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REVIEW

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Monocyte and macrophage function in respiratory viral infections

Mohd Arish[1,2] and Jie Sun[1,2*]

Abstract

Pulmonary macrophages, such as tissue-resident alveolar and interstitial macrophages and recruited monocyte-derived macrophages, are the major macrophages present in the lungs during homeostasis and diseased conditions. While tissue-resident macrophages act as sentinels of the alveolar space and play an important role in maintaining homeostasis and immune regulation, recruited macrophages accumulate in the respiratory tract after acute viral infections. Despite sharing similar anatomical niches, these macrophages are distinct in terms of their origins, surface marker expression, and transcriptional profiles, which impart macrophages with distinguished characteristics in physiological and pathophysiological conditions. In this review, we summarize the current view on these macrophage populations, their shared functions, and what makes them distinct from each other in the context of homeostasis and respiratory viral infections.

Keywords Alveolar macrophages, Interstitial macrophages, Monocytes derived macrophages, Viral infection, IAV, RSV, SARS-CoV-2

Introduction

Lung macrophages play a critical role in shaping homeostasis and immune regulation and encounter pathogens (Hou et al. 2021). Not only are macrophages among the first immune cells to encounter viral particles in the lung, but they also maintain lung function by engulfing small debris and regulating surfactant turnover (Aegerter et al. 2022). Interestingly, these immune populations are further distinguished by the lung microenvironment, differential surface receptor expression, and transcriptional signature, which provide them with distinct characteristics (Aegerter et al. 2022). Alveolar macrophages (AM) and interstitial macrophages (IM) are two pulmonary resident macrophage populations that are present during homeostatic conditions. However, a third major contributor, monocyte-derived macrophages, appeared mostly during inflammatory conditions such as viral infections (Bain and MacDonald 2022). Alveolar macrophages are the predominant macrophage population that are mainly present in alveoli and airways. Lung IM resides specifically in the interstitial space but can also be found in the alveolar space in a low percentage (Duan et al. 2017).

After a respiratory virus infection, the pool of resident macrophages is highly affected. AMs are partially depleted at the peak of viral-induced inflammation, followed by the regeneration of AM pools by AM proliferation and monocyte differentiation into new AMs (Li et al. 2022; Zhu et al. 2021). In particular, the AM pool is later filled by recruited monocyte-derived macrophages, leading to a drastic reshuffling of the macrophage population. Notably, these recruited macrophages may have distinct metabolic, proliferative, and inflammatory gene expression than resident AMs (Mould et al. 2017), leading to the potential development of "trained immunity" in the AM compartment (Fig. 1). These recruited monocyte-derived macrophages also protect lung function

*Correspondence:
Jie Sun
js6re@virginia.edu
[1] Beirne B. Carter Center for Immunology Research, University of Virginia, Charlottesville, VA 22908, USA
[2] Division of Infectious Disease and International Health, Department of Medicine, University of Virginia, Charlottesville, VA 22908, USA

