Monocytes in pneumonia: Functional plasticity and innate memory (Review)

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Abstract. Pneumonia remains one of the most prevalent and deadly respiratory diseases worldwide, imposing substantial clinical and socioeconomic burdens. Monocytes (Mos) and their progeny are key components of the innate immune system and perform highly context-dependent roles. The present review summarizes recent advances in understanding Mo biology in pneumonia and discusses current concepts of their functional plasticity. The review first summarizes the developmental origins, phenotypic heterogeneity and functions of circulating Mo subsets, followed by an overview of their recruitment, activation and differentiation in the steady-state and infected lung. Next, the dual, and at times opposing, roles of Mos and their progeny in pneumonia are examined, including contributions to pathogen clearance and microbial immune evasion, the initiation and resolution of inflammation, and tissue repair vs. fibrotic remodeling. Finally, the review highlights emerging evidence showing that pneumonia can induce durable innate immune memory in Mos, their progenitors and the alveolar macrophage compartment. This reprogramming may reshape subsequent pulmonary and systemic immune responses, with important implications for susceptibility to reinfection, chronic lung dysfunction and host resilience. A deeper understanding of Mo plasticity and innate memory may open new avenues for biomarker discovery and host-directed therapeutic strategies for pneumonia.

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Abbreviations: Mo, monocyte; AM, alveolar macrophage; BMo-AM, blood monocyte-derived AM; cMo, classical monocyte; CMP, common myeloid progenitor; DC, dendritic cell; FeMo-AM, fetal monocyte-derived AM; GMP, granulocyte-monocyte progenitor; HSC, hematopoietic stem cell; HSPC, hematopoietic stem and progenitor cell; IM, interstitial macrophage; InfResAM, inflammation-imprinted resident AM; intMo, intermediate monocyte; IPF, idiopathic pulmonary fibrosis; LLN, lung-draining lymph node; MDM, monocyte-derived macrophage; MDP, monocyte-dendritic cell progenitor; mHLA-DR, monocyte human leukocyte antigen-DR; MoDC, monocyte-derived dendritic cell; ncMo, non-classical monocyte; PF, pulmonary fibrosis

Key words: monocyte, pneumonia, infection, inflammation, innate immune memory

Contents

1. Introduction

Pneumonia is an inflammatory condition of the lung parenchyma, most commonly caused by microbial infection, whereas other factors such as allergens and chemical irritants may cause non-infectious pneumonitis (1-3). Infectious pneumonia has long been one of the respiratory diseases with the highest incidence and mortality rates worldwide (4-6). For non-COVID-19 pneumonia, the incidence rates were 4,350 per 100,000 population in 2021 and 3,001.7 per 100,000 population in 2023, while the mortality rates were 27.7 per 100,000 population in 2021 and 31.0 per 100,000 population in 2023 (4,5). For COVID-19, ~775 million cases and 7.031 million deaths were reported worldwide from 2020 to 2024 (6). Epidemiological data indicate that the burden of pneumonia is particularly high among individuals at the extremes of age (children <5 years and older adults ≥70 years), those with impaired immune function and patients with multiple underlying diseases (3,5). In addition, pneumonia is a major cause of acute respiratory distress syndrome (ARDS) and sepsis (7-10), posing a serious threat to population health and imposing a substantial socioeconomic burden.

The occurrence and progression of pneumonia are regulated by the intricate immune system (11-14), and the role of Mos in this context has garnered increasing research attention (15-18). Mos are a key population of innate immune cells in the peripheral blood and have traditionally been regarded as important precursors of macrophages (Mφs) and dendritic cells (DCs). In recent years, however, numerous studies have demonstrated that the role of Mos in homeostasis and inflammation extends far beyond that of mere cellular precursors; they perform multiple functions, including immune regulation (19,20). Mos are conventionally classified into three subsets: Classical Mos (cMos; human, $CD14^{++}CD16^{-}$; mouse, $Ly6C^{hi}$), intermediate Mos (intMos; human, $CD14^{++}CD16^{+}$) and non-classical Mos (ncMos; human, $CD14^{+}CD16^{+}$; mouse, $Ly6C^{lo}$) (21). Recent advances in single-cell RNA sequencing (scRNA-seq), mass cytometry and spatial transcriptomics have enabled multi-scale analyses of immune dynamics during infectious pneumonia (22-28). In particular, research stimulated by the COVID-19 pandemic has greatly advanced the understanding of the relationships among pneumonia, immune dysregulation and host tissue damage (29-35).

The present review summarizes recent advances in determining the role of Mos in infection-induced pneumonia, drawing on a comprehensive PubMed search of the literature published in the past decade, with earlier studies incorporated when necessary. A focus is specifically placed on infectious pneumonia, excluding pneumonitis with non-infectious causes such as drugs, allergies or chemical exposure. The review first outlines the developmental origins, phenotypic diversity and functional roles of circulating Mo subsets, and then reviews how these cells are recruited, activated and differentiated into Mo-derived DCs (MoDCs) and Mo-derived Mφs (MDMs) in both the healthy and infected lung. The review further summarizes their roles in pathogen clearance, immune evasion, inflammation, resolution, tissue repair and fibrosis. Moreover, emerging evidence is highlighted showing that Mos and their progeny contribute to pneumonia-induced innate immune memory, shaping subsequent pulmonary and systemic immune responses. Finally, the clinical importance of Mos in pneumonia is examined from a precision medicine perspective. Compared with previous reviews, the present review offers a more comprehensive and mechanistic overview of the dynamic roles of Mos throughout the course of pneumonia caused by diverse pathogens. Importantly, the multifaceted functions of Mos during pneumonia are linked to the contributions of Mos and Mo-derived cells, and to innate immune memory following disease resolution. This integrated temporal perspective, spanning acute infection to post-pneumonia immune reprogramming, broadens the understanding of Mo biology in pneumonia and its long-term immunological consequences.

2. Development and fate of Mos

cMos are the predominant Mo subset released from the bone marrow. The conventional model posits that cMos differentiate in a stepwise manner from common myeloid progenitor (CMPs) to Mo-DC progenitors (MDPs) [CMPs-granulocyte-Mo progenitors (GMPs)-MDPs-Mo progenitor (MPs)/common Mo progenitors (cMoPs)-Mos] (36). However, recent studies have revealed that cMos can originate from both GMPs and MDPs, and these two developmental pathways generate cMo subsets with distinct functional characteristics (36-38). Based on transcriptomic differences, these Mos can be categorized as 'neutrophil-like Mos' (NeuMos) and 'DC-like Mos' (DCMos) (Fig. 1). However, under certain conditions, Mo subsets with characteristics distinct from the aforementioned populations may also emerge (39), suggesting that the developmental trajectory of Mos in the bone marrow may involve additional, as yet uncharacterized, intermediate stages or regulatory mechanisms (40). Nevertheless, although the distinct transcriptional features of NeuMos and DCMos have been delineated (36,37), their specific roles in both physiological and pathological contexts remain to be fully characterized (41). Notably, different types of stimuli selectively mobilize specific progenitor cells, thereby promoting the generation of distinct Mo subsets (36). The latest evidence indicates that pneumonia can induce long-term skewing of myelopoiesis, characterized by an expanded GMP compartment (41,42), which constitutes an important component of pneumonia-induced central trained immunity. NeuMos derived from GMPs may mediate a more severe immune pathology in the lungs (41).

cMos represent a transient cell population with diverse differentiation potentials (19). Under homeostatic conditions, cMos, which complete mitosis, migrate from the bone marrow into the peripheral circulation after ~1.6 days. After remaining in the circulation for a certain period (on average 1.0±0.26 days in humans and ~20 h in mice), the vast majority of cMos either undergo cell death or exit the circulation to infiltrate various tissues. Only ~1% of cMos differentiate into intMos and ncMos in the circulation, a process accompanied by decreased Ly6C expression and increased CX3CR1 expression (19,43-45), which is primarily regulated by transcription factors such as Nr4a1 (Nur77) and IRF8 (36,46,47). During inflammation, circulating cMos can be rapidly recruited to sites of inflammation, where they perform a series of immune functions. intMos represent a highly heterogeneous cell population transitioning from cMos to ncMos (with an average circulating lifespan of 4.3±0.36 days) (44). The population is characterized by high expression of genes related to antigen presentation and oxidative stress, and demonstrates increased production of pro-inflammatory cytokines (IL-1β and TNF-α) upon lipopolysaccharide (LPS) stimulation (48-50). ncMos are considered a terminally differentiated Mo subset (43,44,51). ncMos have a longer lifespan (on average 7.4±0.53 days in humans and ~2.2 days in mice); under inflammatory conditions or in the absence of other ncMo sources, ncMos can maintain numerical stability by extending their own lifespan (19,43,44). Under steady-state conditions, ncMos depend on LFA-1, α4-integrins and Kindlin-3, among other proteins, to execute patrolling functions along vascular endothelial cells, and they can also recognize and eliminate dying endothelial cells in a TLR7-dependent manner, thereby preserving vascular homeostasis and integrity. Therefore, ncMos are also referred to as 'patrolling Mos' (45,52). In specific pathological conditions, ncMos may directly and/or indirectly contribute to tissue injury (53,54). Notably, severe COVID-19 is associated with a reduction in circulating intMo and/or ncMo levels (26,29,32,55), which is a potentially specific phenomenon (26), although the underlying mechanisms remain to be fully elucidated.

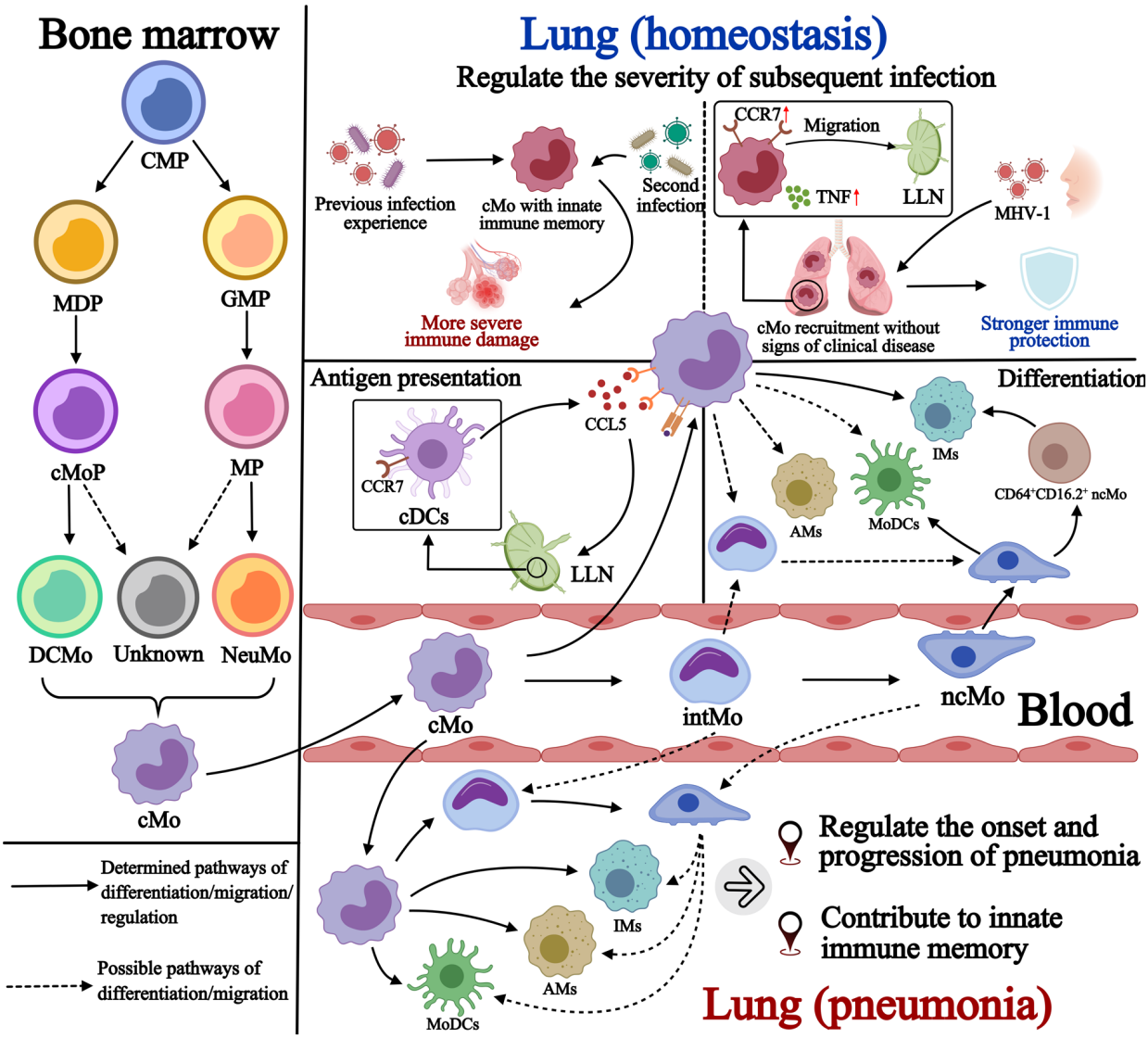

Figure 1. Development, differentiation and function of Mos under both homeostatic conditions and during pneumonia. cMos originate from CMPs in the bone marrow and differentiate into two phenotypic subsets, NeuMos and DCMos, via two distinct developmental pathways, CMPs-GMPs-MPs-NeuMos and CMPs-MDPs-cMoPs-DCMos, respectively. Notably, Mo development in the bone marrow may involve additional intermediate stages that remain to be characterized. cMos represent the predominant Mo subset mobilized from the bone marrow into the peripheral circulation. Within the bloodstream, cMos undergo a sequential differentiation trajectory progressing into intMos and subsequently into ncMos. Circulating cMos can migrate to the lung under both homeostatic conditions and during pneumonia, whereas whether intMos and ncMos also migrate to the lung remains unclear. Under homeostatic conditions, cMos can not only migrate to LLNs to perform antigen presentation functions and regulate the severity of a subsequent infection, but also further differentiate into MDMs and MoDCs. In addition, ncMos that migrate from the bloodstream or (and) differentiate from cMos can further differentiate into IMs and MoDCs in the lung. During pneumonia, circulating cMos recruited to inflammatory sites in the lung can further differentiate into MDMs and MoDCs, and differentiation into intMos and ncMos has also been reported. Collectively, these subsets contribute to the regulation of pneumonia onset and progression, as well as to innate immune memory. Mos, monocytes; cMos, classical Mos; CMPs, common myeloid progenitors; NeuMos, neutrophil-like Mos; DCMos, DC-like Mos; GMPs, granulocyte-Mo progenitors; MPs, Mo progenitors; MDPs, Mo-dendritic cell progenitors; cMoPs, common Mo progenitors; intMos, intermediate Mos; ncMos, non-classical Mos; CCR7, C-C motif chemokine receptor 7; TNF, tumor necrosis factor; LLN, lung-draining lymph node; MHV-1, mouse hepatitis virus type 1; CCL5, C-C motif chemokine ligand 5; cDCs, conventional dendritic cells; AMs, alveolar macrophages; MoDCs, Mo-derived dendritic cells; IMs, interstitial macrophages. Created with MedPeer (medpeer.cn).

