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Targeting alveolar macrophages: a promising intervention for pulmonary infection and acute lung injury

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Abstract

Pulmonary infections are common respiratory diseases caused by a variety of pathogens, some of which can lead to epidemics. When they progress to acute lung injury or acute respiratory distress syndrome, the mortality rate is high and effective treatment options are lacking. Macrophages play a crucial role in the development and progression of lung injury, and serve as core components of immune regulation in the lungs. Therefore, regulation of macrophages to intervene in the progression of infection-induced lung injury is a promising research direction. However, the existence of different macrophage subsets and their inherent heterogeneity has led to the failure of many studies to achieve effective results, thereby limiting their clinical applications. We believe that interventions targeting macrophages must consider factors, such as macrophage subsets, timing of interventions, patients' varying immune states, and clinical stages, rather than simply focusing on regulating their phenotypes. This distinction is the key to the success of macrophage-targeted therapies. In this review, we summarize the characteristics of two distinct macrophage subpopulations, lung-tissue-resident alveolar macrophages and monocyte-derived macrophages, along with intervention strategies and research progress at various time points, with the aim of providing insights and directions for future research.

Keywords: Alveolar macrophage, Pulmonary infection, Acute lung injury, Targeted therapy

Introduction

Pulmonary infections and acute lung injury (ALI) are the most prevalent respiratory ailments. Many pathogens can lead to the development of ALI and acute respiratory distress syndrome (ARDS), which have high mortality rates. During the global severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, approximately 15% of patients with coronavirus 2019 (COVID-19) developed severe pneumonia [1], and approximately 10–15% of hospitalized patients progressed to ARDS [2]. ARDS is a clinical syndrome characterized by acute respiratory failure, often triggered by various etiologies. ARDS has a high mortality rate, typically ranging from 30% to 50%. The treatment primarily relies on mechanical ventilation, oxygen therapy, and

supportive care. However, standard treatment methods (such as protective ventilation strategies) do not fully address the underlying issues of ARDS. A key challenge in the treatment of ALI and ARDS is the substantial heterogeneity [3]. The causes, clinical manifestations, and disease course of ARDS vary widely among patients, making the implementation of standardized treatment protocols more difficult. Approximately 25% of patients with ARDS may develop pulmonary fibrosis during the recovery phase [4], especially in severe cases and those who have undergone prolonged mechanical ventilation, further complicating treatment. Immune dysregulation plays a critical role in severe infections, ARDS, and fibrosis [5]. Excessive activation of the immune system can trigger severe pulmonary inflammation, leading to tissue damage and the systemic inflammatory response syndrome. In ARDS, immune dysregulation not only causes lung injury but may also lead to multi-organ failure and increased mortality. Excessive release of cytokines (such as in cytokine storms) is a key mechanism underlying the progression of infection to ARDS [6]. Therefore, the inhibition of excessive immune responses has become an important therapeutic approach for severe infections and ARDS. Glucocorticoids, IL-6 monoclonal antibodies, and other treatments have demonstrated efficacy in managing lung infections characterized by excessive immune activation [7–9]. Consequently, it is imperative to comprehensively delineate the immune profiles during the progression of lung infection and fibrosis and analyze the immune regulatory mechanisms of key cells. Such endeavors are pivotal for the advancement of novel therapeutic strategies.

Macrophages are key players in pulmonary infection and ARDS, and play crucial roles throughout the inflammatory process, including initiation, amplification, and resolution [10]. Therefore, targeting the macrophage-mediated modulation of inflammation is a key area of research and a promising therapeutic strategy. However, clinical progress in targeting macrophages has been slow to date, primarily because macrophages are highly complex, with various subpopulations and phenotypes that perform different functions at different stages [11, 12]. Distinguishing between these subtypes is essential to ensure the effectiveness of targeted interventions. Two distinct subsets of alveolar macrophages emerge within the context of infection and fibrosis: tissue-resident alveolar macrophages (TR-AMs) and monocyte-derived alveolar macrophages (MDMs), each with important roles. TR-AMs originating from the yolk sac and fetal liver are long-lived residents, whereas MDMs arise from circulating monocytes and most of them have a relatively short lifespan [13–15]. These two cell types exhibit substantial differences in metabolism, function, and other characteristics [16, 17]. TR-AMs are resident immune cells in the lungs, serving as the first line of defense and acting as the "coordinators" of pulmonary immunity [18]. They are also the first immune cell populations to undergo cell death during infection [19]. In contrast, MDMs exhibit classic macrophage characteristics and are dynamic in nature, capable of rapidly changing their phenotype in response to environmental cues [20]. Together, TR-AMs and MDMs play critical roles in the defense against pathogens. However, if either population is disrupted, such as by the excessive death of AMs or sustained activation of MDMs, the immune balance in the lungs can be disturbed, leading to excessive damage. Therefore, to effectively target macrophages, it is essential to understand their specific characteristics and dynamic changes so that targeted interventions can be appropriately applied.

Dynamics of TR-AMs and MDMs

TR-AMs reside on the luminal surface of alveolar spaces, embedded within a specialized niche formed by type I and type II alveolar epithelial cells, capillary endothelial cells, and alveolar interstitial fibroblasts [21]. MDMs can be categorized into interstitial macrophages (IMs) and alveolar lumen-residing MDMs on the basis of their anatomical locations. Under physiological conditions, IMs constitutively reside in peribronchovascular interstitial regions [22]. In contrast, alveolar lumen-localized MDMs are predominantly recruited during infectious challenges. These three macrophage subsets can be distinguished by their unique surface marker profiles [23]. While research on IMs remains in its nascent stage, current investigations predominantly focus on TR-AMs and alveolar recruited MDMs owing to their critical roles in pathogen clearance and disease pathogenesis.

The most significant characteristic of TR-AMs and MDMs lies in their temporal heterogeneity, exhibiting distinct features and exerting diverse functions across different phases. As the first responders following infection, TR-AMs not only phagocytose pathogens but also recognize them through pattern recognition receptors, subsequently releasing type I interferons (IFN-I) and interleukin-1β (IL-1β) [24, 25]. This initiating role of AMs constitutes a critical component in combating pathogens. Concurrently, TR-AMs interact with resident $CD8^+$ T cells to promote their proliferation [26]. During the intermediate inflammatory phase, MDMs replace TR-AMs as the primary effector cells. Both inflammatory and pro-reparative MDM subsets coexist in a dynamic equilibrium throughout this stage [17]. Inflammatory MDMs (iMDMs) enhance inflammatory responses through cytokine secretion, while pro-reparative MDMs (pMDMs) facilitate tissue repair via growth factor production. Simultaneously, MDMs activate lymphocytes to amplify adaptive immunity [17]. In the late phase, TR-AMs regain dominance with part of MDMs differentiation into AM-like macrophages persisting in alveolar spaces [27]. This final stage features three distinct populations: conventional TR-AMs, MHC class II-high AMs, and AM-like MDMs [27, 28]. Notably, the latter two subsets play pivotal roles in establishing innate immune memory (Fig. 1).

TR-AMS

TR-AMs serve as primary sentinels against infections and exhibit limited plasticity [20, 29]. These cells express a suppressed phenotype that mitigates unnecessary inflammation when clearing pathogens and particulates [21, 30]. Upon infection, TR-AMs swiftly activate and propagate inflammation in the lung [31]. Timely and effective signaling by AMs helps to rapidly recruit other inflammatory cells, ensuring the prompt clearance of pathogens [32]. However, both bacterial and viral pathogens can cause death of TR-AMs. Excessive AM death, particularly through necrosis and pyroptosis, exacerbates inflammation and tissue damage [33, 34] (Fig. 2). Necrosis and pyroptosis are accompanied by the release of cytokines, such as TNF, IL-1β, IL-18, CCL2, and CCL5, which amplify the inflammatory response [35, 36]. Multiple factors contribute to the death of patients with TR-AMs, with pathogenic infections being the primary trigger. Influx of pathogens often leads to cell death. Gram-negative bacteria induce AM necrosis via lipopolysaccharide (LPS) stimulation [37]. Similarly, viruses can directly infect TR-AMs, ultimately

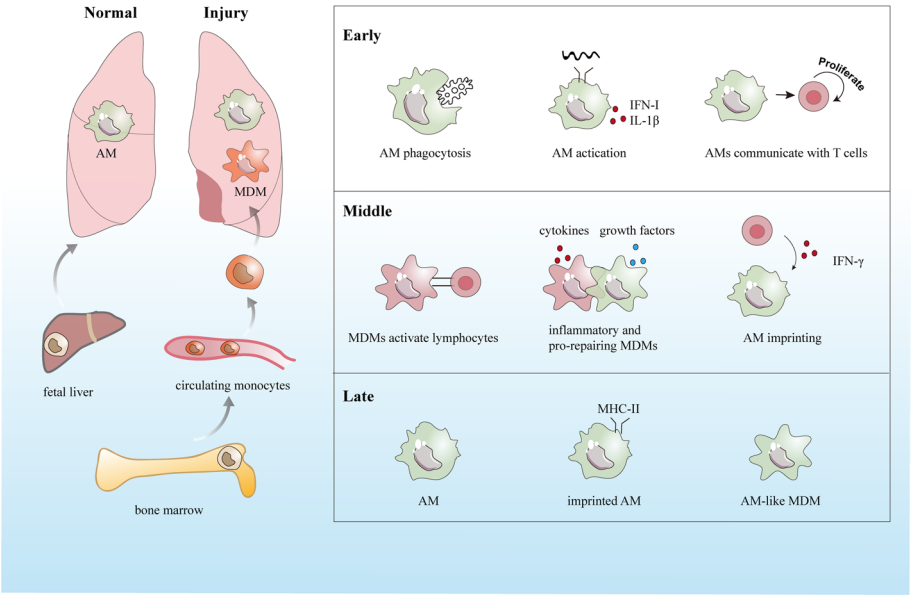

Fig. 1 TR-AMs and MDMs in infection and ALI. Initially, TR-AMs respond to pathogens via phagocytosis and IFN-I/IL-1β secretion while activating $CD8^+$ T cells. During middle phease, MDMs dominate, with iMDMs and pMDMs subtypes maintaining equilibrium—iMDMs drive cytokine responses while pMDMs promote tissue repair, concurrently enhancing adaptive immunity. In resolution, TR-AMs re-emerge alongside MHC II-high AMs and AM-like MDMs derived from MDMs, with the latter two populations crucial for immune memory. Created with Adobe Illustrator