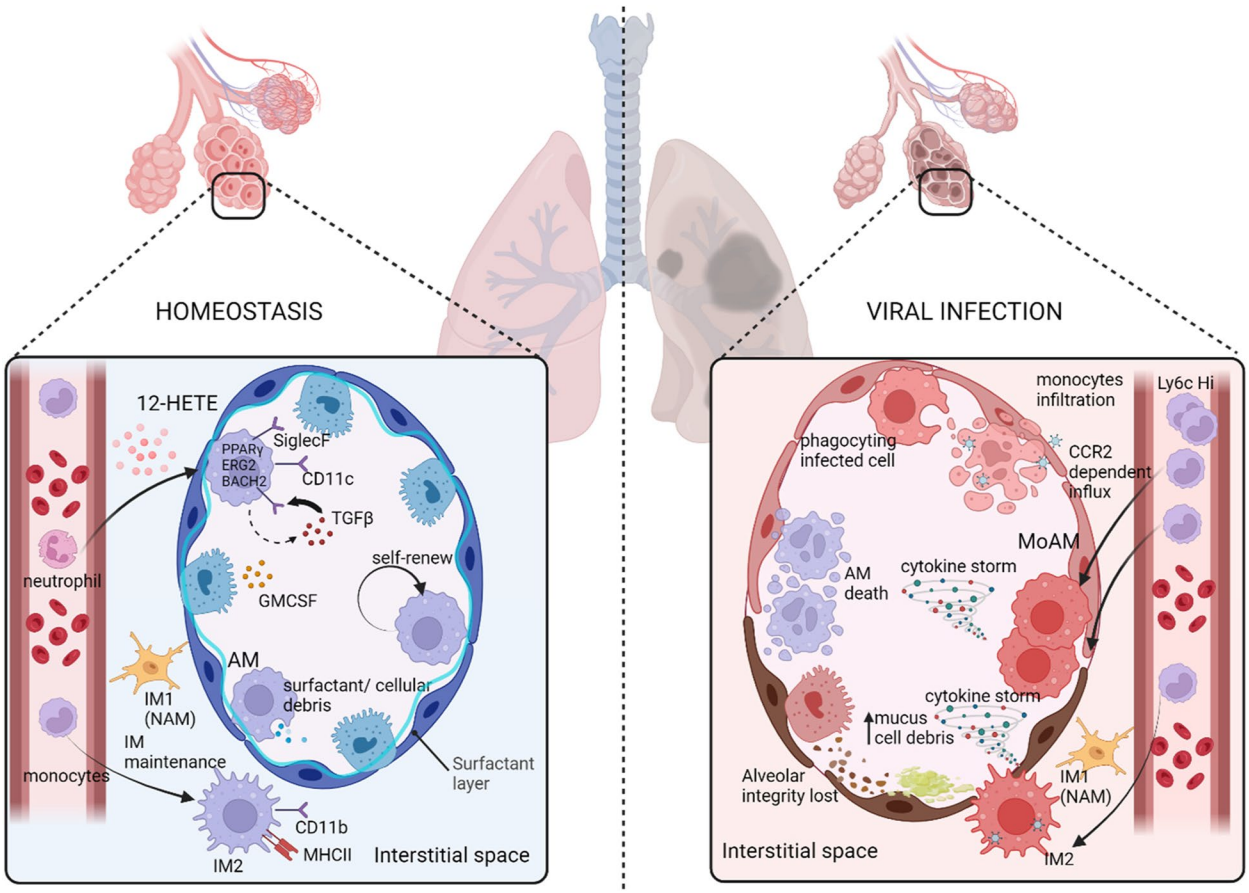

Fig. 1 Pulmonary Macrophages in health and disease: During homeostasis, AM helps in surfactant and cellular debris removal. Transcription factors such as PPAR-γ, ERG2, and BACH2 helps in maturation and differentiation of fetal monocytes that seeds alveolar space during embryonic stage. Together with signals such as GM-CSF, TGF-β, and neonatal derived 12-HETE, AM gain identity, with almost no input from circulatory monocytes. IM1 are also locally maintained, however, IM2 required monocytes for its maintenance. Following a respiratory virus infection, the pool of AM is partially depleted due to cell death. The lung compartment is later experienced CCR2 dependent influx of monocytes, which are later differentiated into monocyte derived alveolar macrophages (MoAM) that can drive lung inflammation and lung fibrosis. IM2 can be infected by respiratory viruses, which further amplify the inflammatory response

by their heightened production of antipathogen factors and active phagocytosis of cellular debris (Aegerter et al. 2020), although "trained" resident AMs may also contribute to heightened antipathogen and/or antitumor immunity after primary infection (Wang et al. 2023; Yao et al. 2018). Conversely, recruited macrophages are also directly responsible for lung fibrosis (McCubbrey et al. 2018; Wendisch et al. 2021), a common repercussion of post-severe viral pneumonia, including coronavirus disease 2019 (COVID-19) (Wendisch et al. 2021).

This review article discusses the crucial role of distinct lung macrophage subsets in the immune response to respiratory viral infections such as influenza (IAV), respiratory syncytial virus (RSV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The review also discusses the potential drawbacks of an excessive or dampened macrophage response, leading to tissue damage and severe complications following viral infection. Last, the article emphasizes the importance of ongoing research to identify critical factors that regulate macrophage function in viral infection or during homeostasis.