Under homeostatic conditions and during pneumonia, cMos can migrate to various tissues, where they either retain their Mo-like state or further differentiate into MDMs and MoDCs, with the latter process being regulated by the tissue microenvironmental signals (56,57). However, our current understanding of the capacity of intMos and ncMos to migrate towards the lung and their subsequent differentiation potential remains limited (40).

Under homeostatic conditions, cMos are detectable in the lung parenchyma, originating from the continual migration of circulating cMos to the lung via both C-C motif chemokine receptor 2 (CCR2)-dependent or -independent pathways (58-60). The transcriptomic profile of these cMos in the lungs closely resembles that of circulating cMos, with only minor differences observable (58,60). These cMos can capture antigens in lung tissue and migrate through lymphatic vessels to the lung-draining lymph node (LLN), thereby facilitating local immune surveillance and antigen transport (60). When the interstitial Mφ (IM) niche is vacant, cMos in the lungs can also differentiate into IMs to replenish it (59,61).

However, whether cMos contribute to the alveolar Mφ (AM) pool under steady-state conditions remains debated. Notably, strategies targeting pulmonary cMos prior to lung infection can enhance immune protection and mitigate the severity of subsequent pneumonia (62). A study by Hua *et al* (62) reported that the intranasal inoculation of mouse hepatitis virus type 1 promotes the recruitment of cMos into the lung parenchyma without directly infecting lung tissue. These cMos exhibit an increased TNF secretion capacity and elevated CCR7 expression, which facilitates efficient pathogen clearance and augments T cell-mediated immune responses during the early phase of pneumonia, thereby providing effective protection against lethal pneumonia. However, after severe infections (such as pneumonia and sepsis), the accumulation of cMos with innate immune memory in the lungs may increase the risk of pulmonary sequelae, augment the local inflammatory burden and mediate more severe lung injury upon reinfection (41,42,63). In addition, ncMos can also be detected in the lungs under homeostatic conditions. Schyns *et al* (64) identified an NR4A1-dependent non-classical $CD64^{+}CD16.2^{+}$ Mo subset located in the alveolar interstitium under steady-state conditions, which can represent an intermediate transitional state between circulating ncMos and $CD206^{-}$ IMs. Additionally, an early study suggest that, under steady-state conditions, ncMos can differentiate into MoDCs within tissues (65).

In pneumonia, Mos and their derivatives, including MDMs [recruited blood Mo-derived AMs (BMo-AMs) and recruited IMs] and MoDCs, perform diverse functions. Furthermore, long-lived MDMs contribute to the establishment of local innate immune memory in the lung. In addition, the evidence from patients with COVID-19 indicates that intMos and ncMos accumulate in the lungs during pneumonia (66,67). These Mos may, on the one hand, be recruited directly from peripheral blood, and, on the other hand, differentiate from cMos that have already been recruited to the lungs; this process may depend on the NF-κB pathway (66,67) (Fig. 1).

3. Roles of Mos and their derived cells in the onset and progression of pneumonia

During pneumonia, pathogens invade the lung tissue and trigger inflammatory responses. Bone marrow stromal cells sense pro-inflammatory signals (including pro-inflammatory cytokines and microbial molecules) in the inflammatory microenvironment and produce C-C motif chemokine ligand 2 (CCL2), thereby driving the migration of cMos from the bone marrow into the circulation. The upregulation of adhesion molecules in local endothelial cells of the lungs and the secretion of chemokines by various cells in the lungs mediate the recruitment of circulating Mos (21). Different waves of Mos may have different functions. Early recruited Mos mainly play a role in recruiting more immune cells, while later recruited Mos promote pathogen clearance and immune damage by secreting pro-inflammatory cytokines or inducing anti-inflammatory genes to promote inflammation resolution (68). During the occurrence and progression of pneumonia, Mos and their derived MDMs and MoDCs are deeply involved in and dynamically regulate a series of core events, including pathogen clearance and escape, inflammatory response regulation, lung tissue repair and fibrosis (15-18). In the following section, the involvement of Mos and Mo-derived cells in these processes are examined, with an emphasis on the emerging findings and persisting controversies.

Pathogen clearance and immune escape. Mos and their derivatives play a critical role in clearing pneumonia-related pathogens. First, they can directly eliminate pathogens through phagocytosis. Phagocytes recognize phagocytic targets through surface receptor binding to pathogen-associated molecular patterns and opsonins (antibodies and complement). Upon internalization, the targets are engulfed in phagosomes, which further fuse with lysosomes to generate phagolysosomes. Within these compartments, pathogens are killed or degraded under the combined actions of an acidic environment, hydrolases and reactive oxygen species (ROS) (69,70). In addition, Mos and their derived cells can generate large amounts of ROS through NADPH oxidase and mitochondrial pathways, and produce reactive nitrogen species (RNS) via inducible nitric oxide synthase, thereby further eliminating pathogens by damaging membrane lipids, proteins and nucleic acids (71-73). Notably, ROS and RNS not only directly kill pathogens but also act as key signaling molecules that regulate inflammation, phagocytosis and cellular phenotypic transitions, thereby synergistically promoting the clearance of pneumonia-related pathogens (71,72). Mo-derived cell types differ in their pathogen-clearing capacity. *In vitro*, MDMs exhibited the strongest phagocytic activity against *Staphylococcus aureus* and *Escherichia Coli* (*E. coli*), followed by cMo and immature MoDCs, whereas mature MoDCs displayed the lowest activity. Similarly, cMos and MDMs exhibited greater killing of internalized bacteria than immature and mature MoDCs, suggesting that cMos and MDMs are specialized for pathogen clearance, while MoDCs are mainly involved in antigen presentation and adaptive immune activation (74).

Importantly, beyond direct pathogen elimination through phagocytosis and the induction of oxidative/nitrosative stress, Mos and their derivative populations contribute to host defense by orchestrating innate and adaptive immune responses, thereby establishing an integrated immune clearance network (Table I; Fig. 2). Mechanistically, these cells regulate the recruitment, activation and functional polarization of other immune cell subsets through the secretion of immunomodulatory mediators, such as cytokines and chemokines, as well as through direct cell-cell communication. In addition, Mos and MoDCs can process pathogen-derived antigens and present peptide-major histocompatibility complex (MHC) complexes to T cells, thereby initiating and shaping adaptive immune responses. Collectively, Mos and their progeny serve as central coordinators of immune-mediated pathogen clearance.

Although the role of Mos in pathogen clearance is well recognized, accumulating evidence indicates that they also contribute to mediating pathogen immune evasion (Fig. 2). Recently, Yu *et al* (75) proposed that excessive Mo activation in the early stages of infection mediates the immune escape of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Researchers divided patients in the silent SARS-CoV-2 infection stage of COVID-19 into an asymptomatic group (positive viral test, with no symptoms or lung imaging abnormalities during observation) and a presymptomatic group (positive viral test without initial symptoms;

Table I. Summary of studies of the immunoregulatory mechanisms by which Mos and Mo-derived cells promote pathogen clearance in pneumonia.

Cell and pathogen types	Mechanisms	(Refs.)
Mos (subtypes are not distinguished)		
Legionella pneumophila	Produces TNF to increase pathogen clearance by AMs by promoting the acidification of lysosomes and their fusion with LCVs	(238)
cMos		
Staphylococcus aureus	Produces IL-12 to increase pathogen clearance by AMs through increased ROS activity	(239)
Legionella pneumophila	Produces IL-12 to increase the production of IFN-γ by NK cells, NKT cells and γδT cells	(240)
Aspergillus fumigatus	Produces cytokines such as TNF to enhance the conidiacidal activity of neutrophils	(241)
HMPV	Upregulates the expression of C1q to increase the secretion of IFN-γ, IL-2 and granzyme B by $CD8^+$ T cells	(242)
Klebsiella pneumoniae	Produces TNF to promote the expansion of IL-17A-producing ILC3s, which subsequently produce IL-17A that increases cMo phagocytic activity and ROS production and further stimulates TNF secretion by cMos	(243)
IAV	Promotes the establishment of virus-specific lung $CD8^+$ TRMs following IAV infection; $CD8^+$ TRMs promote the recruitment of cMos during reinfection	(244,245)
Unspecified	Transports the antigen to the LLN and presents it to T cells; may enhance the Th1 response while concurrently suppressing the Th2 response	(60,246)
MCs		
Legionella pneumophila	Produces IL-12 to stimulate the production of IFN-γ by NK cells, T cells, NKT cells and γδT cells; depends on IFN-γ to induce the best pathogen clearance	(247)
MDMs		
SARS-CoV-2	Promotes the secretion of IFN-α and TNF by pDCs; IFN-α increases the phagocytic activity of MDMs and IL-6 production by MDMs	(248)
	Promotes degranulation and TNF secretion in γδ2T cells	(249)
	Recruits *Isg12*$^+$*Cst7*$^+$ neutrophils to synergistically induce pathogen clearance and inflammation resolution in the later stage of infection	(28)
MoDCs		
Aspergillus fumigatus	Produces cytokines such as TNF to increase the conidiacidal activity of neutrophils	(241)
	Produces CXCL9 and CXCL10 to recruit $CXCR3^+$ pDCs from the circulation to the lung tissue; pDCs increase pathogen clearance by neutrophils	(250)
Chlamydia pneumoniae	Promotes the Th1/Th17 response through the TLR2-ERK1/2 axis	(251)
Staphylococcus aureus IAV	Activates $CD4^+$, $CD8^+$ and double-negative T cells by secreting multiple cytokines	(252)

Mos, monocytes; TNF, tumor necrosis factor; AM, alveolar macrophage; LCV, *L. pneumophila*-containing vacuoles; IL, interleukin; ROS, reactive oxygen species; HMPV, human metapneumovirus; cMo, classical Mo; ILC3, type 3 innate lymphoid cells; IAV, influenza A virus; TRM, tissue-resident memory $CD8^+$ T cells; LLN, lung-draining lymph node; Th, T helper; MC, Mo-derived cell; MDM, Mo-derived macrophage; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; pDC, plasmacytoid dendritic cell; MoDC, Mo-derived DC; IFN, interferon; NK, natural killer; NKT, natural killer T.

follow-up imaging showed progressive pneumonia, confirming early-stage COVID-19). It was found that, compared with the asymptomatic group, the presymptomatic group showed an increased proportion of $CD107a^{hi}$ cMos, accompanied by a marked decrease in the frequencies of $CD107a^{lo}$ cMos, intMos and ncMos. Additionally, a reduced frequency of $CD62L^{hi}$ $CD8^+$ $T_{naïve}$ cells and an increased frequency of immunosuppressive $CD4^+$ NKT cells were observed. These findings suggest that cMo overactivation is accompanied by the disruption of normal differentiation processes and early