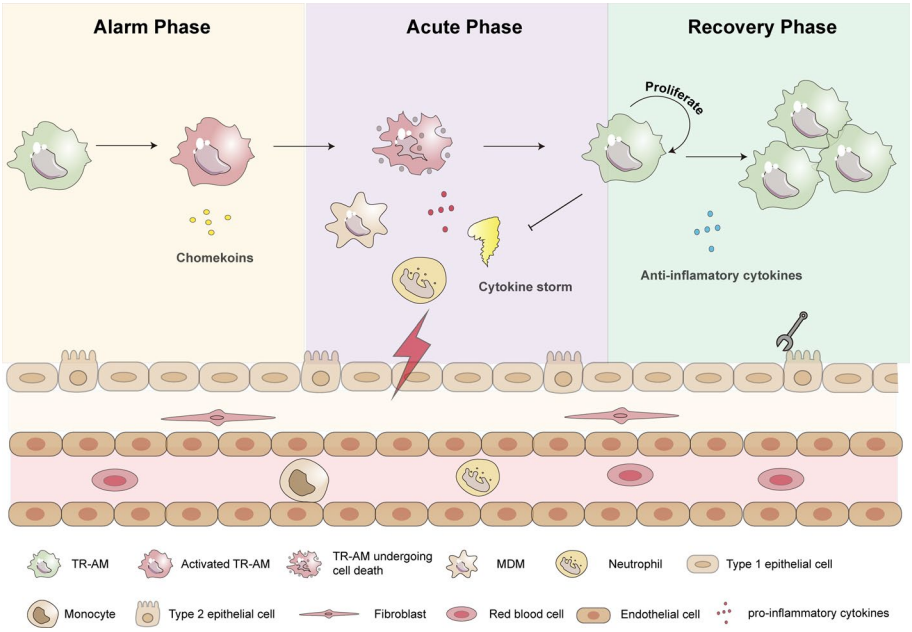

Fig. 2 Dynamic of TR-AMs in infection or ALI. After infection occurs, TR-AMs are rapidly activated, releasing cytokines and chemokines to recruit other immune cells and mediate inflammation. During the early stages of infection, TR-AMs undergo cell death, and excessive necrosis and pyroptosis can lead to uncontrolled inflammation and exacerbate lung injury. In the mid-to-late stages of normal infection, TR-AMs proliferate extensively to restore their population. Effective recovery of TR-AMs promotes inflammation resolution and tissue repair. Created with Adobe Illustrator

resulting in their demise [38]. In the case of human adenovirus infection, macrophage pyroptosis is induced through non-canonical inflammasome activation, orchestrated by NF-kB signaling, culminating in pulmonary inflammatory damage [39]. In addition to direct pathogen-induced death, other cells involved in the infection process can exacerbate AM mortality. Neutrophils release neutrophil extracellular traps, which can trigger pyroptosis in AMs, further contributing to the escalation of inflammation and tissue damage [40]. Monocyte and iMDMs both induce TR-AM death by releasing TNF-α [41].

Following the death of TR-AMs, a recovery process is initiated, which marks the onset of resolution (Fig. 2). The increased proliferation and restoration of TR-AMs signify the beginning of this phase. Newly proliferating TR-AMs often exhibit a suppressed phenotype, which facilitates the resolution of inflammation and promotes lung tissue repair [42]. Currently, the mechanisms underlying TR-AM self-recovery remain unclear; however, alterations in AM Wnt expression levels may be linked to changes in the self-proliferative capacity [43]. During the early stages of infection, the Wnt-β-catenin pathway is upregulated, leading to a pro-inflammatory phenotype in AMs. However, in later stages, the activity of the Wnt-β-catenin pathway decreases in AMs, coinciding with their transition to an anti-inflammatory state and a gradual recovery in numbers [43]. After the resolution of inflammation, the number of TR-AMs returns to normal, typically without relying on replenishment from monocytes [43, 44]. However, this issue remains the subject of ongoing debate.

MDMs

MDMs often exhibit contrasting quantitative characteristics those of AMs [17]. iMDMs are the primary drivers of excessive inflammation. They induce cytokine storms and exacerbate lung injury [34, 45]. The proportion of iMDMs is often correlated with disease severity. In severe cases, numerous iMDMs commonly accumulate in the lungs [46] (Fig. 3). The massive infiltration of iMDMs releases many inflammatory mediators that induce widespread pyroptosis, ultimately leading to lethal viral infection [47]. Therefore, an important characteristic of severe infection is numerous iMDMs in the lungs, which is often accompanied by a reduction in TR-AMs [48].

While performing pro-inflammatory and phagocytic functions, some iMDMs undergo a phenotypic transition from a pro-inflammatory state to a pro-reparative phenotype (Fig. 3). pMDMs secrete various reparative factors, such as platelet-derived growth factor, insulin-like growth factor 1 and fibroblast-derived growth factor that facilitate tissue repair [49]. Thus, MDMs are in a dynamic state, with iMDMs predominating during the early inflammatory phase and pMDMs predominating during the recovery phase [17]. At each stage, both types of MDMs coexist, and the difference lies in their relative proportions. This phenomenon may explain the inconsistent findings of previous studies focusing on macrophage phenotypes. The failure of iMDMs to effectively transition to pMDMs can result in immune dysregulation and a cytokine storm. However, the specific mechanisms governing phenotypic switching of MDMs remain to be elucidated.

Unlike other organs, most MDMs are short-lived cells that do not remain in the lungs for an extended period after fulfilling their role [14]. Instead, they undergo cell death, thereby freeing the space for TR-AMs in the lungs [50]. Normal apoptosis in MDMs is a key factor that ensure the resolution of inflammation. If MDMs persist in the lungs,

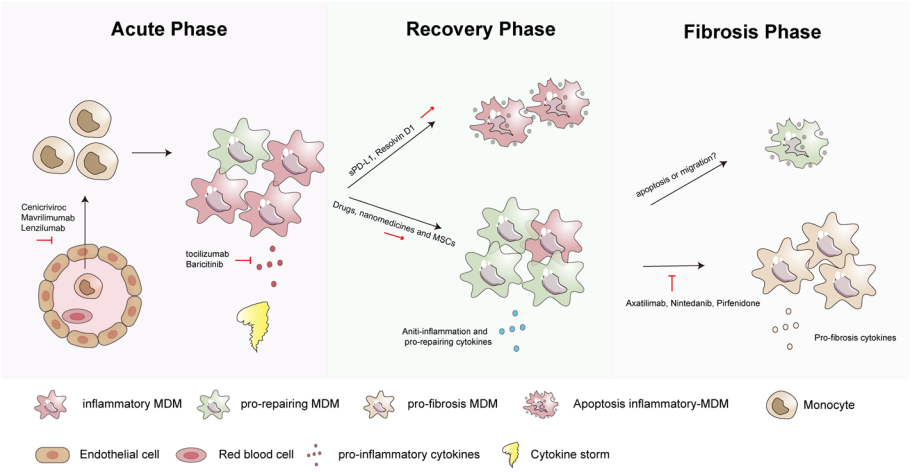

Fig. 3 Dynamic of MDMs in infection or ALI and potential therapeutic targets. In the early stages of infection, monocytes are massively recruited into the lungs and differentiate into MDMs. Excessive iMDMs are key contributors to uncontrolled inflammation and cytokine storms. Studies are ongoing to reduce iMDM infiltration, including blocking the CCL2/CCR2 axis and antagonizing GM-CSF. After exerting pro-inflammatory and pathogen-fighting effects, some iMDMs undergo apoptosis, while others transition into pMDMs. Promoting iMDM apoptosis and their transition to pMDMs helps mitigate excessive inflammation. However, persistent abnormal signaling can drive pMDMs toward a pro-fibrotic phenotype. Inhibiting the M-CSF pathway and other approaches can prevent the generation of pro-fibrotic MDMs. Created with Adobe Illustrator

they can lead to prolonged inflammation, potentially contributing to the development of fibrosis [51] (Fig. 3).

Reconstitution of TR-AMs in lung infections

TR-AMs play a protective role against infection and lung injury. A decrease in absence of TR-AMs is associated with the severity of infection [48, 52, 53]. Reducing excessive AM cell death and promptly promoting their recovery are the key strategies for interrupting promoting TR-AM function.

Preventing excessive death of TR-AMs

Cell death is a key contributor to inflammation. In COVID-19, FasL, which reflects the level of cell death, is a critical determinant of disease severity [54]. During the early phase of infection, TR-AMs act as pivotal regulators of cellular communication, and a sufficient number of TR-AMs are essential for pathogen clearance. TR-AMs are among the first cell types to initiate pyroptosis, and excessive AM death and inflammasome activation may be linked to uncontrolled inflammation [55, 56]. Macrophage pyroptosis, a gasdermin D (GSDMD)-mediated necrosis, is activated by caspase-1 or -11/4/5, which cleaves GSDMD to release its pore-forming N-terminal domain, disrupting membrane integrity [57]. This process is driven by the inflammasome, integrating sensor proteins, adaptor ASC, and procaspase-1 [58]. Caspase-1 activation via CARD interactions cleaves GSDMD and pro-cytokines (IL-1β/IL-18). Canonical activation requires dual signals: priming (TLR/NF-κB-induced NLRP3) and triggering (ATP-P2X7R, K^+ efflux, lysosomal/mitochondrial damage), linking pyroptosis to inflammation [59]. Thus, inhibition of AM pyroptosis can effectively attenuate pathological inflammatory responses.

In a mouse model of lung infection, clearing TR-AMs with clodronate liposomes reduced injury by preventing AM pyroptosis [37]. However, given the critical role of AMs in maintaining homeostasis and resolving inflammation, clearing TR-AMs may not be a suitable clinical option. Therefore, blocking the cell death pathway in AMs is a more viable strategy. Several drugs used to treat other diseases block macrophage death, thereby alleviating lung injury. Sacubitril/valsartan suppressed GSDMD-mediated macrophage pyroptosis and prevented ALI in mice [60]. Afatinib is a second-generation tyrosine kinase inhibitor that targets the epidermal growth factor receptor in non-small-cell lung cancer. Afatinib blocks activation of the NLRP3 inflammasome in macrophages and alleviates LPS-induced sepsis in vivo [61]. Lidocaine pretreatment eliminated NLRP3 activation and IL-1β release in macrophages [62]. Administration of hormones, such as melatonin, significantly attenuates H3N2-induced pulmonary damage, leukocyte infiltration, and edema; inhibits reactive oxygen species (ROS)-mediated pyroptosis; and suppresses the NLRP3/GSDMD pathway and lactate dehydrogenase release [63, 64]. Certain metabolites, such as itaconate and fumarate derivatives, and alpha-linolenic acid, can block the activation of the NLRP3 inflammasome in macrophages [65, 66]. Pretreatment with alpha-linolenic acid inhibits pyrin inflammasome-driven macrophage pyroptosis. 4-hydroxynonenal, a major endogenous product of lipid peroxidation, inhibits pyroptosis and inflammasome activation [67]. Additionally, some plant extracts block AM death. For instance, apigenin inhibited M. hyopneumoniae-induced elevation of TNF-α and necroptosis in alveolar macrophages [68].

