and protein processing in the LPS-induced mouse model. RAMs focus on cell proliferation to supplement the damaged alveolar macrophage pool, and RAMs gradually stop the secretion of pro-inflammatory factors after the onset of inflammation [16, 18]. PPAR-γ expression in RAMs is responsible for the restriction of exaggerated inflammation, promoting tissue repair, thereby controlling the development of the disease following viral infection [59]. At the peak of inflammation, enriched genes in RecAMs are associated with inflammation-related pathway genes, such as NF-κB signaling pathway, TLR signaling pathway, interferon signaling pathway, and the ER-phagosome pathway, while producing high levels of cytokines, such as TNFα, IL1β, CXCL1, CXCL2 and IL-10 [16, 18]. Likewise, Aegerter et al. found that RecAMs immunoreactivity is strongest in the lungs using gene set enrichment analysis (GSEA), whose expression of STAT3-related pathways is the most prominent [31]. After inflammation regression, it revealed MDMs encode growth factors and enrich genes about cell–matrix interactions such as matrix metalloproteinase 14 (MMP14), SPP1, and extracellular matrix protein 1 (ECM1) [18, 60]. The study has shown targeting the Notch/RBP-J (Recombination signal-binding protein Jκ) signaling pathway can regulate RecAMs recruitment and TGF-β secretion, thereby improving pulmonary fibrosis [56].

Moreover, the apoptosis of AMs and MDMs has different effects on the disease, which confirm their different roles in inflammatory reactions. Preventing AMs apoptosis and pyroptosis in the early stage of inflammation can decrease the severity and mortality of ARDS [61–64]. The study found that ghrelin combined with GH secretagogue receptor-1a (GHSR-1α) on the surface of alveolar macrophages can protect AMs from apoptosis and reduce sepsis-induced lung inflammation by activating the Wnt/β-catenin pathway. This study did not describe the apoptosis of RAMs or RecAMs in

detail. But the time for obtaining the sample was 20 h after cecum ligation and puncture (CLP) in mice, and AMs line NR8383 was used to test the anti-apoptotic effect of ghrelin *in vitro*. More importantly, in the LPS-induced lung injury model, the kinetics of RecAMs confirmed that RecAMs were present in the BALF by Day 3 [28]. So we speculate that ghrelin exerts an anti-apoptotic effect on RAMs and thereby reduces the severity of ARDS in early inflammation [62]. According to the report, pyroptosis and apoptosis of macrophages are related to two pathways, respectively: TLR4/TRAF6/NF- κ B/NLRP3/caspase-1 and TLR4/caspase-8/caspase-3 signaling pathways in LPS-induced ALI [61]. It has been reported that inhibition of PKR (double-stranded RNA-dependent kinase), p38 MAPK (mitogen-activated protein kinase), or PIM2 (a member of serine/threonine kinase family) protects macrophages from pyroptosis through NLRP3–pyroptosis pathway as well as inhibits the progression of ALI [63–65]. Furthermore, mesenchymal stem cells (MSCs) can attenuate LPS-induced macrophage apoptosis by mitochondrial transfer [66].

MDMs apoptosis promotes inflammation resolution and attenuates pulmonary fibrosis [28, 35, 67, 68]. After 3–4 days of LPS stimulation in mice, injection of RvD1 (Resolvin D1) via the tail vein promotes the apoptosis of recruited macrophages through the ALX/FasL-FasR/caspase3 signaling pathway, thereby promoting the regression of inflammation [67]. William et al. found that activation of the death receptor Fas leads to depletion of RecAMs but not RAMs, which indicates that apoptosis of RecAMs plays a beneficial role in the processes of resolution of ALI [28]. In the mouse model of ARDS induced by *P. aeruginosa*, after administration of sPD-L1, lung injury was alleviated, and MDMs were reduced. However, when approximately 50% of MDMs were depleted in the lung after the early depletion of circulating monocytes by CL, the protective effect of sPD-L1 on the lung was significantly attenuated [68]. Besides, Alexandra et al. reported that depletion of the anti-apoptotic protein cellular FADD-like IL-1 β -converting enzyme–inhibitory protein (c-FLIP) by targeting C11b^{hi}M Φ promotes C11b^{hi}M Φ cell death after 7–14 days of bleomycin treatment, thereby protecting mice from pulmonary fibrosis [35].