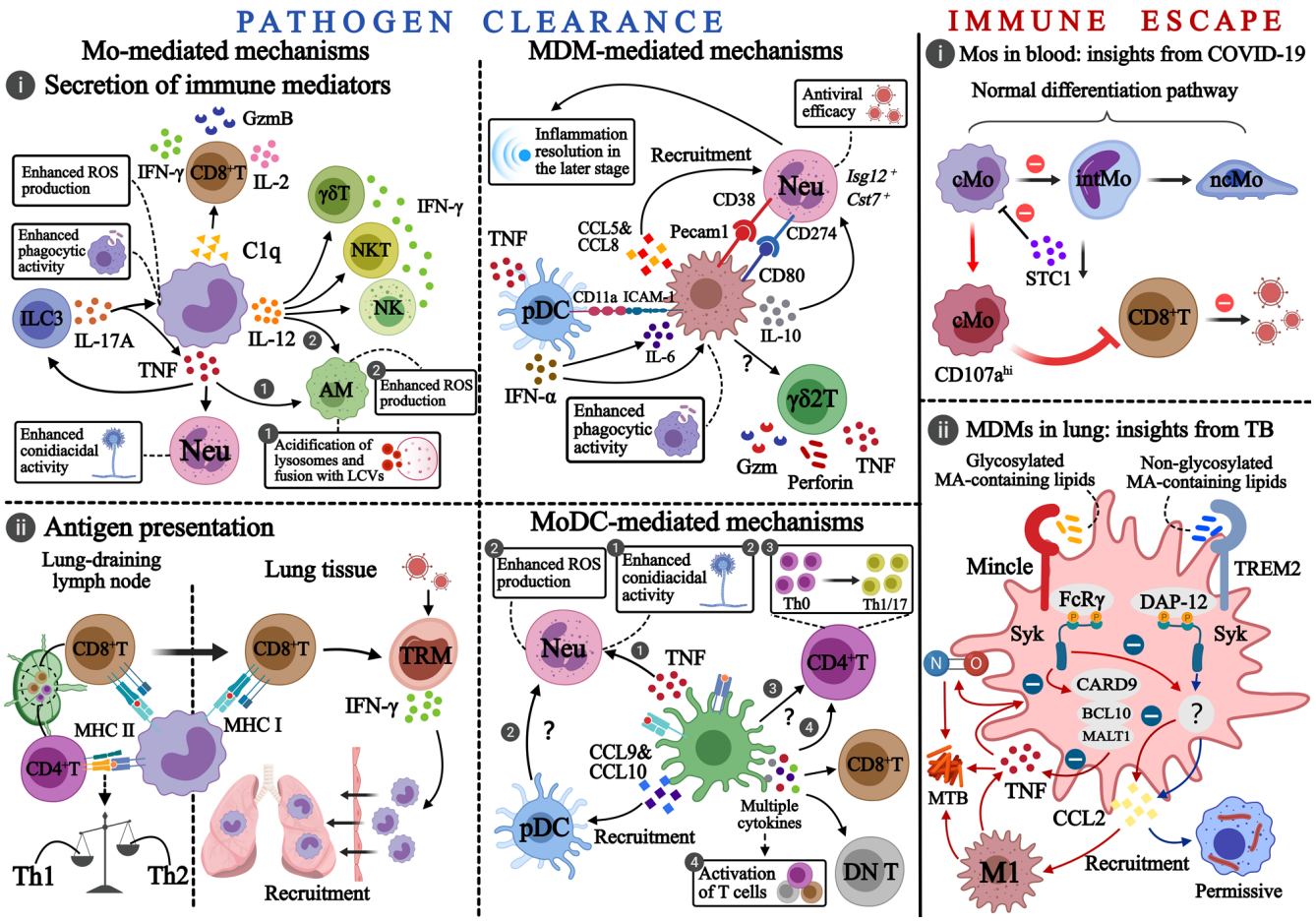

Figure 2. Immune regulation by Mos and their derivatives in pathogen clearance and immune escape during pneumonia. During pneumonia, Mos and their derivative cells in the lungs can promote pathogen clearance through immunoregulatory effects; for specific details, please refer to Table I. Furthermore, they can also facilitate pathogen immune evasion. The underlying mechanisms include the immunosuppression of $CD8^+$ T cells by circulating $CD107a^{hi}$ cMos, as well as the expression of Trem2 on MDMs. Mos, monocytes; LLN, lung-draining lymph node; Trem2, triggering receptor expressed on myeloid cells 2; Th, T helper cell; TRMs, tissue-resident memory T cells; AMs, alveolar macrophages; MoDCs, Mo-derived DCs; ILC3s, type 3 innate lymphoid cells; pDC, plasmacytoid dendritic cell; cMos, classical Mos; MDMs, Mo-derived macrophages; CCL, C-C motif chemokine ligand; CXCL, C-X-C motif chemokine ligand; IL, interleukin; IFN, interferon; TNF, tumor necrosis factor; ROS, reactive oxygen species; Syk, spleen tyrosine kinase; intMos, intermediate Mos; ncMos, non-classical Mos; MTB, *Mycobacterium tuberculosis*; TB, tuberculosis; CARD9, caspase recruitment domain-containing protein 9; NK, natural killer cell; NKT, natural killer T cell; Neu, neutrophil; MHC, major histocompatibility complex; DNT, double-negative T cell; STC1, stanniocalcin-1; MA, mycolic acid. Created with MedPeer (medpeer.cn).

immune exhaustion of T cells. Plasma protein profiling revealed that the level of stanniocalcin-1 (STC1) (an inhibitor of Mo activation) was markedly reduced in the presymptomatic group. Subsequent *in vitro* experiments demonstrated that treatment with recombinant human STC1 restored normal Mo differentiation and maintained the frequency of $CD8^+$ $T_{naïve}$ cells, further supporting a causal relationship between abnormal Mo activation and lymphocyte exhaustion (75). In addition, the activation of triggering receptor expressed on myeloid cells 2 (TREM2) on the surface of MDMs during pneumonia is also considered to mediate pathogen immune evasion (76,77). In individuals with tuberculosis, glycosylated mycolic acid (MA)-containing lipids can induce Mφs to produce TNF and NO through the Mincle/FcRγ/CARD9 axis, accompanied by the CCL2-mediated recruitment of inducible nitric oxide synthase (iNOS)-positive M1 Mφs (77). By contrast, non-glycosylated MA-containing lipids only promote the release of CCL2 under TREM2/DAP12-dependent conditions and recruit iNOS-negative permissive Mφs that facilitate *Mycobacterium tuberculosis* (*M. tuberculosis*) survival and persistence. In addition, TREM2-DAP12 signaling selectively antagonizes the Mincle-FcRγ-CARD9-mediated anti-mycobacterial immune response. *Trem2* knockout can enhance Mincle-induced Mφ activation and the corresponding inflammatory response, and accelerate the clearance of *M. tuberculosis* (77). Moreover, other evidence suggests that TREM2-related signaling may modulate pneumonia pathogen clearance by regulating MDM-mediated phagocytosis and cytokine production (78,79), although the specific mechanisms remain unclear.

Immune injury. A successful host response to infection is invariably accompanied by an inflammatory process. Under ideal circumstances, Mos exert appropriate immune defense functions against invading pathogens, enabling the host to effectively control the infection (80). However, when pathogens with high virulence, a high burden or immune evasion ability persist in the lungs, the host initiates an inflammatory cascade characterized by the continuous and excessive recruitment and activation of Mos. This dysregulated response drives

excessive inflammation, resulting in immune-mediated lung injury that may disseminate systemically and ultimately exacerbate clinical outcomes. In fact, these excessive Mo-mediated inflammatory responses often fail to achieve effective pathogen clearance (16,81,82).

The CCL2/CCR2 axis is the principal pathway mediating the recruitment of cMos. CCL2, a Mo chemotactic factor, is mainly secreted by various immune cells, including resident AMs (ResAMs), as well as by lung epithelial cells during pneumonia. The production of CCL2 is regulated by multiple factors, including pro-inflammatory cytokines and interferon (IFN) signaling pathways (82-84). Meanwhile, recruited cMos can further amplify their own recruitment through the activation of the type I IFN signaling pathway (85). Notably, as observed in coronavirus infections, impaired or delayed type I IFN responses may increase viral replication, which in turn activates NF-κB, increases CCL2 production and ultimately promotes excessive cMo recruitment (86-88). Other pathways, including the CCL3,4,5/CCR5 axis (89) and complement activation [for example, C3a induction in influenza A virus (IAV) pneumonia (90)], also contribute to excessive cMo infiltration.

Once recruited, cMos and MDMs, which are influenced by pathogens, immune cells and immune mediators (17,91), frequently adopt an excessively pro-inflammatory phenotype, thereby creating a highly inflammatory pulmonary microenvironment and driving immune injury through increased production of inflammatory cytokines, chemokines and other mediators. Notably, compared with ResAMs, recruited BMo-AMs exhibit stronger inflammatory signaling, increased glycolysis, and increased production of IL-1β and IL-6 (92). Recruited IMs likewise exhibit pro-inflammatory transcriptional profiles (76,93). The acquisition of a more pro-inflammatory phenotype by MDMs may be attributed to their retention of the chromatin landscape and transcriptomic features of precursor Mos and/or to the differentiation of their precursor Mos within an inflammatory environment. Additionally, the evidence from a study of COVID-19 indicates that intMos and/or ncMos may modulate $CD4^+$T cell polarization toward Th1 and Th17, which is consiered to potentially contribute to an increased severity of pneumonia (66).

Accumulating evidence indicates that severe pneumonia is frequently characterized by a lung inflammatory milieu dominated by cMos and MDMs. In patients with severe COVID-19, these cells exhibit high expression of pro-inflammatory cytokine and chemokine genes, accompanied by elevated levels of inflammatory mediators in bronchoalveolar lavage fluid (BALF) (24,94-96). A similar cMo/MDM-driven inflammatory pattern has been observed in IAV-induced pneumonia, where cMos and M1-like MDMs orchestrate the inflammatory microenvironment (97). In bacterial pneumonia, mild cases are characterized by effective humoral responses, whereas severe cases are characterized by BALF enriched with inflammatory MDMs expressing *CXCL1*,*3*,*8*, *TNF*, *IL6* and *IL1B*, where chemokine-mediated cross-talk among these inflammatory Mφ subsets further amplifies the inflammatory cascade (98).

During the onset and progression of pneumonia, circulating Mos display complex and heterogeneous immunophenotypes. The levels of enrichment of circulating Mos with distinct phenotypes varies considerably across patient populations (23,99,100). Below, the relatively common proinflammatory circulating Mos, which can contribute to and exacerbate immunopathological injury, are discussed; however, Mos with immunosuppressive or mixed phenotypes also exist, highlighting the heterogeneity of circulating Mo populations (101). Several studies of COVID-19 have shown that circulating Mos exhibit a pro-inflammatory phenotype and constitute a major source of elevated levels of pro-inflammatory cytokines in peripheral blood (31,102-104). In patients with bacterial pneumonia, cMos are the major contributors to inflammation and cytokine production. These cells activate their intrinsic TLR4-MYD88 signaling pathway through the secretion of S100A8/A9/A12, thereby forming a positive feedback loop that aggravates immune-mediated injury (105). cMos may also amplify inflammation via ligand-receptor interactions with other inflammatory cell clusters. Moreover, a *C1QA*/*B*/*C*-high ncMo subset, particularly enriched in severe disease, exacerbates inflammation and immune injury through complement activation. Circulating Mos can further acquire a pro-thrombotic phenotype, thereby contributing to the formation of immunothrombosis. In patients with COVID-19, cMos exhibit increased expression of hemostasis- and platelet activation-related genes and increased Mo-platelet aggregate formation, which correlates with disease severity (106).

Finally, the mononuclear phagocyte system in the peripheral circulation and the lungs is not independent; rather, it cooperatively drives local and even systemic inflammatory responses through complex cross-talk. In patients with IAV infection, the expansion of M1-like Mos in peripheral blood leads to the secretion of large amounts of TNF-α, thereby mediating severe immune-mediated tissue injury. Concurrently, their recruitment into the lung may increase the M1/M2 Mφ ratio, further exacerbating pulmonary pathological damage (107). Additionally, in patients with COVID-19, the lung contains highly pro-inflammatory Mono_c1-CD14-CCL3 cells that, through *CCR5* expression, can respond to stimuli from a variety of cells in both the lung and peripheral blood (31).

Inflammation resolution, lung tissue repair, and pneumonia-related pulmonary fibrosis (PF). In the late stage of pneumonia, MDMs exhibiting anti-inflammatory and reparative phenotypes play a crucial role in resolving inflammation and promoting lung tissue repair. Conversely, Mos and MDMs may also contribute to the development of pneumonia-related PF (Fig. 3). This section will review the specific roles of Mos and MDMs in these two processes, as well as the complex mechanisms involved.

Inflammation resolution and lung tissue repair. MDMs can mediate the resolution of inflammation and the repair of lung tissue in patients with various lung injuries, including pneumonia (28,108-110). Repair-associated MDMs may originate from either the phenotypic evolution of early injury-recruited MDMs or from distinct later waves of Mos (15,111,112). After fulfilling their reparative functions, these cells may either integrate into the lung resident tissue macrophages (RTM) pool (28) or undergo clearance (113).