Promoting TR-AM recovery

TR-AMs maintain lung homeostasis and the mechanisms by which they self-renew in a steady state are well recognized. AT2-derived granulocyte–macrophage colony-stimulating factor (GM-CSF) directs AM fate, establishing the postnatal AM compartment and maintaining AMs in adult lungs [69]. However, the mechanisms regulating TR-AM recovery in pulmonary infections and ALI remain poorly understood, and the therapeutic strategies for promoting TR-AM recovery are currently limited. Some studies have highlighted the role of GM-CSF in enhancing innate immunity and promoting TR-AM recovery by acting on TR-AMs [70–72]. Inhalation of GM-CSF may be an effective strategy for driving pulmonary host defense, improving oxygenation, and enhancing outcomes in pneumonia-associated ARDS [73]. Considering the role of GM-CSF in early inflammation, some studies have explored the use of GM-CSF antagonists to treat severe pneumonia [74]. Therefore, whether GM-CSF should be supplemented or blocked depends on the patient's immune status, disease stage, and number of AMs. Blocking GM-CSF during the acute inflammatory phase may help prevent the activation of the inflammatory cascade, whereas supplementing GM-CSF during the recovery phase can promote the restoration of AM numbers and accelerate the resolution of inflammation.

Direct supplementation with TR-AMs has promoted inflammation resolution and tissue repair in animal studies [43]. However, to use TR-AMs for cell therapy, challenges such as obtaining TR-AMs and their limited numbers must be addressed [75]. Researchers have explored the derivation of AMs from other cell types by inducing AMs from pluripotent stem cells and culturing them in vitro. Human induced pluripotent stem cells (iPSCs) are potential sources of AMs. iPSC-derived macrophages exhibit characteristics

and functions similar to those of resident macrophages [76, 77]. Supplementation of ALI mice with PSC-derived AMs improves survival following infection with various pathogens and accelerate tissue repair [78–80]. However, the clinical application of this approach remains unclear.

Targeting MDMs

MDMs undergo several stages of infection and lung injury, including recruitment, pro-inflammatory activation, phenotypic switching, anti-inflammatory responses, and cell death. Effective intervention strategies during inflammation and lung injury include blocking excessive MDM recruitment, inhibiting MDM-mediated inflammation, promoting a phenotypic shift toward an anti-inflammatory phenotype, and inducing iMDM death (Fig. 2).

Preventing excessive infiltration of iMDMs

Chemokine and receptor signaling are essential for MDM recruitment. Chemokines, such as CCL2 and CCL5, which are elevated in the BALF of patients with severe COVID-19, play a crucial role in MDM recruitment [45]. Therefore, blocking this signaling pathway may help inhibit MDM recruitment and alleviate inflammation. In animal studies, blocking CCR2 reduced lung injury induced by both the influenza virus and LPS [17, 81]. Lipoxin A4 downregulates LPS-induced CCL2 secretion from TR-AMs, thereby reducing the infiltration of recruited macrophages [82]. However, in clinical trials, the CCR2/CCR5 inhibitor, cenicriviroc, did not improve the recovery time in patients with COVID-19 [83, 84]. Similarly, CCR5-specific monoclonal antibodies do not effectively improve the condition of patients with COVID-19 [85]. GM-CSF also plays a role in iMDM recruitment. Mavrilimumab treatment has been shown to effectively improve clinical outcomes in patients with severe COVID-19 by reducing excessive inflammation with good tolerability [74]. The phase 3 clinical trial of lenzilumab (NCT04351152) also yielded promising results. However, another randomized controlled trial (RCT) investigating the use of otilimab for severe COVID-19 did not increase the survival and respiratory failure rates on day 28. However, otilimab treatment reduced the levels of inflammatory markers, including CCL-17 [86]**.** In contrast, an RCT of gimsilumab (NCT04351243) did not improve survival rates in patients with COVID-19 nor reduce systemic inflammation [87]. Therefore, clinical treatment is far more complex than animal experiments because animal models exhibit a higher degree of consistency, whereas clinical patients show substantial heterogeneity. In addition to chemokines, other macrophage recruitment mechanisms are also being actively studied, and the oxysterol-sensing receptor GPR183 has been identified as a driver of monocyte-macrophage infiltration into the lungs during influenza virus (IAV) and SARS-CoV-2 infection. Loss-of-function mutations in GPR183 or treatment with a GPR183 antagonist reduced macrophage infiltration and inflammatory cytokine production in the lungs of IAV- or SARS-CoV-2-infected mice. The GPR183 antagonist significantly attenuated the severity of SARS-CoV-2 infection and viral loads [88].

After recruitment to the lungs, MDMs undergo apoptosis within a few days [13]. MDM apoptosis is a normal part of the inflammation resolution process. Therefore, promoting MDM apoptosis can accelerate the resolution of inflammation. Soluble PD-L1

(sPD-L1), a potential PD-1 pathway activator, is upregulated in survivors of direct ARDS compared with that of non-survivors. In mice with direct ARDS, sPD-L1 administration reduced inflammatory lung injury, improved survival, and significantly decreased the number of MDMs exhibiting pro-inflammatory markers [89]. They also found that sPD-L1 induces MDM apoptosis in patients with direct ARDS. Resolvin D1, an endogenous lipid mediator derived from docosahexaenoic acid, can also increase MDM apoptosis, partly via the FasL-FasR/caspase-3 signaling pathway and alleviate acute lung injury [90].

Preventing persistent activation of iMDMs and promoting their transition

The sustained and abnormal activation of MDMs is a key contributor to immune dysregulation [45]. Abnormally activated macrophages continuously release cytokines with high levels of pro-inflammatory factors that drive macrophage activation, thereby creating a positive feedback loop. However, the mechanisms underlying abnormal MDM activation remain unclear. Endothelial cells may play a role in this process. In sepsis, the number of circulating endothelial cell-derived extracellular vesicles increases, exacerbating lung injury by targeting monocytes and reprogramming them into iMDMs [91]. Additionally, overexpressed VCAM1 on EC-EVs activates the NF-κB pathway by interacting with integrin subunit alpha 4 on the monocyte surface, thereby regulating monocyte differentiation [91]. Multiple signaling pathways, such as JNK, Notch, JAK/STAT, and TLR4/NF-κB, mediate the phenotypic modulation of macrophages. JNK promotes M1-associated inflammation mediated partly via cAMP/PKA signaling [92]. Notch activation drives M1 polarization via canonical and non-canonical pathways, suppressing M2 genes [93]. JAK/STAT signaling integrates cytokine cues: STAT1/STAT3 drive M1 polarization and inflammation, while STAT6 mediates IL-4/IL-13-induced M2 activation [94]. TLR4 engages MyD88-dependent and MyD88-independent pathways to promote M1 polarization, while NF-κB also resolves inflammation and supports M2 polarization [95]. Macrophage phenotypic switching is highly complex, and accompanied by a shift in metabolism from fatty acid metabolism to fatty acid oxidation and oxidative phosphorylation [96]. The modulation of macrophage inflammatory responses or promotion of phenotypic transitions is one of the most actively researched areas. From early stage chemical agents and pharmaceuticals to the development of nanodrugs and biological therapies, advancements have underscored the significance of this direction in macrophage-targeted interventions.

Drugs and chemical agents

Owing to the positive feedback loop between aberrant MDM activation and cytokine storm, blocking the cytokine storm can help prevent persistent MDM activation. IL-6 plays a central role in the cytokine storm [97]. Blocking IL-6 or its receptor can interrupt the cytokine storm and prevent further deterioration of the condition. IL-6 receptor antagonists, such as tocilizumab, have shown promising effects in the treatment of severe COVID-19, significantly improving clinical outcomes [9]. Other cytokine and receptor antagonists, such as the IL-1 antagonist anakinra, did not improve clinical outcomes in patients with C-reactive protein (CRP) levels > 25 mg/L [98]. However, it reduced mortality in patients with soluble urokinase plasminogen receptor (suPAR) levels greater than 6 ng/mL [99]. Similarly, the IL-1β antagonist, canakinumab, and the

IL-17 antagonist, secukinumab, did not improve clinical outcomes in severe COVID-19 cases [100, 101]. In addition to cytokines, JAK inhibitors, such as baricitinib and tofacitinib, inhibit excessive inflammation. Both baricitinib and tofacitinib significantly reduced mortality in patients with COVID19 [102, 103].

In addition to specifically antagonizing certain cytokines or signaling pathways, broad-spectrum anti-inflammatory strategies are crucial to prevent excessive inflammation and persistent macrophage activation. Glucocorticoids are the most widely used drugs. Dexamethasone can reduce 28-day all-cause mortality in critically ill patients [104]. However, systemic corticosteroid therapy can lead to significant side effects that limit its clinical use. Some studies have combined dexamethasone with hyaluronic acid for targeted delivery to inflamed lung tissue. Intravenously administered hyaluronic acid-dexamethasone selectively accumulates in lung macrophages, offering superior anti-inflammatory effects compared with that of traditional dexamethasone, while reducing the required dose [105]. Other unconventional therapeutic agents, such as olopatadine hydrochloride, a potential NF-κB inhibitor, reduce mortality in LPS-induced ALI. Olopatadine hydrochloride also attenuates LPS-induced elevation of pro-inflammatory markers, oxidative stress, neutrophil infiltration, edema, and lung damage [106]. Mivebresib, a BET protein-bromodomain-containing protein 4 inhibitor, can suppress the inflammatory phenotype of macrophages as well as the secretion of IL-6 and TNF-α [107]. Through its inhibition of ZEB1, metformin suppresses mitochondrial translation, thereby promoting the transition of inflammatory macrophages to an anti-inflammatory phenotype [108].

Activation of NF-κB is one of the key mechanisms for the activation of monocytes and macrophages. Inhibiting NF-κB may help block the excessive activation of MDMs, preventing the overdevelopment of inflammation [109]. For example, nestorone inhibits the TLR-4/MyD88/NF-κB pathway in macrophages, thereby reducing acute lung inflammation and alleviating diffuse alveolar damage [110]. The thyroid hormone analog GC-1 may suppress NF-κB signaling activation, selectively blocking M1 macrophage polarization through the DNMT3b-PPARγ-NF-κB pathway [111]. Many metabolic products also play roles in regulating macrophage inflammation. Itaconic acid suppresses macrophage inflammation by inhibiting TET family DNA dioxygenases, thereby alleviating lung injury [112]. Trace elements, such as zinc, along with vitamins, such as C and D, are often depleted in patients with sepsis and ARDS. Dietary supplementation with these molecules significantly inhibits NF-κB activation [113–116].