In fact, during the progression of lung injury, MDMs have apoptosis resistance. And mitochondrial dynamics have an important role in mediating apoptosis resistance [69–71]. NADPH oxidase 4 (NOX4) overexpression induced Akt1 activation and Bcl-2-related death [70]. Akt1 regulates posttranslational modification of PGC-1 α (the peroxisome proliferator-activated receptor- γ coactivator) by promoting p38 MAPK activation in a redox-dependent manner to increase mitochondrial biogenesis [69]. Carnitine palmitoyl transferase 1a (Cpt1a) is a rate-limiting enzyme in fatty acid β oxidation in the outer mitochondrial membrane, which

interacts directly with Bcl-2 and anchors Bcl-2 to mitochondria to reduce apoptosis [71]. Additionally, the study proves that extracellular superoxide dismutase (EC-SOD) can induce apoptosis of RecAMs by increasing the expression of pro-apoptotic factor Chac1 (a γ -glutamylcyclotransferase), thereby reducing lung inflammation. R213G SNP (single nucleotide polymorphism) of EC-SOD knock-in mice showed enhanced inflammatory regression and anti-fibrosis protection [72]. Interestingly, the study has found that a GCCT haplotype of EC-SOD has a protective effect in ARDS patients, while R213G SNP is not associated with time on the ventilator or mortality [73].

Effects of metabolism on macrophages

Through phosphoproteomics analysis of LPS-stimulated RAW264.7, it was observed that inflammatory signal transduction, cellular apoptosis, and metabolism were the main processes in the acute inflammatory response. And in these processes, metabolism is important [74]. For instance, it is well known that arginine metabolism is thought to be a determinant of M1/M2 polarization of macrophages [75]. In addition, it was found that M1 activation depended on glycolysis, while M2 activation depended on oxidative phosphorylation and fatty acid oxidation in other studies about cell metabolism on macrophage polarization [76–78]. Heparin-binding protein (HBP) enhances macrophages' glycolysis to produce lactic acid and then activates the NF- κ B pathway to regulate the production and release of proinflammatory cytokines [79]. Coupling of the Wnt/ β -catenin signaling with HIF- α can mediate glycolysis of macrophages, thereby inhibiting proliferation of AMs and promoting secretion of inflammatory factors [80]. Conversely, soluble death receptor 5-Fc (sDR5-Fc) is the extracellular region structure of death receptor 5 (DR5), which can block subsequent apoptotic signals by inhibiting DR5. In the study of acute myocardial infarction, it was found that sDR5-Fc inhibits macrophage M1 polarization by inhibiting the expression of key glycolytic factors HK2 and GLUT1 [81]. When mesenchymal stem cell exosomes were co-cultured with LPS-treated MH-S cells, it was found that exosomes inhibited AMs glycolysis and promoted M2 polarization [82].

Similarly, through RNA sequencing and whole-cell metabolomic profiling of RAMs and RecAMs during the LPS-induced acute inflammatory process, Mould et al. found the metabolism of RAMs are mainly based on the tricarboxylic acid cycle and amino acid synthesis, while RecAMs are mainly based on arginine metabolism and glycolysis. Notably, RecAMs had increased the expression of enzymes involved in glycolysis, but there was no statistical difference in glycolytic intermediates in the process [16]. Svedberg et al. reported that glycolysis of AMs is impaired in the

lung environment, leading to hyporesponsiveness of AMs to IL-4. However, after being removed from the lungs, AMs regained responsiveness to IL-4 in a glycolysis-dependent manner [83]. This result is consistent with the hyporesponsiveness of AMs under the steady-state. Additionally, Yu et al. found that the adenosine triphosphate (ATP) produced by glycolysis of macrophages in LPS-induced inflammation was mainly used for S-adenosylmethionine (SAM) synthesis rather than cell proliferation. Then SAM promotes the production and release of inflammatory cytokines (IL-1 β) in pro-inflammatory macrophages through histone H3 lysine 36 trimethylation (H3K36me3) [84].