AMs in viral infection

AMs have been strongly suggested to play a pivotal role in surfactant turnover and the removal of cellular debris, thus maintaining lung homeostasis under a steady state (Roberts et al. 2017) (Fig. 1). Phenotypically, AMs are designated the CD11c- and Siglec F-high population in mice; in humans, AMs mainly express CD11c, CD36, CD206, Macrophage Receptor With Collagenous Structure (MARCO), and Human Leukocyte Antigen – DR

isotype (HLA-DR) (Aegerter et al. 2022). Peroxisome proliferator-activated receptor gamma (PPAR-γ), hematopoietic protein-1 (Hem-1), early growth response 2 (EGR2), and B lymphoid transcription repressor BTB and CNC homology 2 (BACH2) are some of the AM-specific factors that guide AM development, maturation, and maintenance (Schneider et al. 2014b; Suwankitwat et al. 2021; McCowan et al. 2021; Nakamura et al. 2013). In addition, following infection, AM regulates tissue damage by checking the misfiring of immune responses (Kopf et al. 2015). Increasing evidence has shown that AMs are required for protection against respiratory viral infection (Schneider et al. 2014a; Kolli et al. 2014). Intriguingly, AM can also be detrimental for mice infected with human metapneumovirus (hMPV). Depletion of AM by intranasal instillation of dichloromethylene bisphosphonate resulted in improved morbidity and reduced inflammatory cytokine secretion (Kolli et al. 2014). These contrasting studies suggested a dual behavior of AM in the context of any disease, and hence, to navigate to the exact role of these AMs, it is critical to consider the model of infection.

It is now widely accepted that AMs originate from the yolk sac as progenitor macrophages that seed and populate the alveolar space during the first week of the embryonic stage (Guilliams et al. 2013). These fetal monocyte-derived AMs are maintained and differentiated throughout life by granulocyte-macrophage colony-stimulating factor (GM-CSF) and transforming growth factor beta (TGF-β) (Yu et al. 2017; Schneider et al. 2014b), with minimal input from circulatory monocytes (Hashimoto et al. 2013). GM-CSF is further required for the maintenance of proper lung function, and infection of *Csf2*$^{-/-}$ mice with influenza simply aggregated this phenotype and proved to be lethal despite unaltered T and B-cell responses (Schneider et al. 2014a), suggesting that AMs are required for the maintenance of respiratory function after influenza infection.

AMs are the main immune cell type that produces type I interferons (IFNs) during respiratory viral infection, which is critical to suppress early viral replication (Kumagai et al. 2007; Mallampalli et al. 2021). Intriguingly, AM-secreted IFN-β, a type I IFN, is also associated with alveolar epithelial cell injury following IAV infection (Högner et al. 2013). These contrasting features of type I IFNs are suggested to be due to the timely IFN response, where the early type I response is protective and the prolonged or delayed type I IFN response is detrimental during viral infection (Channappanavar et al. 2016). Similarly, even though AMs are largely anti-inflammatory during homeostasis, they upregulate inflammatory cytokine production after respiratory viral infection (Huang et al. 2019b; Zhu et al. 2021). Thus, while AMs are largely beneficial in viral infection due to their tissue reparative and immune-suppressive properties, AMs can also be detrimental to directly (via their own production of inflammatory cytokines) or indirectly (via recruitment of other inflammatory cells) contribute to pulmonary inflammation during respiratory viral infection. Consistently, Grant showed that a small proportion of AMs can be infected with SARS-CoV-2, resulting in T-cell recruitment, which is required for the feedback loop driving the inflammatory response (Grant et al. 2021). Therefore, the protective versus beneficial function of AMs is largely context- and factor-dependent after respiratory viral infection.

PPAR-γ is considered a master regulator of AM differentiation and maturation, as its deficiency in CD11c+ myeloid cells leads to AM pool impairment (Schneider et al. 2014b). Additionally, deficiency of PPAR-γ in AMs showed enhanced inflammation and associated morbidity following IAV and respiratory syncytial virus (RSV) infection (Huang et al. 2019b; Schneider et al. 2014a), suggesting that PPAR-γ promotes reparative function and limits inflammation in AMs. In contrast, deletion of transcription factors such as β (beta)-catenin and hypoxia-inducible factor 1 subunit alpha (HIF1A) can lead to diminished inflammation and enhance lung repair (Zhu et al. 2021). Hence, it is strongly suggested that these transcription factors play a critical role in defining AMs functions during viral infection, resulting in either host protection or disease exacerbation. Recently, it was demonstrated that the neonatal neutrophil-derived eicosanoid 12-HETE is required for AMs imprinting (Pernet et al. 2023). Furthermore, genetic deletion of 2-lipoxygenase and 15-lipoxygenase in mice results in defects in AMs, which further leads to increased susceptibility to respiratory viruses such as influenza and SARS-CoV-2 (Pernet et al. 2023).