Nanomedicines

Conventional drugs may have drawbacks, such as poor targeting, low bioavailability, and substantial side effects. Combining drugs with nanoparticle platforms can enhance their efficacy, reduce the required dosage, and minimize side effects. For example, encapsulating dexamethasone in liposomes improves targeting, reduces side effects, effectively targets macrophages and alleviates lung inflammation [117, 118]. In addition to liposomes, new nanoparticle platforms have been recently developed to further enhance targeting efficiency and safety. These advanced platforms offer improved specificity for targeted delivery and reduced toxicity, making them promising options for drug delivery and therapeutic intervention. By engineering neutrophil nanovesicles with cholesterols,

Meng et al. made an extracellular nanovesicle-based delivery (iSEND) system, and the nanoDEX, made by encapsulating DEX with the iSEND, showed improved targeting to macrophages and neutralized broad-spectrum cytokines [119]. Liu et al. developed a new inhalable nanoplatform (D-SEL) by conjugating DNase I to a serum exosomal and liposomal hybrid nanocarrier (SEL), and encapsulating methylprednisolone sodium succinate (MPS). After inhalation, MPS/D-SEL remains in the alveoli for more than 24 h, precisely targeting macrophages and promoting their transition to the repair phenotype [120]. Peng et al. [121] developed a novel inhalable nanozyme therapeutic platform. This platform consisted of engineered cerium-based tannic acid nanozymes bound to self-assembling peptides. The nanozyme primarily targets activated macrophages and epithelial cells at sites of inflammation. In a mouse model of viral pneumonia in an oxidative environment, nanozymes assembled into catalytically active structures that reduced the production of ROS and pro-inflammatory cytokines. This promotes macrophage polarization toward the M2 phenotype, which is favorable for healing. In a mouse model of viral pneumonia with a secondary bacterial infection, the nanozyme alleviated bacterial inflammation and reduced tissue damage [121]. Fan et al. synthesized ROS-responsive red light-emitting carbon dots (RCMNs) that target lung macrophages. RCMNs alleviate inflammation in ALI by improved macrophage activity and decreased inflammatory cytokines such as TNF-α and IL-6 [122].

Probiotic-based nanoparticles have been developed to regulate the pulmonary microbiome and modulate macrophages for the treatment of bacterial pneumonia [123]. Probiotic-based nanoparticles of OASCLR were formed by coating live Lactobacillus rhamnosus with chitosan, hyaluronic acid, and ononin. OASCLR interacts with the binding site of CD44 on macrophages, thereby inhibiting their inflammatory response and alleviating excessive inflammation [123]. CRISPR/Cas9 technology can be combined with nanotechnology for specific gene editing in macrophages to enable targeted regulation. This approach allows the precise modification of macrophage function by directly altering the genes involved in inflammation, immune response, or tissue repair, offering a promising therapeutic strategy. Huang et al. [124] found that hexokinase 2 (HK2) is a key regulator of macrophage metabolism and inflammation. They developed an aerosolized core–shell liposomal nanoplatform (CSNs) to encapsulate an mRNA-based CRISPR/Cas9 system (mCas9/gHK2). CSN-mCas9/gHK2 treatment effectively knocked out HK2, thus reducing glycolysis and inflammation in macrophages [124]. This demonstrates that the combination of nanotechnology and CRISPR/Cas9 technology has broad potential as a powerful tool for the precise modulation of macrophage metabolism and immune responses in various therapeutic contexts (Table 1).

Mesenchymal stem cells

Owing to their powerful ability to regulate immune and inflammatory responses, mesenchymal stem cells (MSCs) are emerging as promising tools for cell-based therapies in immune and inflammatory diseases [125]. MSCs suppress inflammation in MDMs and promote their phenotypic shift toward a repair phenotype. The mechanisms by which MSCs regulate MDMs are diverse, the most prominent being their secretome, which includes extracellular vesicles, exosomes, and various other reparative factors [126–128]. Apoptosis of MSCs is another mechanism by which they exert their effects. Blocking

Table 1 New nanoplatforms targeting macrophages in lung infection or ALI

Platforms	Methods	Mechanisms	Models	References
iSEND system	Engineering neutrophil nanovesicles with cholesterols to deliver DEX	Deliver DEX for targeting macrophage	Mice Rats Rhesus macaques COVID-19	120
D-SEL nanoplatform	Conjugating DNase I to a serum exosomal and liposomal hybrid nanocarrier (SEL), and encapsulating met-hylprednisolone sodium succinate	Delivered methylprednisolone sodium succinate into macrophages for promoting M2 macrophage polarization	Mice ALI	121
CeTA-K_1tkP	Engineered cerium-based tannic acid nanozymes bound to self-assembling peptides	Nanozyme aggregates into catalytically active structures that promote macrophage polarization to the M2 phenotype	Mice Viral pneumonia	122
RCMNs	ROS-responsive red fluorescent carbon dot-TK-methyl-prednisolone nanoparticles were generated through a series of chemical reactions and purification steps	Targeting ROS-damaged tissue and improving alveolar macrophage activity, decreased inflammatory cytokines	Mice ALI	123
Probiotic-based nanoparticles	Coating live Lactobacillus rhamnosus with chitosan, hyaluronic acid, and ononin	Targeting inflammatory macrophages by the interaction of OASCLR with the macrophage binding site of CD44 and alleviate overactive immune responses	Mice Bacterial pneumonia	124
The CSN-mCas9/gHK2 system	An aerosolized core–shell liposomal nanoplatform (CSNs) to encapsulate an mRNA-based CRISPR/Cas9 system	CSN-mCas9/gHK2 treatment effectively knocked out HK2, thus reducing glycolysis and inflammation in macrophages	Mice ALI	125

MSC apoptosis may potentially reduce the therapeutic efficacy [129]. In addition to inhibiting inflammation and promoting the phenotypic shift of macrophages toward a repair phenotype, MSCs enhance macrophage phagocytic ability by secreting migrasomes, thereby facilitating bacterial clearance [130].

MSCs commonly used in biological therapy include human placental MSCs (hPMSCs), adipose MSCs (hADMSCs), bone marrow MSCs (hBMMSCs), and umbilical cord MSCs (hUCMSCs) [131]. In bacterial pneumonia and lung injury models, hPMSCs effectively alleviate lung damage, reduce mortality in severe pneumonia, decrease the recruitment of inflammatory macrophages, and reduce the secretion of pro-inflammatory cytokines [132, 133]. Exosomes from ADMSCs enabled macrophages shifting to an anti-inflammatory phenotype, as featured with the downregulation of IL-1β, TNF-α, and iNOS secretion and increase in production of anti-inflammatory cytokines, IL-10 and Arg-1 [134]. Deng et al. [135] compared the efficacy of human MSC-derived exosomes from human adipose tissue, bone marrow, and umbilical cord in the treatment of sepsis-induced ARDS. They found that exosomes derived from different sources of hMSCs effectively downregulated sepsis-induced glycolysis and inflammation in macrophages, ameliorated pathological lung damage, and improved the survival rate of mice with sepsis. Notably, the protective effect of hADMSC-exos was better than that of hBMMSC-exo and hUCMSC-exo [135]. Li et al. compared the therapeutic differences between UCMSCs and PMSCs in treating lung damage and found that UCMSCs demonstrated better therapeutic effects on lung injury than that of PMSCs. Under cytokine stimulation, UCMSCs express higher levels of inflammation-related genes than that with PMSCs and more effectively guide macrophages toward polarization into the M2 phenotype [136]. Current stem cell therapies can be administered via the intravenous or intratracheal routes. Song et al. [137] found that intravenous stem cell therapy provided better outcomes in alleviating lung inflammation and fibrosis. Additionally, early and repeated intravenous treatments significantly enhanced therapeutic efficacy [137].

Priming is considered an effective approach for stimulating and enhancing the therapeutic efficacy of MSCs [138]. The most commonly used priming agents are cytokines, such as IFN-γ and TNF-α [138]. Hypoxia is a commonly used priming strategy. Hypoxia-preconditioned MSCs alleviate inflammation and ALI by promoting efferocytosis and anti-inflammatory polarization of macrophages [139]. Hypoxia-preconditioned MSCs exhibit increased proliferation and decreased cell senescence1 [139]. PGE2-priming MSC therapy significantly reduce the severity of LPS-induced ALI in mice by modulating macrophage polarization and cytokine production. This strategy enhanced the therapeutic efficacy of MSCs in the cell-based treatment for ALI [140].

Targeting pro-fibrosis MDMs

Lung injury is often accompanied by the development of pulmonary fibrosis, and the persistent presence of abnormal MDMs is a major contributor to the onset of fibrosis [141]. These dysfunctional MDMs drive chronic inflammation and fibrosis by releasing cytokines and growth factors, leading to excessive deposition of extracellular matrix and tissue remodeling. As MDMs, rather than AMs, play a primary role in promoting fibrosis [142, 143], blocking MDM recruitment is also a strategy to prevent lung fibrosis. The M-CSF signaling pathway is critical for inducing the pro-fibrotic phenotype of MDMs.

Blocking the M-CSFR signaling pathway reduces the number of MDMs and severity of lung fibrosis without affecting the number of TR-AMs [143]. Axatilimab, a monoclonal antibody targeting the colony-stimulating factor 1 receptor (CSF-1R), is a novel and therapeutically promising approach for inhibiting pro-fibrotic macrophages in phase I/II studies. Its favorable safety profile makes it a viable option for refractory chronic graft-versus-host diseases [144, 145]. In 2024, axatilimab was approved approval in the USA, marking a significant advancement in its clinical application [146]. SHP-1 agonists suppress CSF1R expression, inactivate the STAT3/NF-κB signaling pathways, and ultimately inhibit macrophage survival, disrupting macrophage polarization [147]. Nintedanib, a broad-spectrum kinase inhibitor approved for idiopathic pulmonary fibrosis treatment, inhibits CSF-1R expression in both human and mouse MDMs [148]. Pirfenidone, another drug used for pulmonary fibrosis treatment, inhibits the mechanical activation of MDMs by suppressing integrin αMβ2 and Rho-associated kinase 2 [149]. In addition to the CSF-1R signaling pathway, the Notch signaling pathway may play a role in MDM-induced pulmonary fibrosis. Blocking the Notch signaling pathway reduces the degree of fibrosis and this effect is dependent on MDMs [142]. Chemical agents, such as diphenyleneiodonium chloride, and metabolites, such as itaconate can modulate MDM function and inflammatory responses [150, 151]. Various nanoparticle-based drugs are promising for targeting MDMs. Niclosamide-loaded nanoparticles and mannosylated albumin nanoparticles specifically targeted MDMs in animal studies, blocking the TGF-β/Smad signaling pathway and reducing pulmonary fibrosis [152, 153].