Currently, most studies on macrophages and metabolism are based on the M1/M2 classification. In the future, more studies are needed to explore the effects of metabolism on the biology of resident macrophages and monocyte-derived macrophages.

Interaction between pulmonary macrophages and other cells

AECs

In homeostasis, AECs cannot only produce GM-CSF to ensure the self-maintenance and renewal of AMs but also secrete TGF- β , CD200, and IL-10 to maintain the hyporesponsive state of AMs and maintain the anti-inflammatory phenotype [38, 42]. AMs also reduce NO production and release by autocrine TGF β [85]. During inflammation, AECs secrete CCL-2 and M-CSF to promote the recruitment and self-maintenance of MDMs [22, 86]. Additionally, in the case of viral infection, AECs release type I IFN to induce AMs to release tumor necrosis factor related apoptosis-inducing ligand (TRAIL). TRAIL binds to death receptor-5 (DR5) on AECs and activates stress kinase AMPK, leading to the degradation of cytoplasmic membrane Na, K-ATPase and suppressing the elimination of pulmonary edema [87, 88]. And it is reported that the Lian Hua Qing Wen capsule (LHQW) inhibited LPS-induced TRAIL secretion in macrophages, thereby efficiently protecting epithelial cells against TRAIL-induced apoptosis [89]. In turn, AMs secrete IL-1 to promote AECs to produce GM-CSF, which can amplify the inflammatory response and aggravate the damage of AECs and endothelial cells by enhancing Toll-like receptor (TLR)-induced monocytes glycolysis [90]. In the late stage of inflammation, TFF2 (Treffol factor) secreted by AMs promotes autocrine Wnt4/Wnt16 to induce AECs proliferation and repair [91]. Moreover, it was reported that T-cell immunoglobulin mucin 3 (Tim-3) regulates the function of macrophages, which indirectly regulates PI3K/AKT signaling pathway in AECs, thereby promoting repair of the lung epithelial barrier after injury [92].

RecAMs

Jagdish et al. found that sphingosine-1-phosphate (S1P) produced by RecAMs can inhibit AMs type 1 interferon gene stimulator (STING) signal to up-regulate the anti-inflammatory function of AMs and reduce pulmonary inflammation [93]. Although the main role of RecAMs in ARDS is to promote inflammation, the possibility of a feedback mechanism between RecAMs and RAMs is not ruled out.

T lymphocytes

As mentioned above, in the studies of macrophage polarization, IFN- γ secreted by Th1 lymphocytes can increase the phagocytic activity of macrophages and the production of pro-inflammatory factors. And, IL-4 and IL-13 secreted by Th2 lymphocytes can promote the polarization of macrophages into the anti-inflammatory phenotype. In homeostasis, resident macrophages secrete TGF- β and retinal dehydrogenase (RALDH1 and RALDH2) to promote the differentiation of CD4⁺ T cells into Treg cells and maintain immune tolerance [94]. In inflammatory response, high mobility group protein-1 (HMGB-1) secreted by macrophages regulates the development of Treg cells through PTEN/ β -catenin signaling pathway, thereby promoting lung inflammation [95]. PIMs can also promote the proliferation of CD4⁺ T cells and the differentiation of Treg cells in vitro [45]. In turn, in sepsis, high expression of G protein-coupled receptor-174 (GPR174) in Treg cells promotes tissue damage by amplifying inflammatory response, and GPR174 deficiency promotes macrophage polarization to anti-inflammatory phenotype [96]. In the study of laryngeal squamous cell carcinoma, it was found that there was a positive feedback loop between Treg cells and M2-like macrophages, in which M2-like macrophages could induce CD4⁺T cells to produce Treg cells. In turn, Treg cells could promote the differentiation of monocytes into M2-like macrophages [97]. Morrell et al. found that PD-L1 low expression in pro-inflammatory AMs (PD-L1^{lo}CD169^{lo}CD206⁺CD14⁺) in BALF from RADS patients. The accumulation of these cells was correlated with the severity of ARDS [98]. It was reported that the decreased expression of PD-L1 in macrophages was associated with INF- γ secretion by CD8⁺ T cells in COPD patients [99]. These suggest that in ALI/ARDS, there may be intercellular communication between CD8⁺T cells and macrophages.