AMs have intrinsic self-renewable and niche occupancy properties that are further regulated by the lung microenvironment (Li et al. 2022). During severe respiratory viral infections, including COVID-19, AMs are partially depleted due to increased AM death and/or the inhibition of AM self-renewal by infection-induced Wnt ligands (Zhu et al. 2021). Interestingly, Wnt ligands also promoted AM inflammatory cytokine production, suggesting that Wnt-β-catenin signaling uncouples AM inflammatory activities with their self-renewal ability (Zhu et al. 2021). During the resolution of viral inflammation, AMs regain their self-renewal ability and proliferate to repopulate the AM pool. Two recent studies using parabiosis and bone marrow transfer have demonstrated that AM proliferation is probably the major contributor to the early reconstitution of the depleted AM pool after influenza infection (Li et al. 2022; Zhu et al. 2021). AM

loss during influenza infection is accompanied by the influx of Ly6c^{hi} monocytes after influenza infection (Li et al. 2022).

Notably, the replenished AMs after the resolution of the primary infection are phenotypically, transcriptionally, and epigenetically different than those AMs before infection. Studies have found that AMs exhibit heightened expression of inflammatory molecules and are epigenetically primed for the elevated re-expression of those molecules upon stimulation (Wang et al. 2023; Yao et al. 2018; Aegerter et al. 2020). These macrophages are termed "trained" macrophages, as they acquire immunological imprinting of previous challenges and result in increased responsiveness to secondary challenges (Zahalka et al. 2022). Both resident AMs and recruited monocyte-derived AMs may exhibit "training" properties after infection, leading to increased antipathogen and/or antitumor activities by AMs after primary viral infection (Wang et al. 2023; Yao et al. 2018; Aegerter et al. 2020). Nevertheless, trained immunity in AM is still an underexplored theme, and the functions of "trained" AMs may vary under different disease settings and lung microenvironments. Hence, it is critical to examine the role of AM training in the context of viral infection, which may hold the key to acquiring immune memory in a variety of lung diseases.

IMs in viral infection

IMs are named due to their anatomical residence in the interstitial tissue, where they act as gatekeepers of the vasculature and lung interstitium (Duan et al. 2017; Bain and MacDonald 2022). Phenotypically, IMs are classified as Siglec F^{low} and CD11c^{low} populations but express high CD11b in mice (Duan et al. 2017). Similar to AMs, these IMs express other prominent macrophage markers, such as CD64, MertK, and CD68 (Gautier et al. 2012). Additionally, IMs are significantly outnumbered by AMs in the lungs of mice; hence, these immune populations are poorly studied due to their anatomical niche and lower proportions compared to AMs. Nevertheless, some studies have shown the developmental origin of these unique pulmonary macrophage subsets in human and mouse lungs. In mice, IMs are subdivided into two classes: Lyve1^{low}MHCII^{hi} and Lyve1^{hi}MHCII^{low} macrophages (Chakarov et al. 2019). In humans, IMs are classified as CD45^{+}CD11b^{+} CD64^{+}CD14^{+}CD16^{-} macrophages, which are further divided into two populations. One of the subsets is characterized by high CD11b expression, while another subset is defined by markers such as CD169, CD206, and Lyve1 (Chakarov et al. 2019). Additionally, human IMs exhibit some transcriptional resemblance to murine Lyve1^{low}MHCII^{hi} and Lyve1^{hi}MHCII^{low} macrophages (Chakarov et al. 2019). However, unlike murine IMs, human IMs express high MHCII and CX3CR1 in Lyve1^{+} IM (Chakarov et al. 2019). In addition, both human and murine lung IMs have a common feature of expressing the immunosuppressive cytokine IL-10 in the steady state (Liegeois et al. 2018), suggesting some degree of similarity between human and mouse lung macrophages.

IMs developmentally originate from yolk sac macrophages and fetal monocytes (Guilliams et al. 2013). Then, IMs either self-replenish or are gradually replaced by CCR2^{+} monocytes to a different extent according to the IM subtypes (Aegerter et al. 2022; Sabatel et al. 2017). Recent scRNA-seq analysis of murine lungs revealed distinct IM populations. Chakarov et al. defined these IMs as two distinct populations: Lyve1^{low}MHCII^{hi} and Lyve1^{hi}MHCII^{low} macrophages (Chakarov et al. 2019). Although both IM subsets have antigen presentation ability, Lyve1^{low}MHCII^{hi} IMs are more capable of antigen presentation and can stimulate CD4^{+} T-cell proliferation than Lyve1^{hi}MHCII^{low} IMs. Lyve1^{hi}MHCII^{low} subsets are more enriched in the expression of genes related to wound healing and fibrosis (Chakarov et al. 2019). However, Gibbings et al. categorized IMs into three subtypes based on their expression levels of CD11c and MHCII: IM1 (CD11c^{low}MHCII^{low}), IM2 (CD11c^{low}MHCII^{hi} (IM2), and IM3 (CD11c^{+}MHCII^{hi}). Transcriptionally, IMs and AMs both have macrophage signatures, but these cell types are distinct from each other. IMs were found to have higher expression of monocyte-related genes than AMs, suggesting that IMs are derived from monocytes (Gibbings et al. 2017; Larson et al. 2016).