Watanabe *et al* (111) proposed two non-mutually exclusive models by which MDMs facilitate inflammation resolution and tissue repair: The passive and active repair models. In the passive model, the recovering tissue microenvironment

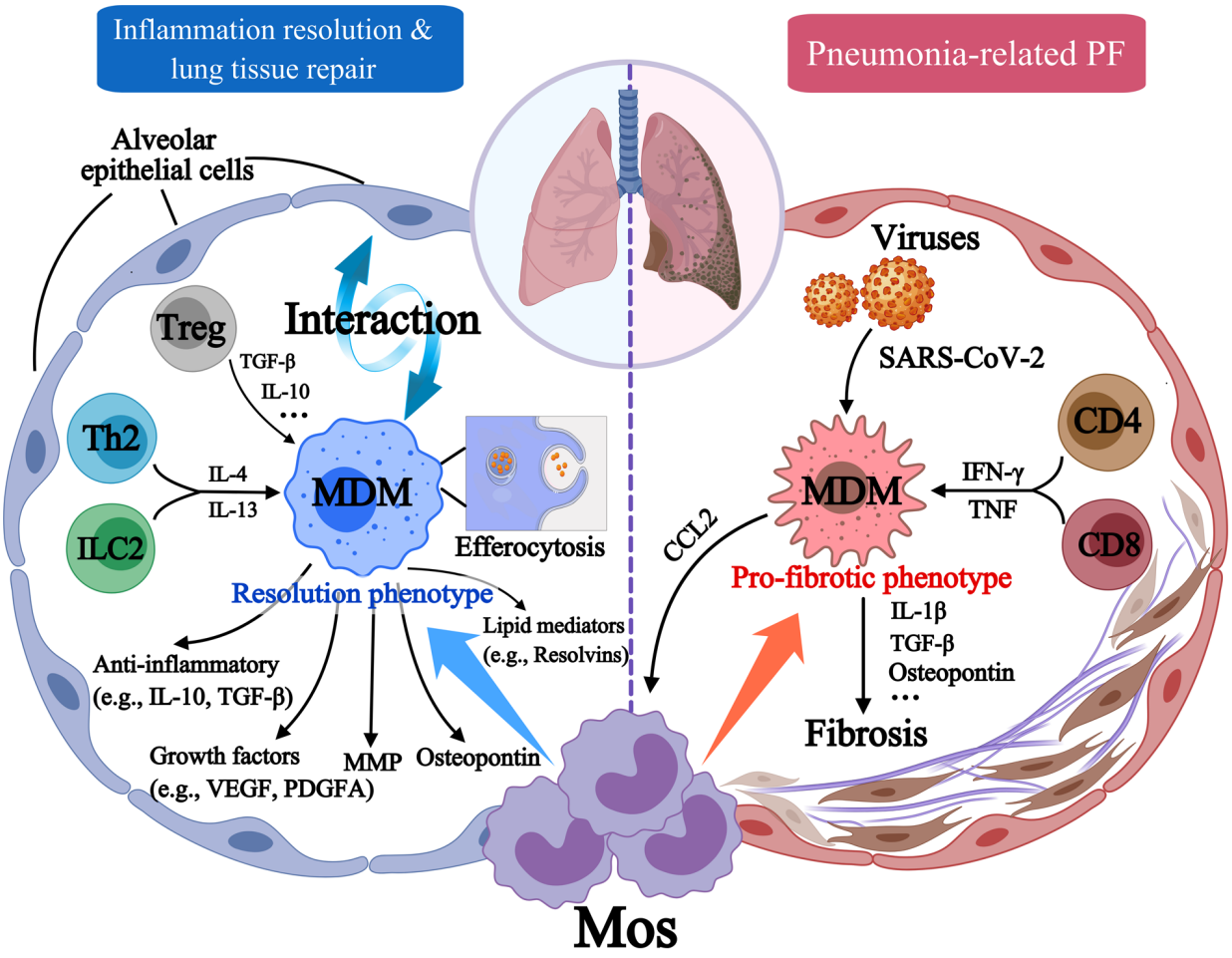

Figure 3. Mechanisms by which MDMs regulate inflammation resolution and lung tissue repair in patients with pneumonia and pneumonia-related PF. Inflammation resolution and lung tissue repair: MDMs can acquire a resolution phenotype through regulation by epithelial cells, Tregs, Th2 cells and ILC2s, as well as through efferocytosis. These MDMs facilitate the resolution of inflammation and the repair of injured lung tissue by secreting pro-reparative soluble mediators. Pneumonia-related PF: The virus (SARS-CoV-2), together with TNF and IFN-γ secreted by $CD4^+$ and $CD8^+$ T cells, induces a pro-fibrotic phenotype in MDMs. These MDMs contribute to pneumonia-related pulmonary fibrosis by secreting soluble mediators, including IL-1β, TGF-β and osteopontin. In addition, pro-fibrotic MDMs can further increase the recruitment of their precursor Mos through the secretion of CCL2. Mos, monocytes; MDMs, Mo-derived macrophages; PF, pulmonary fibrosis; Tregs, regulatory T cells; Th2, T helper 2; ILC2s, group 2 innate lymphoid cells; MMPs, matrix metalloproteinases; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CCL2, C-C motif chemokine ligand 2; TNF, tumor necrosis factor; IFN, interferon. Created with MedPeer (medpeer.cn).

provides progressively stronger steady-state signals that gradually steer MDMs toward RTM-like phenotypes and functions, thereby forming a positive feedback loop that supports tissue normalization; alternatively, MDM apoptosis may facilitate RTMs restoration. In the active model, late-stage injury signals, including efferocytosis, Tregs and epithelial-derived factors, activate specific transcriptional programs in MDMs, inducing the secretion of repair-promoting mediators such as anti-inflammatory molecules, growth factors, matrix metalloproteinases, osteopontin and lipid mediators. IL-4 and IL-13 produced by Th2 cells and group 2 innate lymphoid cells (ILC2s) also serve as key drivers of anti-inflammatory and reparative MDM phenotypes (15,112,113).

The aforementioned term 'efferocytosis' refers to the recognition, phagocytosis, and clearance of dying cells and cell debris by Mφs. This process prevents the release of harmful intracellular contents, helps terminate inflammatory responses, promotes tissue repair and restores lung homeostasis. The review by Kourtzelis *et al* (114) provides a detailed description of the specific mechanisms underlying Mφ-mediated efferocytosis. In most cases, efferocytosis drives Mφs toward an anti-inflammatory, pro-repair phenotype, which represents a key step in re-establishing homeostasis following tissue injury (111,114). However, an *in vitro* study reported that efferocytosis of SARS-CoV-2-infected apoptotic cells by MDMs inhibited the acquisition of an anti-inflammatory phenotype while promoting a pro-inflammatory phenotype characterized by increased secretion of IL-6 and IL-1β. This phenomenon appears to be related to SARS-CoV-2 activity and may be specific, as infection with coxsackievirus did not induce a similar phenotype in MDMs. Moreover, this process impairs the efferocytic capacity of MDMs, which may result in the accumulation of damage-associated molecular patterns in the lung and consequently exacerbate immune-mediated injury. However, the impairment of efferocytosis does not depend on SARS-CoV-2 RNA replication (91).

In addition, a recent study identified a short-lived Ly6G-positive (a neutrophil marker) Mφ subset in the alveolar lumen surrounding the lesion area during the early recovery phase in IAV-infected mice (113). These cells are derived

from recruited cMos ($CD64^{-}Ly6C^{+}$) through inflammatory Mos ($CD64^{+}Ly6C^{+}$), express high levels of *SPP1* and *Arg1*, and exhibit robust metabolic activity, phagocytosis and efferocytosis. $Ly6G^{+}$ Mφs can directly act on AT2 cells by releasing soluble factors, including chemokines, cytokines and osteopontin, thereby supporting AT2 cell proliferation and establishing a permissive environment for the AT2-to-AT1 transdifferentiation program, a process that depends on type II cytokine-mediated stimulation of IL-4R on $Ly6G^{+}$ Mφs. Similar MDM populations were also observed in non-infectious lung and liver injury models and in BALF from patients with suspected pneumonia, suggesting a broader role in tissue repair after lung injury.

Pneumonia-related PF. PF is one of the serious complications of pneumonia. SARS-CoV-2 and other viral pneumonias have been associated with PF, prompting intensive investigations of the underlying mechanisms (115-126). Given the well-established roles of Mos and MDMs in idiopathic PF (IPF) (127-130), Mo recruitment has been proposed as a potential driver of viral pneumonia-associated PF (83). Although direct evidence remains limited, recent studies of COVID-19 have begun to elucidate how Mos and MDMs contribute to pneumonia-related fibrotic remodeling, providing important insights into this as yet unresolved process.

Wauters *et al* (131) used scRNA-seq to demonstrate that Mos in the lungs of critically ill patients with COVID-19 exhibit features of adenosine triphosphate (ATP)-purinergic signaling-inflammasome activation. The measurement of ATP levels in BAL supernatant further confirmed approximately three-fold higher ATP levels in critically ill patients with COVID-19 than in patients without COVID-19. It was speculated that epithelial injury may trigger ATP release, and that extracellular ATP could drive the purinergic-inflammasome signaling pathway, potentially contributing to the development of COVID-19-related PF. In addition, circulating Mos from patients with COVID-19 exhibit both the upregulation of PF-associated genes and pathways (132) and impaired COX-2 production (30), which may further promote COVID-19-related PF.

Compared with Mos, currently, the understanding of researchers in academia of the mechanisms mediated by MDMs in COVID-19-related PF is more comprehensive. Wendisch *et al* (133) reported the accumulation of *CD163*/legumain (*LGMN*) Mφs derived from Mos in the lungs of patients with COVID-19-related ARDS. These cells displayed an enrichment of fibrosis-related gene signatures and robust interactions with mesenchymal cells, including myofibroblasts, fibroblasts and pericytes, suggesting their key role in PF. Furthermore, *in vitro* experiments have demonstrated that viral exposure itself serves as a critical initiating factor driving the pro-fibrotic response; specifically, SARS-CoV-2 can induce cMos to acquire a pro-fibrotic phenotype similar to that of *CD163*/*LGMN* Mφs (133). In addition to the direct effects of SARS-CoV-2, studies have also reported that the pro-fibrotic phenotype of MDMs is associated with the sustained activation of T cells (27,134). Li *et al* (134) found that following acute SARS-CoV-2 infection, IFN-γ produced by tissue-resident T cells in the lungs drives the development of pro-inflammatory and pro-fibrotic phenotypes in BMo-AMs and promotes the recruitment of their precursors, thereby contributing to PF sequelae. Additionally, Narasimhan *et al* (27) identified an aberrant niche composed of $CD8^{+}$ T cells, MDMs and dysplastic epithelial progenitors in post-viral pneumonia-related PF through spatial transcriptomics and imaging. Specifically, $CD8^{+}$ T cells secrete IFN-γ and TNF, thereby promoting chronic IL-1β release from MDMs. IL-1β, in turn, inhibits the normal transdifferentiation of AT2 cells into AT1 cells, arresting them in a high keratin 8 expression transitional state, which impairs effective alveolar regeneration and ultimately drives the development of fibrotic sequelae. Notably, although viral pneumonia-related PF shares histological similarities with IPF, the aforementioned aberrant niche appears to be unique to viral pneumonia-related PF. Moreover, blocking IL-6, which has been shown to alleviate bleomycin-induced PF (135), does not improve fibrotic sequelae or mitigate the associated pathology, underscoring a fundamental mechanistic distinction between IPF and post-viral pneumonia PF sequelae.

Although the pro-fibrotic effects of Mos and MDMs have been partially characterized in viral pneumonias other than COVID-19 (136-138), the majority of current evidence on pneumonia-related PF is derived from studies of COVID-19. Thus, whether the mechanisms identified in COVID-19 reflect shared fibrotic programs across viral pneumonias or pathogen-specific responses remains unclear. Future longitudinal and comparative studies spanning diverse pathogens, disease severities and recovery stages are needed to clarify the conserved and context-dependent roles of Mos and MDMs in pneumonia-related fibrosis.

4. Innate immune memory after pneumonia: The roles of Mos

In pneumonia, Mos and Mo-derived cells are not only involved in the acute phase response but also contribute to the establishment of pneumonia-induced innate immune memory. In addition to the adaptive immune system, the innate immune system has been recently shown to exhibit immune memory, which is defined as a persistently altered state of the innate immune system following an episode of acute inflammation (139). Among these phenomena, trained immunity and tolerance, the principal manifestations of innate immune memory, have attracted widespread attention and intensive investigation (140-143). Trained immunity refers to the phenomenon where innate immune cells (such as Mos and Mφs) undergo long-term functional remodeling after an initial exposure to certain pathogens or their components, thereby mounting enhanced, non-specific immune responses upon re-exposure, whereas immune tolerance represents the opposite state (140-144). In addition, priming and differentiation are also regarded as components of innate immune memory, and the distinctions among these concepts have been discussed in several recent reviews (143-146). Notably, these immune processes exhibit mechanistic overlap, encompassing the sustained reprogramming of immune cells at both epigenetic and metabolic levels (144).

The reasonable utilization of trained immunity (such as Bacillus Calmette-Guérin, BCG) to enhance early innate immune responses is a promising strategy for the prevention and treatment of pneumonia (143,147-149). Furthermore,