Neutrophils

In ARDS, neutrophils are the central link in the inflammatory response, and their excessive aggregation is one of the criteria for the success of the ARDS model [100]. Macrophages and neutrophils are interdependent in migrating

to lung inflammation [101, 102]. Actually, not all alveolars contain RAMs in the normal lung. RAMs can crawl across the alveoli to swallow pathogens such as bacteria and stop neutrophil recruitment through the 'cloaking' mechanism to maintain homeostasis. When the crawling ability of RTM is impaired, or the blocking mechanism is disordered, neutrophils will be recruited to the lungs under the action of chemokine CXCL2/CXCR2, causing tissue damage [103, 104]. Furthermore, TNF- α , G-CSF, and GM-CSF secreted by macrophages can inhibit neutrophil apoptosis and prolong its life span in the inflammatory response [105]. Moreover, macrophages can remove apoptotic neutrophils by efferocytosis. At the same time, macrophages increase IL-4 secretion, thereby inhibiting neutrophil recruitment and NETs formation [106].

Conversely, neutrophils promote monocyte recruitment by releasing harmful substances such as heparin-binding protein (HBP) and cathepsin G and altering vascular permeability [107–109]. In addition, neutrophils promote the proinflammatory phenotype of macrophages through exosomes or neutrophil extracellular traps (NETs), etc. [110, 111]. However, one study has shown that neutrophils inhibit NF- κ B activation in macrophages in an independent-apoptosis manner, resulting in reduced proinflammatory cytokine release and anti-inflammatory reprogramming [112].

More importantly, neutrophils can promote the pyroptosis of AMs, positively correlated with the occurrence of ALI/ARDS [113]. A large number of NETs produced by neutrophils were phagocytosed by AMs under the stimulation of endotoxin, which led to the activation of AIM2 in AMs, thereby inducing the caspase-1-dependent pyroptosis of AMs [114]. Another study found that extracellular histones promote AMs pyroptosis through the NLRP3 inflammasome pathway, thereby aggravating the pulmonary inflammatory response of ARDS. NETs composed of DNA and histones embedded in proteases, so this may be one of the mechanisms of NETs acting on alveolar macrophages [115].

Platelets

Platelet receptor C-type lectin-like 2 (CLEC-2) expressed by platelets is critical for securing vascular integrity in the lungs during inflammation. Siân Lax et al. found that in inflammatory response, CLEC-2 interacted with podoplanin on RECAMs, and inhibited the activities of keratinocyte-derived chemokine (KC) and macrophage inflammatory protein 2 (MIP-2) by promoting AMs to release matrix metalloproteinase-12 (MMP-12), thereby reducing lung inflammation and injury [116]. Platelets release CCL5 in RAC1-dependent manner, which binds

to CCR5 on AMs and stimulates alveolar macrophages to release CXCL2, thus leading to neutrophil recruitment and promoting lung injury [117].

Therapeutic targets and biomarkers

Depletion of circulating monocytes

Using chlorophosphate liposome (CL) to deplete circulating monocytes in the LPS-induced ALI mouse model, the researchers found that lung injury, perivascular edema, and neutrophil infiltration were significantly inhibited [57]. However, in human studies, leukapheresis was used to deplete circulating monocytes, and neither pulmonary neutrophils nor pulmonary inflammation was reduced. It is inconsistent with the results of animal experiments. The most intuitive reason is the average concentration of circulating monocytes was still in the normal range during the experiment [118]. Besides, it is noteworthy that the intestine and other tissues require a continuous supply of monocytes to maintain homeostasis, so the method of exhausting circulating monocytes may have off-target effects.