The responses of IMs after microbial infection are currently poorly defined. Interestingly, local installation of TLR1/2, TLR4, and TLR9 ligands results in the expansion of murine IM subsets (Schyns et al. 2019). The TLR4-driven expansion of the IM was halted in *Ccr2*$^{-/-}$ mice, but intriguingly, there was a nonsignificant decrease in CpG-treated mice, thereby suggesting bone marrow-independent recruitment. These studies indicated inflammation-driven IM expansion. However, it is still not clear whether viral antigens can also drive IM expansion. Nevertheless, TLR2-dependent sensing of the E protein of SARS-CoV-2 and the subsequent inflammatory response have been documented (Zheng et al. 2021). It will be interesting to examine whether there is similar IM expansion in cases of viral infection or viral protein stimulation as in cases of bacterial infection.

After lung insult, a transitional macrophage state is identified that has shared gene expression of both alveolar and interstitial macrophages in the fibrotic mouse model. This transition state is inclined toward alveolar macrophage gene expression, suggesting that during lung injury, some proportions of IM are later differentiated

into the resident AM population (Aran et al. 2019). This could be largely attributed to the influence of the lung microenvironment and growth factors. However, it is still unknown whether this transitional IM state is found during viral resolution.

Another type of IM resides around the large bronchiolar airways adjacent to airway-associated nerves and hence was named nerve-associated macrophages (NAMs) (Ural et al. 2020), which likely represent the Lyve^{low} MHCII^{hi} IM populations identified previously (Chakarov et al. 2019). NAMs have self-renewing capacity but differ from AM morphologically, having more elongated and dendritic cell-like appendages. Furthermore, specific NAM-depleted mice challenged with influenza showed increased morbidity compared to wild-type mice. Additionally, NAM-depleted mice can support inflammation after polyinosinic-polycytidylic acid (poly IC), as shown by increased proinflammatory cytokine IL-6 and chemokines such as CCL2, CCL3, and CCL5 (Ural et al. 2020). Intriguingly, the NAM population was unchanged in *Ccr2*$^{-/-}$ mice treated with poly IC, suggesting that NAM can be locally maintained (Ural et al. 2020).

Not much is known about IMs in the context of SARS-CoV-2; however, a recent preprint study suggested that in ex-vivo cultured human lungs, there are three distinct clusters of macrophages, viz., AMs, IMs and activated IMs, following SARS-CoV-2 infection. These activated IMs differ from the other two populations in terms of increased genes related to nuclear factor-κB (NF-κB), inflammation, and hypoxia-induced factors (Wu et al. 2022). Furthermore, there was striking viral accumulation in these activated IMs compared to AMs, which resulted in the induction of a high degree of cytokine and chemokine expression (Wu et al. 2022). Previously, it was known that alveolar macrophages can be infected with SARS-CoV-2, which amplifies the inflammatory response via T-cell activation (Grant et al. 2021). However, infected IMs show more robust hijacking of transcriptomes leading to inflammatory signatures, which also supports viral replication (Wu et al. 2022).