Discussion

Macrophages play a crucial role in infections and lung injury, and targeting them for the treatment of severe infections and lung damage has considerable therapeutic potential. However, owing to the numerous subtypes and strong heterogeneity of macrophages, multiple populations can coexist at any given time, each of which performs distinct functions. This complexity makes the development of macrophage-targeted therapies challenging. TR-AMs and MDMs have fundamentally different characteristics, requiring distinct targeting strategies. Therefore, we advocate for future research on macrophages to distinguish between these two cell types rather than merely categorizing them into M1 and M2 phenotypes.

TR-AMs play a protective role in infection and ALI owing to their involvement in initiating inflammation and maintaining homeostasis [154]. The excessive death of TR-AMs during the early stages of inflammation exacerbates both inflammation and tissue damage. Beyond this, if the TR-AM numbers are not promptly restored during the recovery phase, inflammation alleviation and tissue repair may be delayed. Therefore, the primary therapeutic strategy for targeting TR-AMs is to prevent excessive cell death, while promoting recovery in terms of quantity. Recently, substantial progress has been made in the study of cell death mechanisms and various approaches for blocking cell death have emerged [59]. However, the mechanisms underlying the restoration of TR-AMs remain unclear, and as a result, targeted strategies for this purpose are limited. Further research is needed to identify how TR-AMs regenerate and how this process can be effectively harnessed to improve recovery from lung injury.

MDMs exhibited greater plasticity and heterogeneity than TR-AMs. In the early stages of inflammation, MDMs are key drivers of pro-inflammatory responses, whereas in the later stages, they transition into crucial cells for tissue repair. Therefore, the core strategy for targeting MDMs is to inhibit excessive inflammation, while promoting their transition to a reparative phenotype. This approach has been the focus of extensive research, and numerous chemical agents, drugs, and biological therapies have emerged as potential solutions [155, 156]. In the later stages of inflammation, MDM apoptosis resolves inflammation. Therefore, the promotion of MDM apoptosis may accelerate recovery. However, the final fate of MDMs is not fully understood. In addition to cell death, MDMs may also undergo migration, which adds complexity to their role in inflammation resolution. Thus, understanding the trajectories of TR-AMs and MDMs is crucial for developing targeted therapies. Furthermore, targeting pro-fibrotic MDMs is a key research focus. Clinical trials involving drugs that block the CSF-1R signaling pathway have yielded promising results in terms of reducing fibrosis. However, the exact mechanisms by which MDMs develop a pro-fibrotic phenotype remain unclear. Further research is needed to understand this process and refine targeted therapeutic strategies.

Regardless of the regulatory approach, it is essential to consider the optimal timing for application because the same treatment may have drastically different effects at different stages. For example, blocking cell death can prevent the exacerbation of inflammation in the early stages; however, inhibiting macrophage death in later stages may interfere with the normal resolution of MDMs, thereby delaying the resolution of inflammation. Similarly, antagonizing GM-CSF can block the occurrence of cytokine storms in the context of excessive immune responses; however, inhibiting GM-CSF during the recovery phase may impair AM function and hinder the recovery of inflammation. Moreover, immunotherapy should be tailored to each patient's immune status. For example, the use of the IL-1 inhibitor anakinra did not improve clinical outcomes in patients when suPAR levels were not stratified [98]. However, when suPAR levels were >6 ng/ml, anakinra significantly improved survival rates [99]. This underscores the importance of personalized immunotherapy, in which treatments are based on patient-specific immune profiles, to optimize therapeutic outcomes. Currently, the assessment of immune status in patients with pulmonary infections and ALI/ARDS is unclear. The evaluation primarily relies on certain inflammatory markers such as CRP and IL-6. However, to achieve optimal results with macrophage-targeted therapies, it is essential to explore better methods for assessing the immune state of the lungs. The ratio of AM to MDM, as well as the proportions of iMDMs and pMDMs, could serve as effective indicators of the immune system within the lungs and guide targeted macrophage therapies. Currently, only single-cell RNA sequencing can accurately distinguish between the different subpopulations and phenotypes of lung macrophages. Owing to the high cost of this technology, its clinical application is limited. Therefore, future targeted therapies will inevitably require precision medicine approaches and the development of more accessible and effective methods for distinguishing immune states is crucial for improving clinical outcomes.

Abbreviations

ALI	Acute lung injury
ARDS	Acute respiratory distress syndrome
TR-AMs	Tissue-resident alveolar macrophages

MDMs	Monocyte-derived alveolar macrophages
iMDMs	Inflammatory MDMs
LPS	Lipopolysaccharide reactive
ROS	Reactive oxygen species
PGE2	Prostaglandin E2
GM-CSF	Granulocyte-macrophage colony-stimulating factor
BALF	Bronchoalveolar lavage fluid
iPSCs	Induced pluripotent stem cells
RCT	Randomized controlled trial
IAV	Influenza virus
CRP	C-reactive protein mesenchymal stem cells
MSC	Mesenchymal stem cells
hPMSCs	Human placental MSCs
hADMSCs	Human adipose MSCs
hBMMSCs	Human bone marrow MSCs
hUCMSCs	Human umbilical cord MSCs
CSF-1R	Colony-stimulating factor 1
suPAR	Receptor plasminogen receptor

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References

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054–62.
2. Azagew AW, Beko ZW, Ferede YM, Mekonnen HS, Abate HK, Mekonnen CK. Global prevalence of COVID-19-induced acute respiratory distress syndrome: systematic review and meta-analysis. Syst Rev. 2023;12(1):212.
3. Khan YA, Fan E, Ferguson ND. Precision medicine and heterogeneity of treatment effect in therapies for ARDS. Chest. 2021;160(5):1729–38.
4. Wu X, Liu X, Zhou Y, Yu H, Li R, Zhan Q, et al. 3-month, 6-month, 9-month, and 12-month respiratory outcomes in patients following COVID-19-related hospitalisation: a prospective study. Lancet Respir Med. 2021;9(7):747–54.
5. Zheng J, Li Y, Kong X, Guo J. Exploring immune-related pathogenesis in lung injury: providing new insights Into ALI/ARDS. Biomed Pharmacother. 2024;175:116773.
6. Fajgenbaum DC, June CH. Cytokine storm. N Engl J Med. 2020;383(23):2255–73.
7. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in hospitalized patients with covid-19. N Engl J Med. 2021;384(8):693–704.
8. Higgins AM, Berry LR, Lorenzi E, Murthy S, McQuilten Z, Mouncey PR, et al. Long-term (180-Day) outcomes in critically ill patients with COVID-19 in the REMAP-CAP randomized clinical trial. JAMA. 2023;329(1):39–51.
9. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021;397(10285):1637–45.
10. Tao H, Xu Y, Zhang S. The role of macrophages and alveolar epithelial cells in the development of ARDS. Inflammation. 2023;46(1):47–55.

11. Murray PJ, Wynn TA. Protective and pathogenic functions of macrophage subsets. Nat Rev Immunol. 2011;11(11):723–37.
12. Morales-Nebreda L, Misharin AV, Perlman H, Budinger GR. The heterogeneity of lung macrophages in the susceptibility to disease. Eur Respir Rev. 2015;24(137):505–9.
13. Janssen WJ, Barthel L, Muldrow A, Oberley-Deegan RE, Kearns MT, Jakubzick C, et al. Fas determines differential fates of resident and recruited macrophages during resolution of acute lung injury. Am J Respir Crit Care Med. 2011;184(5):547–60.
14. Janssen WJ, Bratton DL, Jakubzick CV, Henson PM. Myeloid cell turnover and clearance. Microbiol Spectr. 2016. https://doi.org/10.1128/microbiolspec.MCHD-0005-2015.
15. Yona S, Kim KW, Wolf Y, Mildner A, Varol D, Breker M, et al. Fate mapping reveals origins and dynamics of monocytes and tissue macrophages under homeostasis. Immunity. 2013;38(1):79–91.
16. Mould KJ, Barthel L, Mohning MP, Thomas SM, McCubbrey AL, Danhorn T, et al. Cell origin dictates programming of resident versus recruited macrophages during acute lung injury. Am J Respir Cell Mol Biol. 2017;57(3):294–306.
17. Hou F, Wang H, Zheng K, Yang W, Xiao K, Rong Z, et al. Distinct transcriptional and functional differences of lung resident and monocyte-derived alveolar macrophages during the recovery period of acute lung injury. Immune Netw. 2023;23(3): e24.
18. Pervizaj-Oruqaj L, Ferrero MR, Matt U, Herold S. The guardians of pulmonary harmony: alveolar macrophages orchestrating the symphony of lung inflammation and tissue homeostasis. Eur Respir Rev. 2024;33(172):230263.
19. Grant RA, Morales-Nebreda L, Markov NS, Swaminathan S, Querrey M, Guzman ER, et al. Circuits between infected macrophages and T cells in SARS-CoV-2 pneumonia. Nature. 2021;590(7847):635–41.
20. Kulikauskaite J, Wack A. Teaching old dogs new tricks? The plasticity of lung alveolar macrophage subsets. Trends Immunol. 2020;41(10):864–77.
21. Westphalen K, Gusarova GA, Islam MN, Subramanian M, Cohen TS, Prince AS, et al. Sessile alveolar macrophages communicate with alveolar epithelium to modulate immunity. Nature. 2014;506(7489):503–6.
22. Hume PS, Gibbings SL, Jakubzick CV, Tuder RM, Curran-Everett D, Henson PM, et al. Localization of macrophages in the human lung via design-based stereology. Am J Respir Crit Care Med. 2020;201(10):1209–17.
23. Aegerter H, Lambrecht BN, Jakubzick CV. Biology of lung macrophages in health and disease. Immunity. 2022;55(9):1564–80.
24. Peiró T, Patel DF, Akthar S, Gregory LG, Pyle CJ, Harker JA, et al. Neutrophils drive alveolar macrophage IL-1β release during respiratory viral infection. Thorax. 2018;73(6):546–56.
25. Goritzka M, Makris S, Kausar F, Durant LR, Pereira C, Kumagai Y, et al. Alveolar macrophage-derived type I interferons orchestrate innate immunity to RSV through recruitment of antiviral monocytes. J Exp Med. 2015;212(5):699–714.
26. Kawasaki T, Ikegawa M, Yunoki K, Otani H, Ori D, Ishii KJ, et al. Alveolar macrophages instruct CD8(+) T cell expansion by antigen cross-presentation in lung. Cell Rep. 2022;41(11): 111828.
27. Aegerter H, Kulikauskaite J, Crotta S, Patel H, Kelly G, Hessel EM, et al. Influenza-induced monocyte-derived alveolar macrophages confer prolonged antibacterial protection. Nat Immunol. 2020;21(2):145–57.
28. Yao Y, Jeyanathan M, Haddadi S, Barra NG, Vaseghi-Shanjani M, Damjanovic D, et al. Induction of autonomous memory alveolar macrophages requires T cell help and is critical to trained immunity. Cell. 2018;175(6):1634-1650.e17.
29. Guilliams M, Svedberg FR. Does tissue imprinting restrict macrophage plasticity? Nat Immunol. 2021;22(2):118–27.
30. Neupane AS, Willson M, Chojnacki AK, Vargas ESCF, Morehouse C, Carestia A, et al. Patrolling alveolar macrophages conceal bacteria from the immune system to maintain homeostasis. Cell. 2020;183(1):110-125.e111.
31. Zhang X, Mosser DM. Macrophage activation by endogenous danger signals. J Pathol. 2008;214(2):161–78.
32. Liu X, Boyer MA, Holmgren AM, Shin S. Legionella-infected macrophages engage the alveolar epithelium to metabolically reprogram myeloid cells and promote antibacterial inflammation. Cell Host Microbe. 2020;28(5):683-698.e686.
33. Qin X, Zhou Y, Jia C, Chao Z, Qin H, Liang J, et al. Caspase-1-mediated extracellular vesicles derived from pyroptotic alveolar macrophages promote inflammation in acute lung injury. Int J Biol Sci. 2022;18(4):1521–38.
34. Junqueira C, Crespo Â, Ranjbar S, de Lacerda LB, Lewandrowski M, Ingber J, et al. FcγR-mediated SARS-CoV-2 infection of monocytes activates inflammation. Nature. 2022;606(7914):576–84.
35. Vringer E, Tait SWG. Mitochondria and cell death-associated inflammation. Cell Death Differ. 2023;30(2):304–12.
36. Bertheloot D, Latz E, Franklin BS. Necroptosis, pyroptosis and apoptosis: an intricate game of cell death. Cell Mol Immunol. 2021;18(5):1106–21.
37. Cohen TS, Prince AS. Activation of inflammasome signaling mediates pathology of acute *P. aeruginosa* pneumonia. J Clin Invest. 2013;123(4):1630–7.
38. Santos LD, Antunes KH, Muraro SP, de Souza GF, da Silva AG, de Souza FJ, et al. TNF-mediated alveolar macrophage necroptosis drives disease pathogenesis during respiratory syncytial virus infection. Eur Respir J. 2021;57(6):2003764.
39. Li L, Fan H, Zhou J, Xu X, Yang D, Wu M, et al. Human adenovirus infection induces pulmonary inflammatory damage by triggering noncanonical inflammasomes activation and macrophage pyroptosis. Front Immunol. 2023;14:1169968.
40. Li H, Li Y, Song C, Hu Y, Dai M, Liu B, et al. Neutrophil extracellular traps augmented alveolar macrophage pyroptosis via AIM2 inflammasome activation in LPS-induced ALI/ARDS. J Inflamm Res. 2021;14:4839–58.
41. Xiao J, Hou F, Wang H, Wang R, Liu Y, Wu X, et al. Monocyte-derived macrophages induce alveolar macrophages death via TNF-α in acute lung injury. Immun Inflamm Dis. 2024;12(12):e70081.
42. Pervizaj-Oruqaj L, Selvakumar B, Ferrero MR, Heiner M, Malainou C, Glaser RD, et al. Alveolar macrophage-expressed Plet1 is a driver of lung epithelial repair after viral pneumonia. Nat commun. 2024;15(1):87.
43. Zhu B, Wu Y, Huang S, Zhang R, Son YM, Li C, et al. Uncoupling of macrophage inflammation from self-renewal modulates host recovery from respiratory viral infection. Immunity. 2021;54(6):1200-1218.e1209.