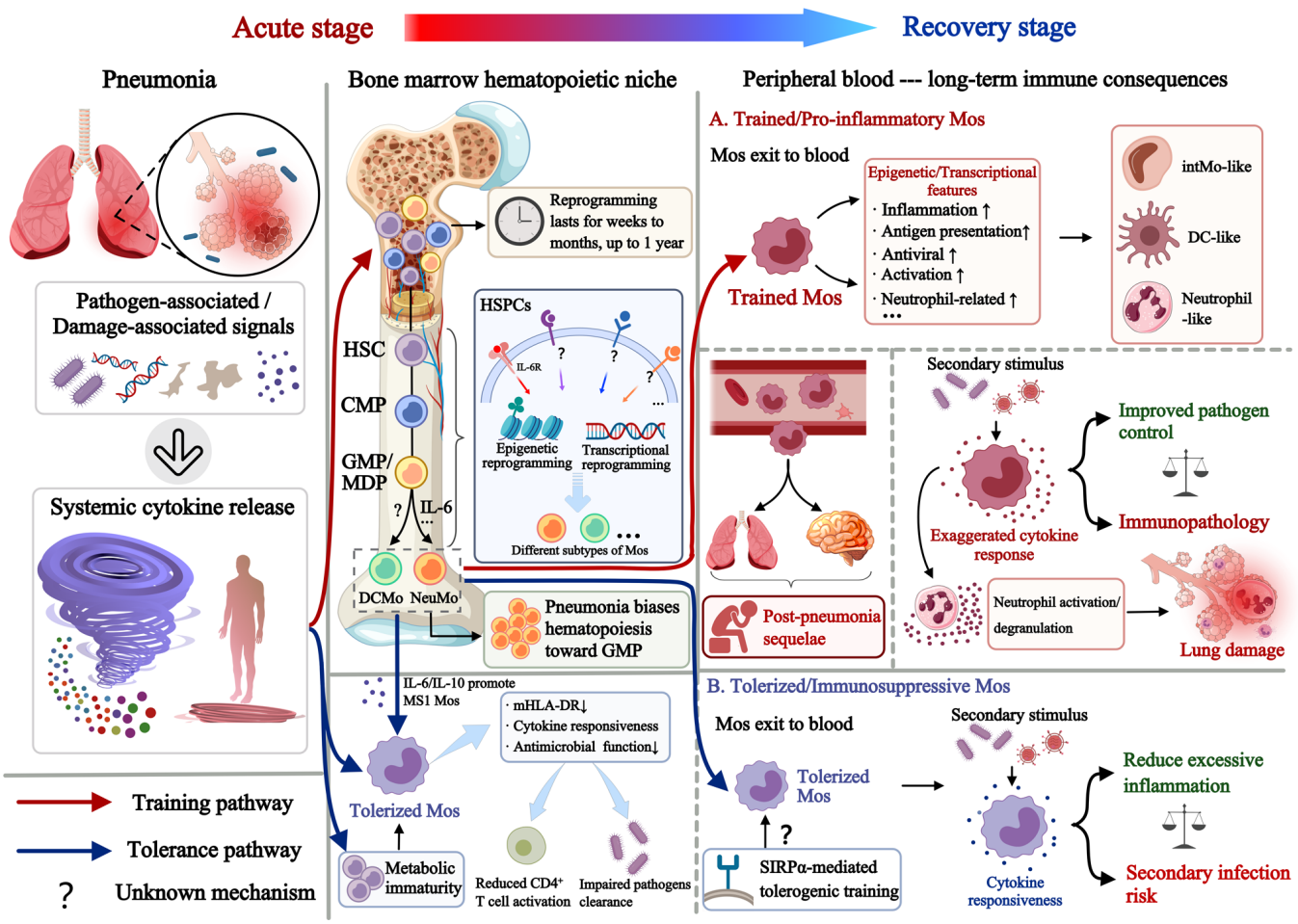

Figure 4. Pneumonia-induced innate immune memory in circulating Mos and its health implications. Pneumonia triggers systemic inflammation through mediators derived from both the lungs and peripheral blood. These inflammatory cues act directly on circulating Mos and reach the bone marrow, where they reprogram HSPCs. The available evidence indicates IL-6-dependent skewing toward the GMP pathway, whereas researchers have not clearly determined whether pneumonia induces a bias toward MDPs. Reprogrammed progenitors generate trained/pro-inflammatory Mos with increased inflammatory responsiveness; however, these cells may also exacerbate neutrophil activation and tissue injury. In parallel, pneumonia promotes Mo tolerance through acute-phase exposure to peripheral cytokines and plasma factors, as well as through central hematopoietic mechanisms, including metabolic immaturity and IL-6/IL-10-driven HSPC programming toward MS1-like Mos. HSPC-level imprinting may explain the persistence of tolerized Mos after pneumonia, and the tolerogenic training mediated by SIRP-α may also contribute. Mos, monocytes; HSCs, hematopoietic stem cells; CMPs, common myeloid progenitors; GMPs, granulocyte-Mo progenitors; MDPs, Mo-dendritic cell progenitors; DCMos, DC-like Mos; NeuMos, neutrophil-like Mos; intMos, intermediate Mos; HSPCs, hematopoietic stem and progenitor cells; mHLA-DR, Mo human leukocyte antigen-DR; SIRPα, signal-regulatory protein α. Created with MedPeer (medpeer.cn).

severe infections such as pneumonia and sepsis can also induce long-term innate immune memory, and this research area has garnered increasing attention in recent years (41,150,151). The present review next summarizes the specific processes by which pneumonia induces the establishment and maintenance of innate immune memory (training and tolerance) in circulating Mos and their progenitor cells, and discussed the implications for human health (Fig. 4). Subsequently, a focus is placed on the role of Mos in the remodeling of AMs after pneumonia. The review emphasizes that, in addition to the previously confirmed training of ResAMs, the replacement of ResAMs by recruited BMo-AMs during pneumonia is also crucial for the establishment of local innate immune memory in the lungs.

Innate immune memory of circulating Mos and their progenitors. Several studies have reported persistent epigenetic changes in circulating Mos weeks to months after COVID-19, suggesting the establishment of innate immune memory (152-156). The reprogramming of hematopoietic stem and progenitor cells (HSPCs) in the bone marrow is considered the key to maintaining innate immune memory in circulating Mos (140-142,157-160). Notably, the work by Cheong *et al* (42) has received widespread attention (42,150,151). Specifically, it was demonstrated that severe COVID-19 can induce durable epigenetic and transcriptional reprogramming of HSPCs, thereby exerting prolonged effects on patients' immune function for up to 1 year. On the one hand, this reprogramming causes a long-term skewing of myelopoiesis, which is characterized by a marked and sustained increase in the frequency of GMPs; on the other hand, the epigenetic and transcriptional reprogramming of HSPCs is transmitted to descendant Mos, leading to the enrichment of epigenetic and transcriptional programs related to activation, differentiation, antigen presentation and antiviral responses, and conferring on Mos features similar to those of intMos and DCs. Mechanistically, the IL-6 signaling pathway is a key driver of the persistent phenotype of HSPCs. The data from clinical cohorts and mouse infection

models consistently indicate that IL-6R blockade treatment during the acute phase can alleviate long-term myelopoiesis skewing and immune function remodeling following infection.

Consistent with the findings of Cheong *et al* (42), Denstaedt *et al* (41) recently studied preclinical sepsis models and showed that sepsis can, on the one hand, reprogram Mos (and their progenitors) into a pro-inflammatory phenotype by enriching the AP-1 motif and activating signaling pathways such as the JAK-STAT pathway; on the other hand, sepsis also reprograms the hematopoietic system by expanding GMPs in the bone marrow and consequently increases downstream NeuMo production. Upon subsequent secondary LPS challenge in the lungs, these reprogrammed Mos mediate more severe tissue damage by activating neutrophils and inducing their degranulation. Consistently, circulating Mos in patients with community-acquired pneumonia (CAP) exhibit upregulated expression of neutrophil-related genes, indicating that pneumonia similarly induces innate immune memory in Mos and their progenitors.

Current views suggest that trained immunity has dual regulatory characteristics: It can provide immune protection, yet may simultaneously drive excessive inflammation or immunopathological damage (141). Similarly, trained immunity induced by pneumonia exerts a 'double-edged sword' effect. On the one hand, *in vitro* experiments have shown that trained Mos can secrete large amounts of pro-inflammatory cytokines upon re-stimulation (42,155). While these cytokines are critical for early pathogen clearance, they may also exacerbate tissue pathology. Due to the lack of *in vivo* studies that systematically assess the overall function of trained Mos during secondary infection, whether their net effect predominantly enhances immune protection or primarily promotes immunopathology remains unclear. On the other hand, evidence from patients with COVID-19 suggests that trained Mos may represent one of the potential mechanisms underlying post-acute sequelae of SARS-CoV-2 infection (PASC) (151). PASC is characterized by persistent chronic inflammation (81,161). Notably, although not specific, pro-inflammatory Mos with phenotypes similar to the trained Mos aforementioned have been detected in the peripheral blood of patients with PASC (162,163). Moreover, Cheong *et al* (42) demonstrated that trained Mos can be persistently recruited to the lungs and brain in preclinical models, where they mediate immunopathology. Notably, although less well recognized, sequelae have been reported for viral pneumonias other than COVID-19 (81,161,164). Elucidating the role of trained immunity in Mos and their progenitors in the development of pneumonia-related sequelae is an important question warranting further investigation in the future.

In addition to enhancing innate responses, pneumonia can also induce a durable tolerized state in circulating Mos. During the acute phase of COVID-19 and other CAPs, peripheral blood Mos frequently exhibit altered cytokine responsiveness, reduced Mo human leukocyte antigen-DR (mHLA-DR) expression and/or impaired antimicrobial functions (32,165-171), despite the frequent coexistence of systemic inflammation (26,166-170,172,173). In fact, previous studies of the tolerant phenotype of Mos have mainly focused on sepsis (174-177), and this phenomenon has only been gradually recognized and appreciated in the context of pneumonia in recent years. Notably, two recent consecutive studies conducted by the same research group preliminarily explored the transcriptomic, epigenetic and metabolic features of tolerant Mos in the peripheral blood of patients with CAP (178,179). Importantly, this tolerant phenotype has been reported to persist for weeks to months following both mild and severe pneumonia (178,180,181), arguing against a purely transient deactivation state and instead suggesting durable immune imprinting. From a clinical perspective, the 'tolerant' state may help mitigate excessive inflammatory responses, but it also increases the risk of secondary infections. Moreover, these observations, especially the reduction in mHLA-DR (165), provide a biological rationale for dynamic immune monitoring and for considering immunomodulatory interventions in selected patients.

The precise mechanisms underlying the development of the tolerance phenotype in circulating Mos may be associated with large-scale cytokine production during pneumonia. On the one hand, according to the conjecture proposed by Joshi *et al* (175), pro-inflammatory cytokines drive rapid myeloid proliferation; however, this process outpaces Mo metabolic maturation and/or adequate GM-CSF stimulation, rendering newly generated Mos metabolically insufficient and therefore prone to tolerance. On the other hand, various cytokines can also directly influence the phenotype of circulating Mos (23,168,169). However, the aforementioned mechanism does not appear to provide a satisfactory explanation for the long-term persistence of Mo tolerance. Instead, this phenomenon suggests reprogramming at the HSPC level (178,181); however, the specific process remains unexplored, and cytokines may also play a key role. *In vitro* experiments have demonstrated that IL-6 and IL-10 drive HSPCs to differentiate into MS1 Mos, which exhibit a tolerant phenotype characterized by reduced cytokine induction and the suppression of T-cell responses (182). In addition, Roquilly *et al* (139) proposed a further hypothesis. Specifically, it was speculated that signal-regulatory protein α (SIRPα) functions as a pivotal sensor of inflammation and as a trigger for tolerogenic training throughout the body, and that *in vitro* anti-SIRPα treatment can restore the phagocytic capacity of circulating Mos.

Roles of Mos in AM remodeling. AM remodeling represents another important form of pneumonia-induced innate immune memory. Before birth, fetal Mos colonize the alveoli and differentiate into fetal Mo-derived AMs (FeMo-AMs), which constitute the initial ResAM population. Under physiological conditions, ResAMs maintain alveolar microenvironmental homeostasis without eliciting unnecessary inflammation. In the steady state, ResAMs can be replenished through either self-renewal or the recruitment of circulating Mos. The prevailing view is that ResAMs primarily sustain their numbers through local proliferation, with only a limited contribution from external input (60,183,184); in other words, FeMo-AMs account for the majority of ResAMs that have not experienced infection or injury. However, some studies suggest that, under steady-state conditions, the proportion of BMo-AMs may gradually increase with age (38,185). Pneumonia leads to the depletion of ResAMs, and both the self-renewal of residual ResAMs and the recruitment of BMo-AMs act to replenish the depleted AM pool. Pneumonia not only remodels the compositional landscape of AMs but, more importantly,

induces durable functional alterations in AMs that persist even after clinical recovery. The mechanisms underlying these persistent functional changes in AMs after pneumonia remain incompletely understood; potential contributing factors include a 'Mo legacy', the influence of inflammatory cues on Mo differentiation into BMo-AMs, the training of AMs of distinct ontogenies by the lung microenvironment, and the training of BMo-AM precursor cells, such as Mos and hematopoietic stem cells (HSCs) (Fig. 5A). Notably, although the persistent functional changes in AMs following pneumonia resemble the processes described in peripheral RTM-trained immunity, the pneumonic process involves the emergence of new cellular subsets (BMo-AMs). This result underscores the critical need to carefully distinguish between the unique functions of recruited BMo-AMs and the concept of ResAM training when investigating long-term AM functional reprogramming after pneumonia, as this distinction is critical for the development of targeted interventions (186). A number of studies have further elucidated the intricate mechanisms that may drive post-pneumonia AM remodeling (139,156,185,187), and multiple theoretical models have been proposed to describe this process (61,188), although substantial controversies and knowledge gaps remain. Table II presents a comprehensive summary of studies examining post-pneumonia AM remodeling.

Remodeling of the composition of the AM pool. Pneumonia induces extensive Mo infiltration into the alveoli, where these cells can further differentiate into BMo-AMs during inflammation, thereby mediating immune pathology while concurrently contributing to pathogen clearance (92). A portion (potentially even the majority) of recruited BMo-AMs disappears once inflammation resolves (92,183,189), whereas the remaining cells [referred to as long-lived BMo-AMs to distinguish them from transient AMs (TransAMs)] contribute to the reconstitution of the post-pneumonia AM pool. This short-lived BMo-AM subset can be referred as TransAMs, yet current research on TransAMs remains very limited (61,190). Similarly, ResAMs (of which FeMo-AMs are considered to constitute a large proportion in naïve mice) can also contribute to the post-pneumonia AM pool through self-renewal (Fig. 5B). Notably, the findings of Li *et al* (185) suggest that these two routes of replenishment of the AM pool occur in a temporally ordered manner. Specifically, IAV infection induces the substantial depletion of FeMo-AMs, after which the surviving FeMo-AMs promptly reconstitute the AM pool through self-renewal. Subsequently, the recruited Mos progressively differentiate into BMo-AMs, which further replenish the AM pool and ultimately supersede FeMo-AMs as the dominant component of the AM pool within weeks to months following infection clearance. By contrast, in naïve mice, bone marrow-derived Mos exhibit a weaker ability to colonize empty AM niches than fetal Mos. One possible explanation is that lung infection increases alveolar glucose levels, thereby increasing glycolysis and proliferation in BMo-AMs.