In our opinion, circulating monocytes may be more suitable for biomarkers. In the human study, it was found that the amplification of CD14⁺⁺ CD16⁻ monocytes was the most obvious in the leukocytes of BALF after LPS inhalation, which was 400 times that of the control group. There was no difference in the concentration of peripheral blood monocytes between the two groups [119]. CD14 and CD163 are surface proteins on monocytes and macrophages. When cells were activated, sCD14 (soluble form of CD14) and sCD163 (extracellular part of CD163) entered the blood circulation. The days from hospitalization to the onset of ARDS were negatively correlated with sCD163 plasma levels. sCD14 plasma level was negatively correlated with the percentage of non-classical monocytes [120]. Furthermore, the accuracy of CD14 monocytes in predicting the survival rate of patients with COVID-19 was 90%, and the characteristics of four genes (CEBPD, MAFB, IFITM3 and LGLS1) were determined [121]. Moreover, Jiang et al. found that the expression of suppressors of cytokine signaling-3 (SOCS3) was deficient in ARDS patients compared with non-ARDS patients through single-cell RNA sequencing of peripheral blood of patients with and without ARDS in sepsis. Importantly, gene expression profiles showed that increased RAB11A expression in monocytes was associated with neutrophil clearance deficiency, increased ATP2B1 expression was associated with vascular leakage in ARDS, and SPARC was associated with lung fibrosis [122]. Besides, different studies in the peripheral blood of patients with COVID-19

showed that the proportion of intermediate and non-classical monocytes in the blood circulation increased or decreased [120, 123]. Researchers consider that this controversial result may be related to different disease stages corresponding to the sample collection time. Therefore, it may be possible to identify disease stages, ARDS subtypes and guide administration time by characterizing circulating monocytes [124].

Inhibiting recruitment of RecAMs

Studies have shown that CCL2/CCR2, CSF-1/CSF-1R or GM-CSF/GM-CSFR signals play an important role in the recruitment of inflammatory monocytes and RecAMs [56, 125]. Lipoxin A4 (LXA4) is arachidonic acid metabolite formed during inflammation.

CCL2/CCR2

LXA4 can inhibit the secretion of CCL2 and CXCL2 by RAMs, thereby reducing the accumulation of RecAMs and neutrophils and alleviating inflammation [126]. CCR2/5-iPS-ECs (rat-induced pluripotent stem cell-derived endothelial cells overexpressing CCR2/5) attenuates LPS-induced lung injury by competing with monocytes for chemokines. Of course, in addition to competitive effects, it may be related to repairing endothelial cells derived from pluripotent stem cells or the secretion of vesicles and cytokines [127]. Moreover, interleukin-1 receptor-associated kinase (IRAK-M) is a negative regulator of Toll-like receptor signaling secreted by bone marrow-derived cells. IRAK-M promotes RecAMs recruitment and aggravates pulmonary fibrosis by upregulating CCR2 expression in monocytes. Conversely, gene ablation of IRAK-M reduces the recruitment of monocytes [128]. Preclinical experiments show that CCL2/CCR2 signal is a promising therapeutic target. In the study of atherosclerosis, the clinical research of targeted inhibition of the CCL2/CCR2 signal is in the ascendant, which provides a reference for the treatment of ARDS (CCL2/CCR2) [129]. But the side effects of blocking the signal leading to impaired bacterial clearance and the dual role of CCL2/CCR2 signaling in ARDS concomitant diseases such as diabetes and cancer should be taken into account [130, 131].

CSF-1/CSF-1R

CSF-1 is necessary for the accumulation of inflammatory macrophages. Studies have shown that blocking CSF-1/CSF-1R signaling leads to selective loss of monocyte-derived alveolar macrophages and improvement of pulmonary fibrosis in fibrotic niches [22, 125]. CSF1R antibody AMB-05X

(formerly AMG 820) has been designated for clinical trials of idiopathic pulmonary fibrosis (IPF), and axatilimab has recently been approved by the US Food and Drug Administration as an orphan drug for IPF [132].