44. Hashimoto D, Chow A, Noizat C, Teo P, Beasley MB, Leboeuf M, et al. Tissue-resident macrophages self-maintain locally throughout adult life with minimal contribution from circulating monocytes. Immunity. 2013;38(4):792–804.
45. Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol. 2020;20(6):355–62.
46. Zhang F, Mears JR, Shakib L, Beynor JI, Shanaj S, Korsunsky I, et al. IFN-γ and TNF-α drive a CXCL10+ CCL2+ macrophage phenotype expanded in severe COVID-19 lungs and inflammatory diseases with tissue inflammation. Genome Med. 2021;13(1):64.
47. Corry J, Kettenburg G, Upadhyay AA, Wallace M, Marti MM, Wonderlich ER, et al. Infiltration of inflammatory macrophages and neutrophils and widespread pyroptosis in lung drive influenza lethality in nonhuman primates. PLoS Pathog. 2022;18(3):e1010395.
48. Liao M, Liu Y, Yuan J, Wen Y, Xu G, Zhao J, et al. Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19. Nat Med. 2020;26(6):842–4.
49. Malainou C, Abdin SM, Lachmann N, Matt U, Herold S. Alveolar macrophages in tissue homeostasis, inflammation, and infection: evolving concepts of therapeutic targeting. J Clin Invest. 2023;133(19):e170501.
50. Guilliams M, Scott CL. Does niche competition determine the origin of tissue-resident macrophages? Nat Rev Immunol. 2017;17(7):451–60.
51. Bailey JI, Puritz CH, Senkow KJ, Markov NS, Diaz E, Jonasson E, et al. Profibrotic monocyte-derived alveolar macrophages are expanded in patients with persistent respiratory symptoms and radiographic abnormalities after COVID-19. Nat Immunol. 2024;25(11):2097–109.
52. Cardani A, Boulton A, Kim TS, Braciale TJ. Alveolar macrophages prevent lethal influenza pneumonia by inhibiting infection of type-1 alveolar epithelial cells. PLoS Pathog. 2017;13(1):e1006140.
53. Schneider C, Nobs SP, Heer AK, Kurrer M, Klinke G, van Rooijen N, et al. Alveolar macrophages are essential for protection from respiratory failure and associated morbidity following influenza virus infection. PLoS Pathog. 2014;10(4):e1004053.
54. Albert MC, Uranga-Murillo I, Arias M, De Miguel D, Peña N, Montinaro A, et al. Identification of FasL as a crucial host factor driving COVID-19 pathology and lethality. Cell Death Differ. 2024;31(5):544–57.
55. Zhang M, Lan H, Jiang M, Yang M, Chen H, Peng S, et al. NLRP3 inflammasome mediates pyroptosis of alveolar macrophages to induce radiation lung injury. J Hazard Mater. 2024;484:136740.
56. Sefik E, Qu R, Junqueira C, Kaffe E, Mirza H, Zhao J, et al. Inflammasome activation in infected macrophages drives COVID-19 pathology. Nature. 2022;606(7914):585–93.
57. Shi J, Zhao Y, Wang K, Shi X, Wang Y, Huang H, et al. Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death. Nature. 2015;526(7575):660–5.
58. von Moltke J, Ayres JS, Kofoed EM, Chavarría-Smith J, Vance RE. Recognition of bacteria by inflammasomes. Annu Rev Immunol. 2013;31:73–106.
59. Fan EKY, Fan J. Regulation of alveolar macrophage death in acute lung inflammation. Respir Res. 2018;19(1):50.
60. Wang J, Li J, Lou A, Lin Y, Xu Q, Cui W, et al. Sacubitril/valsartan alleviates sepsis-induced acute lung injury via inhibiting GSDMD-dependent macrophage pyroptosis in mice. FEBS J. 2022;290:2180–98.
61. Xie S, Liang J, Zhao Y, Zhang J, Chen X, Jiang H, et al. The second-generation tyrosine kinase inhibitor afatinib inhibits IL-1β secretion via blocking assembly of NLRP3 inflammasome independent of epidermal growth factor receptor signaling in macrophage. Mol Immunol. 2022;153:135–45.
62. Su K, Li X-T, Hong F-X, Jin M, Xue F-S. Lidocaine pretreatment attenuates inflammatory response and protects against sepsis-induced acute lung injury via inhibiting potassium efflux-dependent NLRP3 activation. Inflamm Res. 2023;72(12):2221–35.
63. Xu MM, Kang JY, Ji S, Wei YY, Wei SL, Ye JJ, et al. Melatonin suppresses macrophage M1 polarization and ROS-mediated pyroptosis via activating ApoE/LDLR pathway in influenza a-induced acute lung injury. Oxid Med Cell Longev. 2022;2022:2520348.
64. Kang J-Y, Xu M-M, Sun Y, Ding Z-X, Wei Y-Y, Zhang D-W, et al. Melatonin attenuates LPS-induced pyroptosis in acute lung injury by inhibiting NLRP3-GSDMD pathway via activating Nrf2/HO-1 signaling axis. Int Immunopharmacol. 2022;109: 108782.
65. Hoyle C, Green JP, Allan SM, Brough D, Lemarchand E. Itaconate and fumarate derivatives inhibit priming and activation of the canonical NLRP3 inflammasome in macrophages. Immunology. 2022;165(4):460–80.
66. Liu C, Zhou Y, Tu Q, Yao L, Li J, Yang Z. Alpha-linolenic acid pretreatment alleviates NETs-induced alveolar macrophage pyroptosis by inhibiting pyrin inflammasome activation in a mouse model of sepsis-induced ALI/ARDS. Front Immunol. 2023;14:1146612.
67. Hsu CG, Chávez CL, Zhang C, Sowden M, Yan C, Berk BC. The lipid peroxidation product 4-hydroxynonenal inhibits NLRP3 inflammasome activation and macrophage pyroptosis. Cell Death Differ. 2022;29(9):1790–803.
68. Mei X, Wang J, Zhang C, Zhu J, Liu B, Xie Q, et al. Apigenin suppresses mycoplasma-induced alveolar macrophages necroptosis via enhancing the methylation of TNF-α promoter by PPARγ-Uhrf1 axis. Phytomedicine. 2022;108:154504.
69. Gschwend J, Sherman SPM, Ridder F, Feng X, Liang HE, Locksley RM, et al. Alveolar macrophages rely on GM-CSF from alveolar epithelial type 2 cells before and after birth. J Exp Med. 2021;218(10):e20210745.
70. Huang F-F, Barnes PF, Feng Y, Donis R, Chroneos ZC, Idell S, et al. GM-CSF in the lung protects against lethal influenza infection. Am J Respir Crit Care Med. 2011;184(2):259–68.
71. Lang FM, Lee KM, Teijaro JR, Becher B, Hamilton JA. GM-CSF-based treatments in COVID-19: reconciling opposing therapeutic approaches. Nat Rev Immunol. 2020;20(8):507–14.
72. Petrina M, Martin J, Basta S. Granulocyte macrophage colony-stimulating factor has come of age: From a vaccine adjuvant to antiviral immunotherapy. Cytokine Growth Factor Rev. 2021;59:101–10.
73. Herold S, Hoegner K, Vadász I, Gessler T, Wilhelm J, Mayer K, et al. Inhaled granulocyte/macrophage colony-stimulating factor as treatment of pneumonia-associated acute respiratory distress syndrome. Am J Respir Crit Care Med. 2014;189(5):609–11.