Monocytes and monocyte-derived macrophages in viral infection

After the onset of respiratory viral infection, there is a high degree of inflammation followed by infiltration of monocytes into the lungs (Li et al. 2022). These recruited monocytes eventually fill the void created by the deficiency of tissue-resident macrophages at the site of infection (Li et al. 2022). These recruited Ly6C^{+} monocytes can then differentiate into macrophages, which further orchestrate local inflammation (McQuattie-Pimentel et al. 2018; Li et al. 2022). In the case of IAV infection, type I (IFNα/β) and type II (IFN-γ) IFNs appear to regulate the recruitment of monocytes and promote an inflammatory phenotype in monocytes (Schmit et al. 2022). Accumulation of pulmonary CCR2^{+} inflammatory monocytes and monocyte-derived macrophages is a hallmark of severe respiratory viral infection, including influenza and severe COVID-19 (Alon et al. 2021) (Wei et al. 2023). Recruited monocytes can be stimulated by a variety of viral or host factors, including IFNs, to drive excessive pulmonary inflammation and tissue injury. Interestingly, it was shown that SARS-CoV-2-infected epithelial cells cocultured with monocytes have a more robust and distinct inflammatory response than those infected with IAV (Leon et al. 2022). Cytokines and chemokines such as TNF, IL1B, CCL3, IL10 and IFN-responsive genes were specifically enriched in SARS-CoV-2 compared to IAV coculture infection (Leon et al. 2022). Similarly, SARS-CoV-2 infection in monocytes can also trigger more elevated profibrotic signatures in monocytes than in IAV-infected monocytes (Wendisch et al. 2021). Monocytes in COVID-19 undergo pyroptosis due to NLR family pyrin domain containing 3 (NLRP3), absent in melanoma 2 (AIM2), caspase-1, and gasdermin D activation. These pyroptotic events occur because of the direct infection of monocytes, which is quite intriguing, as monocytes do not express ACE2 receptors. It was further demonstrated that monocytes express Fcγ receptors that recognize antibody-opsonized SARS-CoV-2, which promotes monocyte infection (Junqueira et al. 2022).

As inflammation resolves, these macrophages are rapidly depleted from the air spaces, mediated by apoptosis (Janssen et al. 2011), and tissue-resident AMs again repopulate the lung (Li et al. 2022), most likely by virtue of their self-renewal property and/or newly derived macrophages from monocytes. Monocyte-derived AMs represent a major AM population after 3 weeks postinfluenza infection but not early during infection (within 2 weeks), likely due to the time needed for monocyte maturation into AMs (Li et al. 2022; Zhu et al. 2021). Few of the monocyte-derived macrophages that survive weeks after disease resolution coexist within these AM populations and eventually acquire a bona fide AM-like phenotype (Gibbings et al. 2015; Li et al. 2022). This feature of adopting an AM-like phenotype after disease resolution is also shared by IMs, and hence, it is anticipated that IMs and recruited monocyte-derived macrophages are highly plastic in nature. Furthermore, the lung microenvironment also plays a decisive role in guiding the terminal differentiation of these macrophages into resident AMs (Bain and MacDonald 2022).

Interestingly, recruited monocyte-derived macrophages may contribute to the development of chronic

lung pathology and tissue fibrosis after viral pneumonia, including influenza and SARS-CoV-2 (Misharin et al. 2017; Cui et al. 2023; Narasimhan et al. 2022; Huang et al. 2019a). A recent study has shown that IL-6 and CD47 expressed by monocyte-derived macrophages are key factors that lead to sustained inflammation and fibrosis progression in long COVID (Cui et al. 2023). Taken together, these studies suggest that monocyte-derived macrophages play a major role in initiating and sustaining inflammation together with the adoption of profibrotic features in respiratory viral infections. Targeting these inflammatory/profibrotic programs may be helpful in the management of the severity of acute or chronic viral infection.

Conclusion

In respiratory viral diseases, resident AMs, IMs, or recruited monocytes and macrophages were suggested to have a pro-host or pro-viral response depending on their origin, phenotypes, timing, and type of infection being evaluated (Arish et al. 2023; Wei et al. 2023). However, it is broadly considered that resident AMs and IMs are mostly beneficial (Pernet et al. 2023), while recruited monocytes and macrophages are mainly detrimental to the host (Li et al. 2022; Wu et al. 2022). These contrasting characteristics in almost the same immune cell type in a similar anatomical niche are considered to be due to the imprinting of regulatory genes because of the different ontogeny of these immune cells (McCowan et al. 2021; Pernet et al. 2023). Therefore, it is necessary to identify those critical regulatory genes, transcription factors, or modulatory factors that can dictate the function of these macrophage subsets in diseased conditions (Arish and Naz 2022). Identifying these factors may be helpful to provide important insights into pulmonary macrophage biology in homeostasis or disease but also pave the way for macrophage-targeted therapies, in which macrophages could be re-educated to acquire anti-pathogen, immunomodulatory or tissue-reparative characteristics for viral resolution.

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Authors' contributions
JS conceptualized the idea. MA and JS wrote the manuscript. All authors read and approved the final manuscript.

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