GM-CSF/GM-CSFR

GM-CSF recruits neutrophils and monocytes to the inflammatory site and promotes the release of proinflammatory cytokines during inflammation [133]. Clinical trials showed that early treatment with Mavrilimumab (an anti-GM-CSF-receptor- α monoclonal antibody) and Lenzilumab (an anti-human GM-CSF monoclonal antibody) could benefit patients without ventilator [134, 135]. However, Gimsilumab (an anti-GM-CSF monoclonal antibody) did not show any benefit in the treatment of COVID-19 patients [136]. The differences in the results of different clinical trials may be related to drug dosage, timing, and target population. Interestingly, GM-CSF plays an important role in maintaining RAMs homeostasis. GM-CSF levels in BALF of surviving ARDS patients were significantly higher than those of dead patients at the early stage of disease [137]. Exogenous GM-CSF was beneficial to ARDS patients with non-COVID19, and the clinical trial of Sargramostim (a man-made form of the naturally occurring protein GM-CSF) in the treatment of COVID19 (NCT04326920) was ongoing [138, 139]. However, another randomized trial of GM-CSF in the treating ARDS failed to improve the clinical outcome of ARDS patients with non-COVID-19. Researchers believe that the cause of this outcome may be related to too late administration [140]. The treatment of two completely different targets may be beneficial to the disease, while the same therapeutic target has completely different effects, which may be related to the time point of administration. It emphasizes the importance of determining the optimal treatment time window. It is, therefore, more essential and urgent to appoint reliable predictive biomarkers. By the way, HLA-DR expression in monocytes plays a guiding role in GM-CSF therapy in sepsis [141].

Morrell, ED et al. identified three different subtypes of AMs defined by surface expression of CD169 and PD-L1 in bronchoalveolar lavage fluid by cyTOF (a technology that combines elements of flow cytometry with elemental mass spectrometry). The percentages of these three types of cells were significantly different between mechanical and non-mechanical patients. And PD-L1 gene expression and PD-L1/PD-1 pathway-associated gene sets were significantly decreased in AMs from patients who experienced prolonged mechanical ventilation or death [98]. Furthermore, another study by Morrell, ED et al. proved that the expression pattern of AMs gene was highly dynamic in ARDS, especially in the first 8 days after the onset of ARDS, the inflammatory transcription characteristics of AMs were related to

meaningful endpoints [9]. Moreover, Zhao et al. determined an alveolar macrophage-related core gene set variation score (CGSVA score) composed of eight genes (PTCRA, JAG1, C1QB, ADAM17, C1QA, MMP9, VSIG4, and TNFAIP3) through bioinformatics analysis. The CGSVA score of ARDS patients was significantly higher than that of healthy patients in BALF and whole blood so that it can be used as a circulating biomarker for ARDS. It should be noted that this study's limitation is to select significantly up-regulated genes at all time points without studying the changes of the genes over time [142]. In summary, the highly dynamic expression pattern of the AMs gene can be used to determine the subtype of ARDS and guide the administration time by characterizing AMs.

Regulation of macrophage death

PD-1/PD-L1 is expected to be a biomarker and therapeutic target for ARDS. Xu, J. et al. found that the expression of PD-1 on MDMs increased in mice and humans with direct ARDS. sPD-L1 could induce apoptosis of MDM cells and alleviate lung injury in vivo [68]. Similarly, in indirect ARDS, the concentration of sPD-1 in serum and BALF increased [143]. It is reported that high expression of PD-1 in monocytes may be involved in developing sepsis [144].

Enhancing phagocytosis of macrophages

In LPS-induced inflammation, the phagocytosis of macrophages is inhibited, leading to the accumulation of apoptotic neutrophils in the lung, the sustained release of inflammatory factors, and the aggravation of inflammatory response [145, 146]. So strengthening the phagocytosis of macrophages may be an effective target for treating ARDS.

The researchers found that after incubation with BALF of ARDS patients, the expression of vascular endothelial growth factor receptor-3 (VEGFR-3) in human alveolar macrophages decreased, and the phagocytosis efficiency reduced, while VEGF-C/VEGFR-3 signaling enhances macrophage phagocytosis by upregulating integrin alpha [147]. The mitogen-activated protein kinases MEK1/2 act as an important role in acute lung injury. Compared with normal subjects, the activation level of MEK1/2-ERK1/2 pathway in alveolar macrophages of ARDS patients was increased. It is reported that Mek1 (a MEK1/2 inhibitor) enhances macrophage efferocytosis of apoptotic cells [148, 149]. AMPK is a serine-threonine protein kinase whose activator (Metformin) improves macrophage endocytosis and increases NETs (neutrophil extracellular traps) clearance [150]. And mesenchymal stem cells also can increase macrophage phagocytosis and improve ARDS by mitochondrial transfer [151]. Additionally, it was found that alpha 1 antitrypsin (A1AT) deficiency impairs macrophage phagocytosis.