74. De Luca G, Cavalli G, Campochiaro C, Della-Torre E, Angelillo P, Tomelleri A, et al. GM-CSF blockade with mavrilimumab in severe COVID-19 pneumonia and systemic hyperinflammation: a single-centre, prospective cohort study. Lancet Rheumatol. 2020;2(8):e465–73.
75. Better J, Estiri M, Matt U. Cultured mouse alveolar macrophages: a new step toward targeted cell therapy? Am J Respir Cell Mol Biol. 2022;66(1):3–4.
76. Ackermann M, Rafiei Hashtchin A, Manstein F, Carvalho Oliveira M, Kempf H, Zweigerdt R, et al. Continuous human iPSC-macrophage mass production by suspension culture in stirred tank bioreactors. Nat Protoc. 2022;17(2):513–39.
77. Takata K, Kozaki T, Lee CZW, Thion MS, Otsuka M, Lim S, et al. Induced-pluripotent-stem-cell-derived primitive macrophages provide a platform for modeling tissue-resident macrophage differentiation and function. Immunity. 2017;47(1):183-198.e186.
78. Litvack ML, Wigle TJ, Lee J, Wang J, Ackerley C, Grunebaum E, et al. Alveolar-like stem cell-derived Myb(-) macrophages promote recovery and survival in airway disease. Am J Respir Crit Care Med. 2016;193(11):1219–29.
79. Ackermann M, Kempf H, Hetzel M, Hesse C, Hashtchin AR, Brinkert K, et al. Bioreactor-based mass production of human iPSC-derived macrophages enables immunotherapies against bacterial airway infections. Nat Commun. 2018;9(1):5088.
80. Rafiei Hashtchin A, Fehlhaber B, Hetzel M, Manstein F, Stalp JL, Glage S, et al. Human iPSC-derived macrophages for efficient *Staphylococcus aureus* clearance in a murine pulmonary infection model. Blood Adv. 2021;5(23):5190–201.
81. Lin KL, Sweeney S, Kang BD, Ramsburg E, Gunn MD. CCR2-antagonist prophylaxis reduces pulmonary immune pathology and markedly improves survival during influenza infection. J Immunol. 2011;186(1):508–15.
82. Mei HX, Ye Y, Xu HR, Xiang SY, Yang Q, Ma HY, et al. LXA4 inhibits lipopolysaccharide-induced inflammatory cell accumulation by resident macrophages in mice. J Inflamm Res. 2021;14:1375–85.
83. O'Halloran JA, Ko ER, Anstrom KJ, Kedar E, McCarthy MW, Panettieri RA Jr, et al. Abatacept, cenicriviroc, or infliximab for treatment of adults hospitalized with COVID-19 pneumonia: a randomized clinical trial. JAMA. 2023;330(4):328–39.
84. Lin DY, Wang J, Anstrom KJ, LaVange LM, Wen J, Bozzette SA, et al. Efficacy of infliximab, abatacept, and cenicriviroc for the treatment of adults hospitalized with COVID-19 pneumonia. Int J Infect Dis. 2024;146: 107168.
85. Seethamraju H, Yang OO, Loftus R, Ogbuagu O, Sammartino D, Mansour A, et al. A randomized placebo-controlled trial of leronlimab in mild-to-moderate COVID-19. Clin Ther. 2024;46(11):891–9.
86. Patel J, Bass D, Beishuizen A, Bocca Ruiz X, Boughanmi H, Cahn A, et al. A randomised trial of anti-GM-CSF otilimab in severe COVID-19 pneumonia (OSCAR). Eur Respir J. 2023;61(2):2101870.
87. Criner GJ, Lang FM, Gottlieb RL, Mathews KS, Wang TS, Rice TW, et al. Anti-granulocyte-macrophage colony-stimulating factor monoclonal antibody gimsilumab for COVID-19 pneumonia: a randomized, double-blind, placebo-controlled trial. Am J Respir Crit Care Med. 2022;205(11):1290–9.
88. Foo CX, Bartlett S, Chew KY, Ngo MD, Bielefeldt-Ohmann H, Arachchige BJ, et al. GPR183 antagonism reduces macrophage infiltration in influenza and SARS-CoV-2 infection. Eur Respir J. 2023;61(3):2201306.
89. Xu J, Wang J, Wang X, Tan R, Qi X, Liu Z, et al. Soluble PD-L1 improved direct ARDS by reducing monocyte-derived macrophages. Cell Death Dis. 2020;11(10):934.
90. Xiang SY, Ye Y, Yang Q, Xu HR, Shen CX, Ma MQ, et al. RvD1 accelerates the resolution of inflammation by promoting apoptosis of the recruited macrophages via the ALX/FasL-FasR/caspase-3 signaling pathway. Cell Death Discov. 2021;7(1):339.
91. Wang L, Tang Y, Tang J, Liu X, Zi S, Li S, et al. Endothelial cell-derived extracellular vesicles expressing surface VCAM1 promote sepsis-related acute lung injury by targeting and reprogramming monocytes. J Extracell Vesicles. 2024;13(3): e12423.
92. Mao Y, Wang B, Xu X, Du W, Li W, Wang Y. Glycyrrhizic acid promotes M1 macrophage polarization in murine bone marrow-derived macrophages associated with the activation of JNK and NF-κB. Mediators Inflamm. 2015;2015:372931.
93. Pagie S, Gérard N, Charreau B. Notch signaling triggered via the ligand DLL4 impedes M2 macrophage differentiation and promotes their apoptosis. Cell Commun Signal. 2018;16(1):4.
94. Murray PJ. The JAK-STAT signaling pathway: input and output integration. J Immunol. 2007;178(5):2623–9.
95. Sica A, Mantovani A. Macrophage plasticity and polarization: in vivo veritas. J Clin Invest. 2012;122(3):787–95.
96. Dong T, Chen X, Xu H, Song Y, Wang H, Gao Y, et al. Mitochondrial metabolism mediated macrophage polarization in chronic lung diseases. Pharmacol Ther. 2022;239:108208.
97. Yang Y, Zhang Y, Xing X, Xu G, Lin X, Wang Y, et al. IL-6 translation is a therapeutic target of human cytokine release syndrome. J Exp Med. 2023;220(11):e20230577.
98. CORIMUNO-19 Collaborative group. Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild-to-moderate pneumonia (CORIMUNO-ANA-1): a randomised controlled trial. Lancet Respir Med. 2021;9(3):295–304.
99. Kyriazopoulou E, Poulakou G, Milionis H, Metallidis S, Adamis G, Tsiakos K, et al. Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial. Nat Med. 2021;27(10):1752–60.
100. Caricchio R, Abbate A, Gordeev I, Meng J, Hsue PY, Neogi T, et al. Effect of canakinumab vs placebo on survival without invasive mechanical ventilation in patients hospitalized with severe COVID-19: a randomized clinical trial. JAMA. 2021;326(3):230–9.
101. Resende GG, da Cruz LR, Lobê SQ, Medeiros AF, Costa ESAD, Nogueira Sá AT, et al. Blockade of interleukin seventeen (IL-17A) with secukinumab in hospitalized COVID-19 patients - the BISHOP study. Infect Dis (Lond). 2022;54(8):591–9.
102. RECOVERY Collaborative Group. Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis. Lancet. 2022;400(10349):359–68.