A number of studies have relied on the 'niche' model (61,187,188,190), a framework originally proposed by Guilliams *et al* (191,192), to explain the divergent proportions of BMo-AMs and FeMo-AMs observed after pneumonia. The Mφ niche constitutes a multifunctional microenvironment that provides structural support, trophic factors for self-renewal and tissue-specific signals that shape Mφ identity, while Mφs in turn help maintain the niche (191,192); the AM niche may comprise alveolar epithelial cells, fibroblasts, ILC2s and basophils (61,193). Guilliams *et al* (191) further suggested that the extent of RTM depletion, the intensity and nature of inflammation, and Mo access to the niche collectively determine the proportion of MDMs within the RTM pool during inflammatory remodeling. Accordingly, numerous scholars posit that the remodeling of the composition of the AM pool after pneumonia depends largely on the extent of ResAM depletion, namely, the severity of pneumonia (61,188,190,194).

This pioneering theory provides a reasonable explanation for the discrepancies in the results of the existing research, but several contradictory findings also merit discussion. On the one hand, in the study by Wang *et al* (195), although IAV infection depleted nearly 90% of ResAMs, their replenishment still relied predominantly on ResAM self-renewal, with BMo-AMs contributing only minimally. This result suggests that, in addition to the extent of ResAM depletion, other factors must be considered when determining the composition of the AM pool after pneumonia, such as differences in competitive capacity between ResAMs and recruited BMo-AMs for vacant niches. On the other hand, niche availability represents one of the key variables in the 'niche' model, which posits that once organ growth ceases, niches become fully occupied, thereby limiting the contribution of circulating precursors unless niches reopen (192). The limited niche number does not refer to a restriction in physical space but rather to the availability of trophic factors (51,191,196). Notably, in some mouse models of viral pneumonia, the number of AMs after pneumonia actually increased compared with the baseline number (185,194,197), and similar phenomena were observed even in *Ccr2*$^{-/-}$ mice (194). The mechanisms underlying this phenomenon remain unclear; pneumonia may induce the generation of new niches (185) or could indicate the presence of more complex and as yet unexplained mechanisms within the 'niche' model.

Moreover, differences in mouse strains may be a major contributor to these contradictory results (197,198). A typical example is that Gilliaux and Desmecht (197) found that the AM pool in BALB/c mice was markedly expanded 28 days after intranasal infection with MuHV-4 compared with that in control mice, whereas no differences were observed in mice of the CD-1 and C57BL/6 strains. In addition, the Siglec-F fluorescence (Siglec F^{lo} AMs represent BMo-AMs, whereas Siglec F^{hi} AMs represent FeMo-AMs) in BALB/c MHC II^{hi} AMs showed a bimodal distribution, suggesting dual AM origins; in contrast, in CD-1 and C57BL/6 mice, Siglec-F exhibited a unimodal distribution and its levels remained comparable to those in control mice, indicating the self-renewal of ResAMs.

Mechanism underlying the continuous changes in AM functionality. Pneumonia can also induce long-lasting alterations in AM function (Fig. 5C). Given that recruited BMo-AMs exhibit greater plasticity than ResAMs, researchers presumed that these recruited BMo-AMs play a central role in the sustained functional reprogramming of AMs following pneumonia. Several theoretical models have been proposed to delineate the potential scenarios involved in this process.

Based on the work of Aegerterg *et al* (194), Kulikauskaite and Wack (188) further proposed the theoretical model of

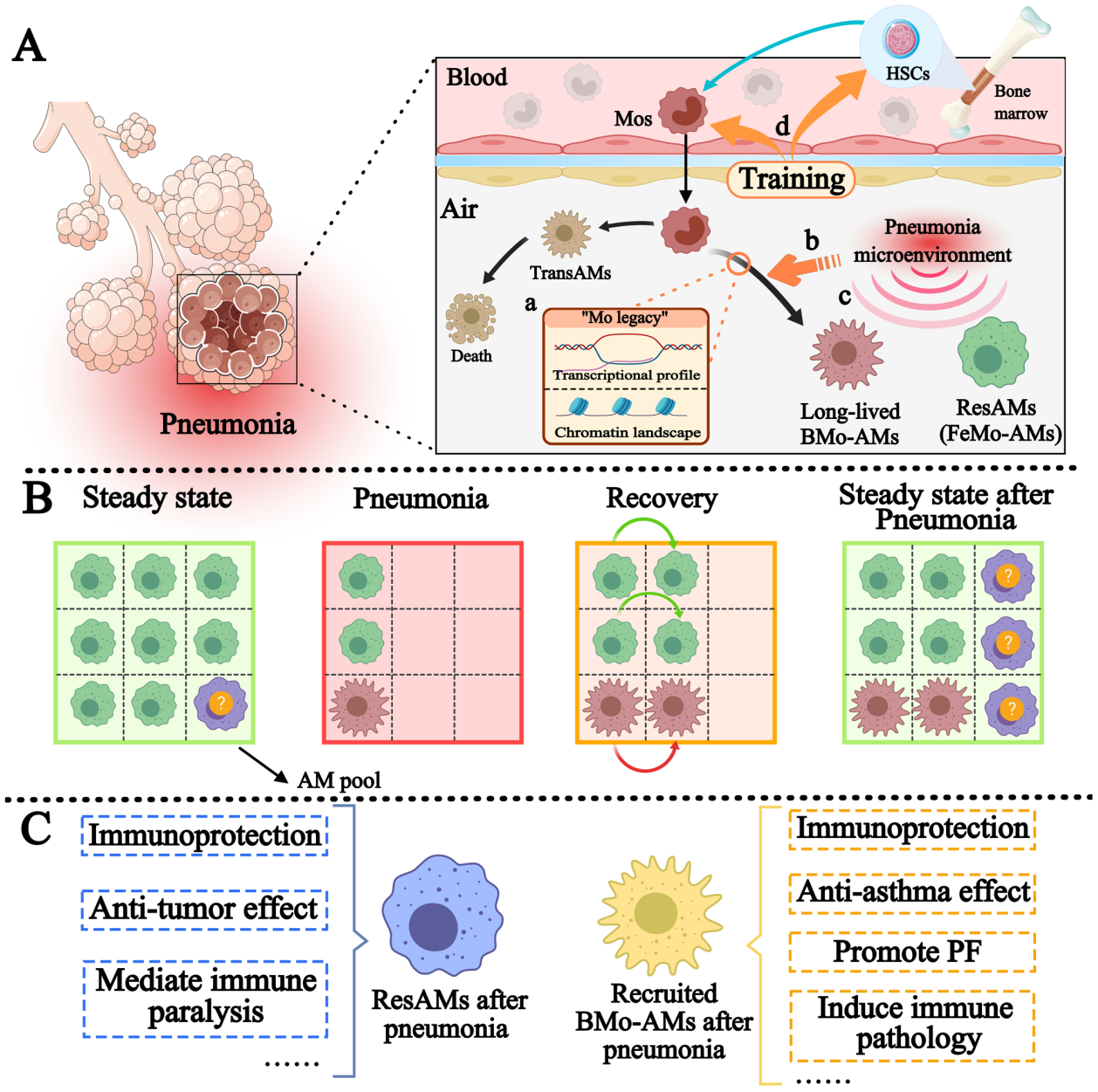

Figure 5. Remodeling of the composition of the AM pool and sustaining functional alterations following pneumonia. (A) Pneumonia induces the recruitment of Mos, which are derived from HSCs in the bone marrow, to the alveoli through the bloodstream, where they subsequently differentiate into recruited BMo-AMs. Some of these macrophages are short-lived and are referred to as TransAMs, whereas others are longer-lived and designated as long-lived BMo-AMs. Pneumonia can induce sustained alterations in AM function, which may be mediated by multiple potential mechanisms. a) The 'Mo legacy' model suggests that the recruited BMo-AMs can, to some extent, retain the chromatin landscape and transcriptional profile features of their precursor Mos. b) Inflammatory signals may modulate the differentiation of Mos into recruited BMo-AMs. c) The pneumonia microenvironment may induce trained immunity in both ResAMs and recruited BMo-AMs. d) Trained immunity may also occur during the differentiation of HSCs into the recruited BMo-AMs, such as in Mos and HSCs. (B) In the steady state, the niche within the AM pool is predominantly occupied by ResAMs (ideally originating mostly from embryos, although the possibility of a bone marrow origin cannot be entirely excluded). Pneumonia can lead to the depletion of ResAMs and the subsequent emergence of recruited BMo-AMs within the AM pool. Following pneumonia, both ResAMs and recruited BMo-AMs collaboratively occupy the vacant niche. However, the factors ultimately determining the relative proportions of these two cell types remain unclear. (C) Pneumonia can cause long-term alterations in AM function, and several potential scenarios may arise. Mos, monocytes; HSCs, hematopoietic stem cells; AMs, alveolar macrophages; TransAMs, transient AMs; BMo-AMs, blood Mo-derived AMs; ResAMs, resident AMs; FeMo-AMs, fetal Mo-derived AMs; PF, pulmonary fibrosis. Created with MedPeer (medpeer.cn).

the 'Mo legacy'. It was argued that BMo-AMs can, to some extent, retain specific features of the chromatin landscape and transcriptional profile of Mos, and that the pulmonary inflammatory environment may contribute to preserving the increased immunoreactivity of BMo-AMs inherited from Mos. As inflammation subsides, the pulmonary homeostatic environment influences BMo-AMs through two main pathways, cytokine signals, such as TGF-β and GM-CSF, and metabolic constraints, which together remodel their phenotype and ultimately convert them into steady-state cells resembling ResAMs that are characterized by tissue maintenance and low immunoreactivity. The authors also highlighted that the high reactivity of BMo-AMs may also arise from training during the differentiation of HSCs into BMo-AMs, or may be

Table II. Evidence for the remodelling of the composition of the AM pool composition and sustained alterations in AM function following pneumonia.

Pathogen type	Mouse strain	Proportion of BMo-AMs after pneumonia	Changes in the AM surface marker phenotype	Persistent changes in AM functionality	Mechanisms underlying the changes in AM functionality	Duration of AM remodelling after pneumonia	Impact of *Ccr2*$^{-/-}$	(Refs.)
Streptococcus pneumoniae serotype 19F	C57BL/6	?	Siglec F↓; MHC II↑;	Mediates immune protection against another *Streptococcus pneumoniae* infection, which may relate to the increased expression of *Cxcl9*	Related to the metabolism and transcriptomic reprogramming of AMs by an infection history, but the specific mechanisms are unclear	Surface marker phenotypic changes persist for at least 6 months; immune protection persists for at least 1 month	?	(253)
		~80%			Training of both ResAMs and recruited BMo-AMs; increased MHC II is related to IFN-γ, other mechanisms are unclear	Surface marker phenotypic changes persist for at least 4 weeks	No marked differences in the surface marker phenotype and quantity of remodelled AMs	(204)
IAV strain X31 (H3N2)	C57BL/6	~50% at ~ 1 month after infection and increases over time	CD11b↑; CD64↑; MHC II↑; CD200R↑	Mediates immune protection against pneumococcal pneumonia by secreting IL-6	The inflammatory microenvironment of pneumonia promotes the retention of Ly6C^{+} Mos through 'epigenetic legacy'	The immunoprotective effect was evident in the first month but disappeared in the second month	The immunoprotective effect completely disappeared	(194)
IAV strain PR8 (H1N1)	C57BL/6	~5% on day 19 after infection, and increases over time, reached >50% on day 81	Compared with naïve AMs-BMo-AMs: Siglec F↓; MHC II↑; CD88↓; FeMo-AMs present only minor changes in MHC II and CD11b levels	Mediates increased disease severity in subsequent IAV pneumonia	Related to the ontogeny of BMo-AMs	The changes in the BMo-AM transcriptome and metabolic characteristics persisted for at least 2 months; BMo-AMs increase vulnerability to pulmonary viral infection for at least 4 months	?	(185)

Table II. Continued.

Pathogen type	Mouse strain	Proportion of BMo-AMs after pneumonia	Changes in the AM surface marker phenotype	Persistent changes in AM functionality	Mechanisms underlying the changes in AM functionality	Duration of AM remodelling after pneumonia	Impact of *Ccr2*$^{-/-}$	(Refs.)
IAV strain PR8 (H1N1)	BALB/c; C57BL/6	Very small proportion (<5%)	MHC II↑	Antitumor functions; mediates an immuno-protective effect on pneumococcal pneumonia	Trained immunity: related to IFN-γ and NK cells	The antitumor functions persists for at least 4 months	The quantity, surface marker phenotype, and functional properties of trained AMs were comparable to those observed in WT mice	(195)
MuHV-4, wild-type MHV-68 strain	BALB/c; C57BL/6	80/90% on day 28	Siglec F↓; MHC II↑; CD86↑; CCR2↑	Inhibits HDM-induced airway allergy by blocking the ability of DCs to elicit a Th2 response, but without affecting the Th1 response	Related to the recruitment of BMo-AMs; the specific mechanism may include a cellular origin, inflammatory microenvironment or a combination of both	The anti-allergy function persists for at least 1 month	?	(187)
MuHV-4, MHV-68 strain CD-1	BALB/c; C57BL/6;	?	BALB/c: Siglec F↓; MHC II↑; C57BL/6/CD-1: MHC II↑; CD64↑	Mediates an immuno-protective effect on PVM by changing the secretion pattern of cytokines and chemokines	Priming may be related to $CD8^+$ T cells and cMos, but the specific mechanisms are unclear	Immune protection persists for at least 28 days	The expression of MHC II and CD64 on AMs remained elevated after MuHV-4 priming, but the levels were markedly lower than those in C57BL/6 WT	(197)

Table II. Continued.