In a study of patients with chronic obstructive pulmonary disease, it was found that exposure to tobacco reduced the phagocytosis of macrophages, whereas intravenous administration of A1AT increased macrophage phagocytosis and delayed disease progression and deterioration [152, 153]. Several clinical trials on A1AT treatment of COVID-19 disease are ongoing due to the anti-inflammatory, antioxidative stress response, and anti-apoptotic effects of A1AT [154, 155].

Additionally, CD47/SIRP α signal plays a vital role in macrophage phagocytosis. Shen et al. found that inhibition of SIRP α enhanced macrophage phagocytosis and alleviated acute lung injury in mice [156]. In addition, anti-SIRP α therapy can also increase the phagocytosis of circulating monocytes, prevent the long-term formation of paralyzed AMs and provide therapeutic targets for patients with impaired immune function [157]. Several CD47-SIRP α targeted drugs are currently under clinical research in the field of cancer [158]. Importantly, in the study of atherosclerosis, researchers have developed single-walled carbon nanotubes (SWNTs) containing CD47/SIRP α inhibitors based on the accumulation characteristics of SWNTs in Ly-6Chi monocytes and macrophages, which can specifically enhance the phagocytosis of cells [159]. The nano-treatment scheme provides a possibility to target mononuclear macrophages in acute lung injury. More importantly, SIRP α is expected to become a biomarker and molecular target for the treatment of ALI/ARDS in mice.

Highlight

In people with immunocompromised, the elderly is the representative group. Both chronic diseases and acute lung infections can easily attack them [160]. Among them, the increased susceptibility to lung disease in the elderly is associated with ineffective innate sensing, impaired phagocytosis, and quantitative changes in macrophages [147, 161–163]. The dysfunction of macrophages is related to pulmonary microenvironment. In the aging microenvironment, alveolar macrophages are resistant to GM-CSF signaling. The study found that treatment with GM-CSF resulted in changes in cell cycle gene expression in young adult mice, favoring a higher proliferative phenotype. Still, these were not altered in older mice [5]. By the way, it was found that hyaluronic acid levels continued to be significantly increased in the alveolar microenvironment of aged animals compared to young adult animals [5]. Hyaluronic acid is a ligand for CD44, expressed by alveolar macrophages. And the study found binding of CD44 and hyaluronic acid promotes the survival of AMs, which could be a target for treating lung inflammation [164].

Conclusion

Pulmonary macrophages are important sensors in the inflammatory response, and are responsive to changes in the microenvironment. In the course of ARDS, the functional regulation of pulmonary macrophages is complex, which is affected by cell origin, cell metabolism, and other tissue cells in the lung microenvironment. Alveolar macrophages are divided into RAMs and RecAMs, which have anti-inflammatory and pro-inflammatory functions, respectively. Both PIMs and PVMs are derived from monocytes. The former mainly plays the role of anti-inflammation and promoting fibrosis, while the latter plays the role of pro-inflammation. Moreover, RecAMs and PIMs are differentiated from classical monocytes, and PIMs can differentiate into RecAMs to promote the development of pulmonary fibrosis. But the relationship between vascular-associated PIMs or neural-associated PIMs and RecAMs is not clear. Besides, the cellular communication and interaction among AMs, PIMs and PVMs have not been fully elucidated. Among them, because there are no constitutive pulmonary vascular macrophages in the human lung, there is little research on PVMs. But PVMs may play an indispensable role in ARDS, especially ARDS caused by extrapulmonary factors. Although many studies have shown that glycolysis is associated with M1 polarization and pro-inflammatory function of lung macrophages, the mechanism between glycolysis and lung macrophages of different origins remains unclear. As a heterogeneous syndrome, different ARDS patients have different responses to treatment. In the future, it is necessary to further study the cellular dynamics of monocytes/macrophages and time-dependent changes of biomarkers in the pathogenesis of ARDS.

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