103. Guimarães PO, Quirk D, Furtado RH, Maia LN, Saraiva JF, Antunes MO, et al. Tofacitinib in patients hospitalized with Covid-19 pneumonia. N Engl J Med. 2021;385(5):406–15.
104. Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, Angus DC, et al. Association between administration of systemic corticosteroids and mortality among critically Ill patients with COVID-19: a meta-analysis. JAMA. 2020;324(13):1330–41.
105. Chen TY, Chen KC, Zhang YH, Lin CA, Hsu WY, Lin NY, et al. Development of a dexamethasone-hyaluronic acid conjugate with selective targeting effect for acute lung injury therapy. Int J Biol Macromol. 2024;280(Pt 1): 136149.
106. Kaur J, Rana P, Matta T, Sodhi RK, Pathania K, Pawar SV, et al. Protective effect of olopatadine hydrochloride against LPS-induced acute lung injury: via targeting NF-κB signaling pathway. Inflammopharmacology. 2024;32(1):603–27.
107. He X, Jiang L, Hu L, Du P, Zhu M, Wu H, et al. Mivebresib alleviates systemic lupus erythematosus-associated diffuse alveolar hemorrhage via inhibiting infiltration of monocytes and M1 polarization of macrophages. Int Immunopharmacol. 2023;120:110305.
108. Cortés M, Brischetto A, Martinez-Campanario MC, Ninfali C, Domínguez V, Fernández S, et al. Inflammatory macrophages reprogram to immunosuppression by reducing mitochondrial translation. Nat Commun. 2023;14(1):7471.
109. Liu SF, Malik AB. NF-kappa B activation as a pathological mechanism of septic shock and inflammation. Am J Physiol Lung Cell Mol Physiol. 2006;290(4):L622-l645.
110. Ma A, Zhou J, Zou H, Yuan L, Zhong R, Zhu Y, et al. Anti-inflammatory effect of nestorone in a lipopolysaccharide-induced acute lung injury model through regulation of the TLR-4/Myd88/NF-κB signaling pathway. Inflammopharmacology. 2025;33(3):1473–89.
111. Li B, Xia C, He W, Liu J, Duan R, Ji Z, et al. The thyroid hormone analog GC-1 mitigates acute lung injury by inhibiting M1 macrophage polarization. Adv Sci (Weinh). 2024;11(44):e2401931.
112. Chen LL, Morcelle C, Cheng ZL, Chen X, Xu Y, Gao Y, et al. Itaconate inhibits TET DNA dioxygenases to dampen inflammatory responses. Nat Cell Biol. 2022;24(3):353–63.
113. Bao S, Liu MJ, Lee B, Besecker B, Lai JP, Guttridge DC, et al. Zinc modulates the innate immune response in vivo to polymicrobial sepsis through regulation of NF-kappaB. Am J Physiol Lung Cell Mol Physiol. 2010;298(6):L744-754.
114. Besecker BY, Exline MC, Hollyfield J, Phillips G, Disilvestro RA, Wewers MD, et al. A comparison of zinc metabolism, inflammation, and disease severity in critically ill infected and noninfected adults early after intensive care unit admission. Am J Clin Nutr. 2011;93(6):1356–64.
115. Alissa A, Alrashed MA, Alshaya AI, Al Sulaiman K, Alharbi S. Reevaluating vitamin C in sepsis and septic shock: a potential benefit in severe cases? Front Med (Lausanne). 2024;11:1476242.
116. Renieris G, Foutadakis S, Andriopoulou T, Spanou VM, Droggiti DE, Kafousopoulos D, et al. Association of vitamin D with severity and outcome of COVID-19: clinical and experimental evidence. J Innate Immun. 2024;16(1):1–11.
117. Kwon JW, Quan H, Song J, Chung H, Jung D, Hong JJ, et al. Liposomal dexamethasone reduces A/h1n1 influenza-associated morbidity in mice. Front Microbiol. 2022;13:845795.
118. Bohne Japiassu K, Fay F, Marengo A, Mendanha SA, Cailleau C, Louaguenouni Y, et al. Hyaluronic acid-conjugated liposomes loaded with dexamethasone: a promising approach for the treatment of inflammatory diseases. Int J Pharm. 2023;639:122946.
119. Meng QF, Tai W, Tian M, Zhuang X, Pan Y, Lai J, et al. Inhalation delivery of dexamethasone with iSEND nanoparticles attenuates the COVID-19 cytokine storm in mice and nonhuman primates. Sci Adv. 2023;9(24):eadg277.
120. Liu C, Xi L, Liu Y, Mak JCW, Mao S, Wang Z, et al. An Inhalable hybrid biomimetic nanoplatform for sequential drug release and remodeling lung immune homeostasis in acute lung injury treatment. ACS Nano. 2023;17(12):11626–44.
121. Peng W, Tai W, Li B, Wang H, Wang T, Guo S, et al. Inhalable nanocatalytic therapeutics for viral pneumonia. Nat Mater. 2025;24(4):637–48.
122. Fan W, Tang Y, Liu Y, Ran Y, Pan G, Song X, et al. ROS-responsive nanoparticles for bioimaging and treating acute lung injury by releasing dexamethasone and improving alveolar macrophage homeostasis. J Nanobiotechnology. 2024;22(1):729.
123. Fu J, Liu X, Cui Z, Zheng Y, Jiang H, Zhang Y, et al. Probiotic-based nanoparticles for targeted microbiota modulation and immune restoration in bacterial pneumonia. Natl Sci Rev. 2023;10(2):nwac221.
124. Huang W, Fu G, Wang Y, Chen C, Luo Y, Yan Q, et al. Immunometabolic reprogramming of macrophages with inhalable CRISPR/Cas9 nanotherapeutics for acute lung injury intervention. Acta Biomater. 2024;181:308–16.
125. Galipeau J, Sensébé L. Mesenchymal stromal cells: clinical challenges and therapeutic opportunities. Cell Stem Cell. 2018;22(6):824–33.
126. Morrison TJ, Jackson MV, Cunningham EK, Kissenpfennig A, McAuley DF, O'Kane CM, et al. Mesenchymal stromal cells modulate macrophages in clinically relevant lung injury models by extracellular vesicle mitochondrial transfer. Am J Respir Crit Care Med. 2017;196(10):1275–86.
127. Willis GR, Fernandez-Gonzalez A, Anastas J, Vitali SH, Liu X, Ericsson M, et al. Mesenchymal stromal cell exosomes ameliorate experimental bronchopulmonary dysplasia and restore lung function through macrophage immunomodulation. Am J Respir Crit Care Med. 2018;197(1):104–16.
128. Liu F, Qiu H, Xue M, Zhang S, Zhang X, Xu J, et al. MSC-secreted TGF-β regulates lipopolysaccharide-stimulated macrophage M2-like polarization via the Akt/FoxO1 pathway. Stem Cell Res Ther. 2019;10(1):345.
129. Pang SHM, D'Rozario J, Mendonca S, Bhuvan T, Payne NL, Zheng D, et al. Mesenchymal stromal cell apoptosis is required for their therapeutic function. Nat comm. 2021;12(1):6495.
130. Li T, Su X, Lu P, Kang X, Hu M, Li C, et al. Bone marrow mesenchymal stem cell-derived dermcidin-containing migrasomes enhance LC3-associated phagocytosis of pulmonary macrophages and protect against post-stroke pneumonia. Adv Sci (Weinh). 2023;10(22):e2206432.
131. Liu C, Xiao K, Xie L. Advances in mesenchymal stromal cell therapy for acute lung injury/acute respiratory distress syndrome. Front Cell Dev Biol. 2022;10:951764.

132. Wang LT, Yen BL, Wang HH, Chao YY, Lee W, Huang LY, et al. Placental mesenchymal stem cells boost M2 alveolar over M1 bone marrow macrophages via IL-1β in Klebsiella-mediated acute respiratory distress syndrome. Thorax. 2023;78(5):504–14.
133. Nie Z, Fan Q, Jiang W, Wei S, Luo R, Hu H, et al. Placental mesenchymal stem cells suppress inflammation and promote M2-like macrophage polarization through the IL-10/STAT3/NLRP3 axis in acute lung injury. Front Immunol. 2024;15:1422355.
134. Xia L, Zhang C, Lv N, Liang Z, Ma T, Cheng H, et al. AdMSC-derived exosomes alleviate acute lung injury via transferring mitochondrial component to improve homeostasis of alveolar macrophages. Theranostics. 2022;12(6):2928–47.
135. Deng H, Zhu L, Zhang Y, Zheng L, Hu S, Zhou W, et al. Differential lung protective capacity of exosomes derived from human adipose tissue, bone marrow, and umbilical cord mesenchymal stem cells in sepsis-induced acute lung injury. Oxid Med Cell Longev. 2022;2022:7837837.
136. Li M, Li J, Wang Y, Jiang G, Jiang H, Li M, et al. Umbilical cord-derived mesenchymal stem cells preferentially modulate macrophages to alleviate pulmonary fibrosis. Stem Cell Res Ther. 2024;15(1):475.
137. Song D, Li Z, Sun F, Wu K, Zhang K, Liu W, et al. Optimized administration of human embryonic stem cell-derived immunity-and-matrix regulatory cells for mouse lung injury and fibrosis. Stem Cell Res Ther. 2024;15(1):344.
138. Noronha NC, Mizukami A, Caliári-Oliveira C, Cominal JG, Rocha JLM, Covas DT, et al. Priming approaches to improve the efficacy of mesenchymal stromal cell-based therapies. Stem Cell Res Ther. 2019;10(1):131.
139. Xu Z, Lin L, Fan Y, Huselstein C, De Isla N, He X, et al. Secretome of mesenchymal stem cells from consecutive hypoxic cultures promotes resolution of lung inflammation by reprogramming anti-inflammatory macrophages. Int J Mol Sci. 2022;23(8):4333.
140. Hezam K, Wang C, Fu E, Zhou M, Liu Y, Wang H, et al. Superior protective effects of PGE2 priming mesenchymal stem cells against LPS-induced acute lung injury (ALI) through macrophage immunomodulation. Stem Cell Res Ther. 2023;14(1):48.
141. Misharin AV, Morales-Nebreda L, Reyfman PA, Cuda CM, Walter JM, McQuattie-Pimentel AC, et al. Monocyte-derived alveolar macrophages drive lung fibrosis and persist in the lung over the life span. J Exp Med. 2017;214(8):2387–404.
142. Zhang N, Yang K, Bai J, Yi J, Gao C, Zhao J, et al. Myeloid-specific blockade of Notch signaling alleviates murine pulmonary fibrosis through regulating monocyte-derived Ly6c(lo) MHCII(hi) alveolar macrophages recruitment and TGF-β secretion. FASEB J. 2020;34(8):11168–84.
143. Joshi N, Watanabe S, Verma R, Jablonski RP, Chen C-I, Cheresh P, et al. A spatially restricted fibrotic niche in pulmonary fibrosis is sustained by M-CSF/M-CSFR signalling in monocyte-derived alveolar macrophages. Eur Respir J. 2020;55(1):1900646.
144. Kitko CL, Arora M, DeFilipp Z, Zaid MA, Di Stasi A, Radojcic V, et al. Axatilimab for chronic graft-versus-host disease after failure of at least two prior systemic therapies: results of a phase I/II study. J Clin Oncol. 2023;41(10):1864–75.
145. Wolff D, Cutler C, Lee SJ, Pusic I, Bittencourt H, White J, et al. Axatilimab in recurrent or refractory chronic graft-versus-host disease. N Engl J Med. 2024;391(11):1002–14.
146. Keam SJ. Axatilimab: first approval. Drugs. 2024;84(11):1475–80.
147. Hong SY, Lu YT, Chen SY, Hsu CF, Lu YC, Wang CY, et al. Targeting pathogenic macrophages by the application of SHP-1 agonists reduces inflammation and alleviates pulmonary fibrosis. Cell Death Dis. 2023;14(6):352.
148. Watson CK, Schloesser D, Fundel-Clemens K, Lerner C, Gabler S, Baskaran P, et al. Anti-fibrotic drug nintedanib inhibits CSF1R to promote IL-4-associated tissue repair macrophages. Am J Respir Cell Mol Biol. 2023;68(4):366–80.
149. Xu Y, Ying L, Lang JK, Hinz B, Zhao R. Modeling mechanical activation of macrophages during pulmonary fibrogenesis for targeted anti-fibrosis therapy. Sci Adv. 2024;10(13):eadj9559.
150. Wang H, Gao Y, Wang L, Yu Y, Zhang J, Liu C, et al. Lung specific homing of diphenyleneiodonium chloride improves pulmonary fibrosis by inhibiting macrophage M2 metabolic program. J Adv Res. 2023;44:213–25.
151. Ogger PP, Albers GJ, Hewitt RJ, O'Sullivan BJ, Powell JE, Calamita E, et al. Itaconate controls the severity of pulmonary fibrosis. Sci Immunol. 2020;5(52):eabc1884.
152. Gan C, Wang Y, Xiang Z, Liu H, Tan Z, Xie Y, et al. Niclosamide-loaded nanoparticles (Ncl-NPs) reverse pulmonary fibrosis in vivo and in vitro. J Adv Res. 2023;51:109–20.
153. Singh A, Chakraborty S, Wong SW, Hefner NA, Stuart A, Qadir AS, et al. Nanoparticle targeting of de novo profibrotic macrophages mitigates lung fibrosis. Proc Natl Acad Sci U S A. 2022;119(15):e2121098119.
154. Zhao J, Andreev I, Silva HM. Resident tissue macrophages: Key coordinators of tissue homeostasis beyond immunity. Sci Immunol. 2024;9(94):eadd1967.
155. Vichare R, Janjic JM. Macrophage-targeted nanomedicines for ARDS/ALI: promise and potential. Inflammation. 2022;45(6):2124–41.
156. Morris G, Bortolasci CC, Puri BK, Olive L, Marx W, O'Neil A, et al. The pathophysiology of SARS-CoV-2: a suggested model and therapeutic approach. Life Sci. 2020;258:118166.

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