Pathogen type	Mouse strain	Proportion of BMo-AMs after pneumonia	Changes in the AM surface marker phenotype	Persistent changes in AM functionality	Mechanisms underlying the changes in AM functionality	Duration of AM remodelling after pneumonia	Impact of *Ccr2*$^{-/-}$	(Refs.)
							mice, and the functions of AMs induced by priming were impaired	
Escherichia coli strain DH5α; *Staphylococcus aureus* strain RN4220; IAV strain WSN x31;	C57BL/6	Very small proportion	F4/80↑; CD11c↑; CD11b↑; CD64↑; FcεR1α↑; SIRPα↑	Severe impairment of phagocytic function	Tolerogenic training: SIRPα present in the early stage of pneumonia triggers the establishment of an immunosuppressive environment, leading to the training of ResAMs; increased SIRPα expression on AMs at early stages of paralysis directly impairs phagocytosis	In mice, the deficiency in AM phagocytic function persisted for at least 28 days, and in humans, it may last even longer	?	(139)
SARS-CoV-2[12] strain MA10	C57BL/6	Very small proportion	Similar	Mediates immune protection against IAV infection by hyper-inducing ISGs	Trained immunity: the viral PAMP and type I IFN signaling are crucial for the establishment of this innate immune memory	Immune protection persists for at least 1 month	The administration of anti-CCL2 neutralizing antibodies during acute SARS2 infection did not diminish the protective efficacy of rained AM	(156)

Table II. Continued.

Pathogen type	Mouse strain	Proportion of BMo-AMs after pneumonia	Changes in the AM surface marker phenotype	Persistent changes in AM functionality	Mechanisms underlying the changes in AM functionality	Duration of AM remodelling after pneumonia	Impact of *Ccr2*$^{-/-}$	(Refs.)
Human serotype 5 adenovirus	BALB/c; C57BL/6	Very small proportion (1-2%)	MHC II↑	Mediates an immunoprotective effect on bacterial infection by accelerating the secretion of chemokines to promote neutrophil recruitment	Trained immunity: $CD8^+$ T cells prime the formation of memory AMs via IFN-γ production and cellular contact	Immune protection persists for at least 16 weeks	No marked differences were observed in the quantity, surface marker phenotype and levels of chemokine production in trained AMs compared with those in WT mice	(203)

Mos, monocytes; AM, alveolar macrophage; BMo-AM, blood Mo-derived AM; ?,not involved in the study; ResAM, resident Ams; IAV, influenza A virus; FeMo-AM, fetal Mo-derived AM; WT, wild-type, HDM, house dust mite; PVM, pneumonia virus of mice; cMo, classical Mo; SIRPα, signal-regulatory protein α; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ISG, interferon-stimulated genes; PAMP, pathogen-associated molecular patter; IFN, interferon; MHV, mouse hepatitis virus; MHC, major histocompatibility complex; NK, natural killer; DC, dendritic cell; CCR2, C motif chemokine receptor 2; CCL2, C-C motif chemokine ligand 2; MuHV-4, murid herpesvirus 4; FcεR1α, Fc epsilon receptor Iα chain.

acquired by BMo-AMs within the inflammatory pulmonary microenvironment (141,158,199,200). By contrast, Guilliams and Svedberg (61) posited that the inflammatory differentiation trajectory of Mos, rather than cellular ontogeny, underly the sustained hyperreactivity of recruited BMo-AMs. Specifically, they infer that tissue homeostatic signals constrain the transcriptional plasticity of ResAMs, thereby preventing excessive inflammation-induced tissue damage. Consequently, inflammatory signals during pulmonary inflammation elicit only modest effects. By contrast, after recruited Mos enter the tissue, their differentiation is shaped by dual imprinting from both tissue-specific and inflammatory signals, ultimately giving rise to inflammation-imprinted resident AMs (InfResAMs) with high plasticity that retain certain pro-inflammatory features for a period following the resolution of inflammation. Over time, under the influence of homeostatic signals, InfResAMs undergo phenotypic remodeling and progressively acquire characteristics resembling ResAMs.

Together, these models suggest that recruited BMo-AMs acquire distinct functions following pneumonia but, in response to homeostatic pulmonary cues, gradually become ResAM-like and contribute to the ResAM pool, although some origin-dependent transcriptional differences persist (201,202). However, the intrinsic differences between ResAMs of distinct origins and their functions may have long been underestimated. A recent study by Li *et al* (185) suggested that BMo-AMs themselves indirectly tend to mediate more severe immunopathology during IAV infection than FeMo-AMs by modulating the activity of other cells within the niche. This important finding suggests that once conditions such as infection or aging expand the BMo-AM fraction within ResAMs, they may potentiate subsequent pneumonia, underscoring the need to re-evaluate the heterogeneity between BMo-AMs and FeMo-AMs and to define the specific functional roles of BMo-AMs, rather than treating them as interchangeable homeostatic populations. Additionally, although ResAMs are generally considered to exhibit limited plasticity and to be only modestly influenced by the pneumonia microenvironment (185,194), studies have reported infection-induced training effects on ResAMs (139,156,195,203), suggesting that their contribution to long-term AM reprogramming should not be overlooked. Furthermore, the preclinical evidence from pneumococcal pneumonia shows that both FeMo-AMs and recruited BMo-AMs undergo pronounced and sustained phenotypic changes, even though FeMo-AMs constitute only a minor AM subset, suggesting that the lung microenvironment is a key driver (204). However, why recruited BMo-Ams, with their high plasticity and potential 'Mo legacy', exhibit post-pneumonia phenotypes comparable to those of the less plastic FeMo-AMs remains unclear, especially given that FeMo-AMs can even acquire an increased phagocytic capacity following infection (204). Finally, one study reported that recruited IMs in models of LPS-induced lung injury initially exhibit robust inflammatory signatures, which subsequently wane as their transcriptional profile progressively converges toward that of resident IMs, while still maintaining *Il1b* upregulation, a characteristic potentially associated with innate immune memory (93). However, the current understanding of the precise changes in the abundance and functional properties of IMs during pneumonia progression and throughout the recovery phase remains limited (15,61,205).

In summary, pneumonia can induce sustained remodeling and functional alterations in AMs, with recruited BMo-AMs potentially playing a key role. Although this phenomenon has been extensively discussed (15,193), its precise mechanisms and potential modulatory factors remain incompletely understood. Moreover, ResAMs appear to independently contribute to AM remodeling, and the use of different experimental models and protocols may yield conflicting results. Therefore, future research should prioritize delineating the respective contributions of AMs from different ontogenies in post-pneumonia remodeling and rigorously defining the underlying mechanisms to avoid misleading researchers performing subsequent studies. Notably, the majority of the existing evidence is derived from animal experiments, in which the number and sequence of infections can be strictly controlled and defined. Furthermore, most animal models examined in previous studies were free from preceding respiratory infections and other diseases, enabling a direct observation of AM remodeling after pneumonia. However, the situation in human populations is far more complex. As highlighted in a number of reviews (188,190,193), due to factors such as age, a prior infection history and other pulmonary diseases, human AMs may have undergone long-term remodeling, potentially resulting in discrepancies between the preclinical experimental results and actual clinical conditions.

5. Clinical significance of Mos in pneumonia: Implications for precision medicine

The preceding discussion has systematically outlined the multifaceted roles of Mos and their derived cells in pneumonia, encompassing their regulatory influence on disease progression and prognosis, alongside their involvement in the formation of pneumonia-induced innate immune memory. It also highlights the important clinical potential of Mos in this context. This following section examines the clinical significance of Mos in pneumonia within the framework of precision medicine, encompassing the roles of circulating Mos phenotypes in pneumonia stratification and prognosis, as well as potential therapeutic strategies targeting Mos.

Circulating Mo phenotypes for pneumonia stratification and prognosis. Interindividual variations in Mo phenotypes may underlie the clinical heterogeneity of pneumonia. These phenotypic variations may reflect disease endotypes or stages and are closely associated with the disease severity, treatment response and clinical outcomes (23,99,100). Given that circulating Mo phenotypes are readily detectable in peripheral blood, which can be collected minimally invasively and repeatedly for dynamic monitoring, they hold promise as valuable tools for the stratification, risk assessment and personalized treatment decision-making in patients with pneumonia (26,32,173).

Liu *et al* (99) identified three heterogeneous patient clusters by integrating single-cell transcriptomes of peripheral blood mononuclear cells from patients with COVID-19, primarily based on distinct inflammatory phenotypes of Mos, and proposed a 'three-stage' model. Cluster 1 is characterized by enhanced adaptive T-cell immune responses and subtle Mo

inflammatory features, and predominantly comprises healthy donors and convalescent patients. Cluster 2 is characterized by a markedly increased proportion of immunosuppressive MS1-like Mos (exhibiting high expression of *S100A8*, *S100A9*, *IL18* and *RETN*, with low expression of MHC II genes), resembling the immunosuppressive phenotype observed in patients with sepsis, with the majority of patients in the convalescent phase and a small subset in the active phase. Cluster 3 is characterized by a markedly increased proportion of hyperinflammatory Mono-CD14-CCL3 Mos and megakaryocytes displaying high expression of pro-inflammatory cytokines such as *IL6*, *IL1B*, *CCL3* and *TNF*, which contribute to the development of a cytokine storm, and predominantly consists of patients with severe active-phase disease (99). Heterogeneous endotypes in patients with pneumonia may necessitate differentiated clinical interventions.

Furthermore, the detection of mHLA-DR offers a more convenient approach for assessing the disease state of patients with pneumonia than a single-cell transcriptomic analysis. Indeed, while circulating mHLA-DR expression levels have been well-established as a critical indicator for evaluating immunosuppression in patients with sepsis (175,176,206), their clinical significance in patients with pneumonia remains incompletely understood. In recent years, accumulating evidence from studies of COVID-19 has have shown that circulating mHLA-DR expression progressively decreases with increasing COVID-19 severity. Reduced mHLA-DR levels are markedly associated with poor pneumonia outcomes (165,167,168,207,208) and may serve as a robust biomarker for predicting disease severity and/or the mortality risk (208-211). Importantly, circulating mHLA-DR levels also facilitate the identification of pneumonia subphenotypes. Marais *et al* (100) reported that among adult patients with severe COVID-19, persistently high mHLA-DR expression (hyperactivated Mo/Mφ phenotype) correlated with increased mortality, whereas persistently low mHLA-DR expression was associated with secondary infections. Similarly, by leveraging differences in ferritin and mHLA-DR levels, patients with severe respiratory failure due to COVID-19 were successfully classified into two distinct subgroups: Those with Mφ activation-like syndrome (MALS) and those with immune dysregulation (23). In addition, there have been reports examining the clinical importance of circulating mHLA-DR levels in patients with non-COVID-19 pneumonias, although the available evidence remains limited and predominantly derived from studies of critically ill patients (212-216). The detailed findings of these studies are summarized in Table III.

In summary, the cellular and molecular signatures of circulating Mos may help identify clinically relevant pneumonia endotypes or subphenotypes and facilitate personalized, precision management.

Mo-targeted clinical strategies. Therapeutic strategies targeting Mos, including IFN-γ, GM-CSF and the inhibition of the IL-1 pathway, remain inadequately explored in patients with pneumonia. Nevertheless, several randomized controlled trials (RCTs) conducted in patients with sepsis have evaluated these immunomodulatory approaches and may provide indirect, hypothesis-generating evidence to guide therapeutic development and the design of trials of these drugs for pneumonia.

In terms of anti-inflammatory therapy, IL-1 pathway blockade therapy has garnered widespread attention. Anakinra is a recombinant IL-1 receptor antagonist that blocks IL-1 receptor type 1 signaling mediated by both IL-1α and IL-1β. In two early large RCTs of unselected patients with sepsis, IL-1 receptor antagonist did not result in an overall survival benefit (217,218). However, a post hoc reanalysis of one of these studies demonstrated that anakinra was associated with reduced 28-day mortality among patients with hepatobiliary dysfunction and disseminated intravascular coagulation, a phenotype characteristic of Mφ activation syndrome (MAS) (219). MAS is characterized by the aberrant activation of Mφs and $CD8^+$ T cells, which leads to a cytokine storm and a systemic hyperinflammatory state, with IL-1β serving as a pivotal mediator of its pathogenesis (220). Notably, IL-1β-driven MALS can also be observed in patients with pneumonia, suggesting a potential therapeutic effect of anakinra (221,222). The recent phase 2a INSPIRE RCT investigated the efficacy of anakinra in patients with non-COVID-19 pneumonia (223). Specifically, presepsin was employed as a marker to indicate the initiation of the early IL-1-mediated inflammatory cascade in Mos/Mφs obtained from patients. In hospitalized patients with a qSOFA score (224)=1 and presepsin levels >350 pg/ml, anakinra administration may reduce organ dysfunction progression and 90-day mortality while accelerating discharge (223). For COVID-19, a Cochrane review of four RCTs in the study by Davidson *et al* (225) demonstrated no evidence of a benefit from anakinra in patients with COVID-19, whether assessed by a clinical improvement, the proportion of patients with World Health Organization clinical progression scores (226) ≥7 or all-cause mortality. However, a pooled analysis of three non-RCTs conducted by Wang *et al* (227) demonstrated that anakinra treatment markedly reduced mortality among patients with COVID-19 with a SOFA score ≥2.

Canakinumab is a fully human monoclonal antibody that neutralizes IL-1β. Unlike anakinra, it is primarily indicated for the management of autoinflammatory diseases, and its application in treating sepsis or pneumonia has remained limited, with only a few RCTs assessing its therapeutic efficacy against COVID-19 (228,229). A phase 3 RCT involving 454 patients showed that for those patients with severe COVID-19 with systemic hyperinflammation but not requiring invasive mechanical ventilation, canakinumab treatment did not improve the survival rate without invasive mechanical ventilation at day 29 (228).

GM-CSF and IFN-γ-based immunostimulatory therapies are considered to be capable of restoring normal immune function in Mos/Mφs from septic patients with immunoparalysis (175,206). With respect to Mo function, several RCTs have demonstrated that GM-CSF increases mHLA-DR expression in septic patients (230-233), with one study additionally reporting the restoration of the Mo capacity to secrete pro-inflammatory cytokines (230). Meanwhile, the findings from early RCTs indicate that, compared with the placebo, GM-CSF treatment markedly improves infection cure/improvement rates, shortens the duration of mechanical ventilation, improves APACHE-II scores in patients with sepsis and increases the partial pressure of arterial oxygen to fraction of inspired oxygen ratio

Table III. Clinical importance of circulating mHLA-DR levels in patients with pneumonia other than COVID-19.

Characteristics of the patients	Main conclusions regarding mHLA-DR	(Refs.)
Children with MP pneumonia	HLA-DR expression on intMos was specifically downregulated at admission, with this reduction being more pronounced in patients with severe disease. HLA-DR expression on the other two Mo subgroups did not exhibit similar alterations.	(212)
Adults with influenza A H1N1pdm09 pneumonia	The expression of mHLA-DR can help predict the disease severity and mortality in patients. The severity and mortality were increased in patients who were immunocompromised (mHLA-DR expression <4,500 MFI) and presented with hyperinflammation (ferritin level >350 ng/ml). Hospital mortality was independently associated with low mHLA-DR values collected within 24 h of hospital admission. mHLA-DR expression was negatively correlated with MR-proADM and CRP levels.	(213)
Adults with confirme influenza A (H1N1) virus infection admitted to the ICU	Patients with IPF infection exhibited a reduction in mHLA-DR expression on the 7th day of hospitalization compared with the 1st day.	(214)
Patients with severe CAP who were treated in the emergency ICU (the pathogens were primarily bacteria and fungi)	The mHLA-DR level in non-survivors at 24 h after admission was markedly lower than that in survivors. The mHLA-DR level at 24 h after admission (threshold: 27.2%) displays high sensitivity (84.1%) and moderate specificity (58.6%) for predicting 28-day outcomes in patients.	(215)
Adults with acute CAP (the pathogens were primarily *Streptococcus pneumoniae*, MP and SARS-CoV-2)	Although no marked difference in circulating mHLA-DR levels at admission were observed between patients with deteriorating conditions and those without deterioration, mHLA-DR has emerged as a key biomarker for identifying high-risk patients in hierarchical clustering analyses based on relevant clinical, biological and immunological variables.	(216)

Mos, monocytes; mHLA-DR, Mo human leukocyte antigen-DR; MP, *Mycoplasma pneumoniae*; MR-proADM, MR-proadrenomedullin; ICU, intensive care unit; IPF, invasive pulmonary fungal; CAP, community-acquired pneumonia; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CRP, C-reactive protein; intMos, intermediate Mos; MFI, mean fluorescence intensity.

in individuals with respiratory dysfunction (230,231,234). However, in a recent multicenter RCT involving 98 septic patients with low mHLA-DR levels, no marked differences were observed between patients receiving GM-CSF therapy and those receiving the placebo in terms of the incidence of ICU-acquired infections, the frequency of mechanical ventilation or renal replacement therapy, the duration of the ICU stay or the length of the hospital stay (233). Notably, the findings of this study were influenced by the limited sample size resulting from the early termination of the trial (233). Furthermore, the results of multiple RCTs have consistently shown that GM-CSF therapy does not reduce the risk of mortality in patients with sepsis (230,231,233,234).

A small RCT demonstrated that IFN-γ treatment markedly increases TNF-α levels and mHLA-DR expression in healthy volunteers administered *E. coli* endotoxin, with more pronounced therapeutic effects than GM-CSF (235). Recent RCTs findings suggest that IFN-γ therapy may provide a clinical benefit for septic patients with immunoparalysis, as described next.

Notably, two recent RCTs have investigated the clinical efficacy of precision immunotherapy by identifying septic patients with distinct immune statuses (236,237). These findings provide an important reference for the clinical application of the aforementioned Mo-targeted therapeutic strategies in the context of precision medicine for patients with pneumonia. The PROVIDE RCT stratified patients with sepsis according to their immune status into three distinct categories: MALS (ferritin level >4,420 ng/ml), immunoparalysis (mHLA-DR expression <5,000/cell) and an intermediate group. Among the 240 enrolled patients, these groups comprised 20.0, 42.9 and 37.1% of the cohort, with corresponding 28-day mortality rates of 79.1, 66.9 and 41.6%, respectively. Within the MALS subgroup, anakinra markedly increased the proportion of survivors achieving a reduced SOFA score by day 7 (42.9 vs. 10.0%); however, it did not improve 28-day survival, which was potentially attributable to the limited 7-day treatment duration (236). Additionally, the initial limitations in the diagnostic criteria for immunoparalysis resulted in only a small number of patients receiving IFN-γ therapy, thereby precluding a meaningful efficacy evaluation (236). Overall, the PROVIDE trial offers preliminary evidence supporting immune-based stratification and targeted therapy in sepsis management. A subsequent RCT (237) adopted this classification criterion and employed an extended treatment duration (15 days) to further investigate the clinical efficacy of precision immunotherapy strategies in patients with sepsis. This study found that in the precision immunotherapy group

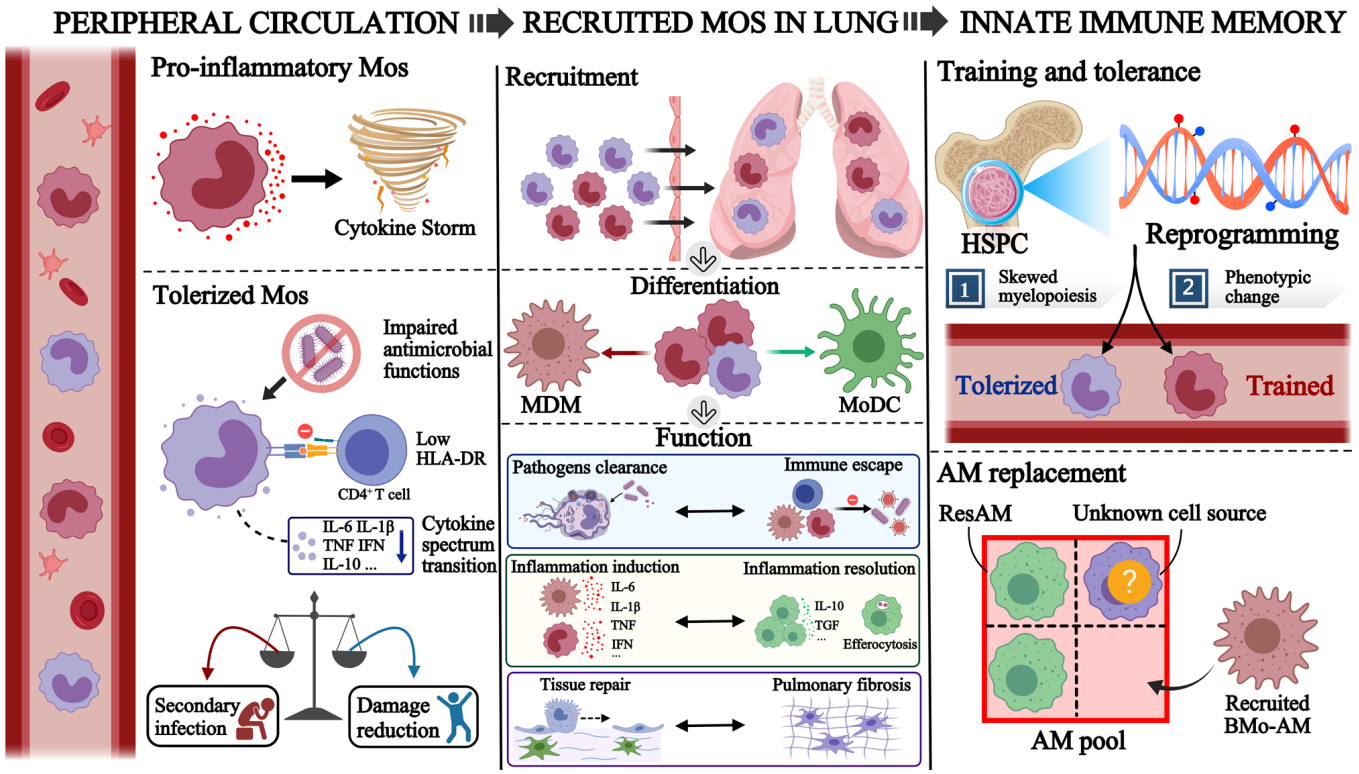

Figure 6. Overview of the roles of Mos during pneumonia progression. During pneumonia, circulating Mos display heterogeneous phenotypes. The pro-inflammatory phenotype promotes inflammation through the pro-inflammatory cytokines, whereas the tolerant phenotype is characterized by impaired antimicrobial functions, downregulated HLA-DR expression and a shifted cytokine spectrum, thereby facilitating inflammation resolution while potentially predisposing patients to secondary infections. Circulating Mos can migrate to sites of pneumonia and further differentiate into MDMs and MoDCs. Mos and their derivatives can collectively mediate pathogen clearance and/or immune evasion, inflammation initiation and/or resolution, and tissue repair and/or pulmonary fibrosis. Mos also contribute to pneumonia-induced innate immune memory. On the one hand, pneumonia induces the phenotypic reprogramming of HSPCs and skewed myelopoiesis, ultimately generating trained and/or tolerant Mos; on the other hand, long-lived BMo-AMs alter the composition of the AM pool and induce long-term functional alterations. Mos, monocytes; HLA-DR, human leukocyte antigen-DR; HSPCs, hematopoietic stem and progenitor cells; MDMs, Mo-derived macrophages; MoDCs, Mo-derived dendritic cells; AMs, alveolar macrophages; BMo-AMs, blood Mo-derived AMs; ResAMs, Resident Ams; TNF, tumor necrosis factor; IFN, interferon. Created with MedPeer (medpeer.cn).

(anakinra for MALS and IFN-γ for immunoparalysis), the proportion of patients achieving a mean decrease in the SOFA score of ≥1.4 points by day 9 was markedly increased (35.1 vs. 17.9%). The treatment also promoted immune recovery and infection resolution (237). However, consistent with the findings of the PROVIDE RCT (236), no improvements in 28- or 90-day mortality were observed. Notably, anakinra was associated with a higher incidence of anemia, whereas IFN-γ was associated with more hemorrhagic events (237).

Moreover, the therapeutic interruption of defined pathogenic signaling pathways may theoretically mitigate pneumonia-associated immunopathology. For instance, preclinical studies have demonstrated that the blockade of TNF and IFN-γ attenuates the generation of pro-fibrotic MDMs, thereby alleviating PF in patients with COVID-19 (27,134). However, these interventions may also disrupt other essential pathophysiological processes and lead to unforeseen consequences. These concerns, together with other limitations inherent to preclinical models, have impeded the translation of promising experimental findings into clinical practice. Further mechanistic studies and clinical validation are needed to facilitate translation.

Finally, targeting Mos to modulate pneumonia-induced innate immune memory may represent a promising clinical strategy. On the one hand, blocking pathways that drive HSPC reprogramming could alleviate the harmful effects of trained or tolerized Mos after pneumonia. To date, however, IL-6 remains the only cytokine demonstrated to mediate HSPC reprogramming during a severe viral respiratory infection (42), highlighting the urgent need for further investigations of additional key regulatory signals. On the other hand, although post-pneumonia alterations in AM function could theoretically be modulated by controlling the inflammatory milieu and specific signaling mediators during infection (61,188), the precise mechanisms underlying AM remodeling following pneumonia remain incompletely understood, and the findings are inconsistent. Thus, interventions targeting post-pneumonia AM remodeling remain premature, and future investigations are warranted to address these uncertainties.

6. Conclusions and future directions

With ongoing advances in research technologies, the multifaceted roles of Mos in pneumonia have been increasingly elucidated. However, while the COVID-19 pandemic has catalyzed extensive research into the immunopathology of SARS-CoV-2 infection, substantially advancing our understanding of the complex and dynamic roles of Mos in pneumonia, the predominance of COVID-19-related studies inevitably constrains the generalizability of some mechanisms

discussed in the present review. Although the review incorporates evidence from patients with non-COVID-19 pneumonia where available, a substantial proportion of the current literature is derived from patients infected with SARS-CoV-2. Consequently, the observations from patients with COVID-19 should be interpreted with caution and not be extrapolated uncritically to patients with other forms of pneumonia without direct comparative evidence. Future cross-etiology studies are warranted to differentiate shared Mo responses from pathogen-specific features.

Mos and their progeny are deeply involved in the development and outcomes of pneumonia by regulating pathogen clearance, the magnitude of inflammation and tissue repair processes. In addition, Mos play a critical role in pneumonia-induced innate immune memory, a process that may confer immune protection but can also lead to various adverse consequences (Fig. 6). Clinically, the characteristics of circulating Mos enable the stratification and prognostic assessment of patients with pneumonia. Various therapeutic strategies targeting Mos hold promise for establishing new frontiers in the precise prevention and treatment of pneumonia. However, as emphasized in the relevant sections of this review, current studies in these fields remain limited, and a number of controversies and unresolved questions require further investigation. Future preclinical and clinical investigations should further delineate the multifaceted roles of Mos in pneumonia. Integrating mechanistic studies with prospective clinical investigations may facilitate the identification of robust Mo-derived biomarkers and therapeutic targets. These translational endeavors hold promise for advancing risk stratification, refining personalized treatment approaches, and ultimately improving patient outcomes in pneumonia management.

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Authors' contributions

RZL and ZHX drafted the original manuscript and prepared the figures and tables. LC YXS and FW reviewed and revised the manuscript, and prepared the figures. QC and WJH contributed to reviewing, editing and supervision. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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