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Review

Journey of monocytes and macrophages upon influenza A virus infection☆

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Influenza A virus (IAV) infections pose a global health challenge that necessitates a comprehensive understanding of the host immune response to devise effective therapeutic interventions. As monocytes and macrophages play crucial roles in host defence, inflammation, and repair, this review explores the intricate journey of these cells during and after IAV infection. First, we highlight the dynamics and functions of lung-resident macrophage populations post-IAV. Second, we review the current knowledge of recruited monocytes and monocyte-derived cells, emphasising their roles in viral clearance, inflammation, immunomodulation, and tissue repair. Third, we shed light on the consequences of IAV-induced macrophage alterations on long-term lung immunity. We conclude by underscoring current knowledge gaps and exciting prospects for future research in unravelling the complexities of macrophage responses to respiratory viral infections.

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Introduction

Influenza viruses are enveloped, single-stranded, negative-sense RNA viruses belonging to the *Orthomyxoviridae* family. Infections with influenza A viruses (IAV), classified based on hemagglutinin (HA) and neuraminidase glycoproteins, represent a significant global health issue with an annual estimate of 1 billion cases and 250–500 000 deaths worldwide [1].

IAV infections pose a formidable challenge to the host, which needs to mount effective defence and repair responses while avoiding excessive lung inflammation and damage associated with severe hypoxemia and acute respiratory distress syndrome (ARDS) [2–5]. Indeed, in order to allow efficient gas diffusion and support life, the airways must be permeable, and the air–blood barrier must remain very thin. Hence, the lung immune system has evolved as a sophisticated surveillance and defence system to sustain physiological functions and host protection. Dedicated to these tasks, distinct populations of monocytes and resident tissue macrophages (ResMacs) populate the steady-state lung (Box 1). Upon IAV infection, additional monocytes and monocyte-derived Macs (Mo-Macs) are recruited and undergo a dynamic response postinfection, which unfolds with remarkable complexity [6,7]. In this article, we aim to review the journey of monocytes and macrophages during and after IAV infection, thus unravelling the intricacies of their roles in viral clearance, inflammation, tissue repair, immunomodulation, and tissue imprinting (Figure 1).

Influenza A virus–triggered perturbations and functions of resident homeostatic alveolar macrophages

Alveolar macrophages (AMs) are strategically located in the alveolar lumen to be the first responders to IAV (Box 1), and investigations about resident AMs in IAV infections consistently pointed towards beneficial, protective roles, as reviewed in detail elsewhere [8,9]. Human and mouse AMs are permissive to IAV, and AMs can uptake viruses by direct infection or by phagocytosis of infected apoptotic cells [10]. Viral replication in AMs is limited by their production of type I interferons (IFNs) [11,12], which can also orchestrate recruitment of other immune cells [13] (Figure 1a, b).

Of note, AM infection rate is highly variable, with higher infectivity by highly pathogenic strains and rather unproductive infections by moderate viral strains, which is

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Box 1 The homeostatic landscape of monocytes and macrophages in the lung.

In mice, CCR2^{-}CX3CR1^{hi}Ly6C^{-} 'patrolling' monocytes depend on the transcription factor Nr4a1 and constantly clear the luminal side of capillary endothelial cells from cell debris [88,89]. A small proportion of Ly6C^{-} monocytes also resides in the lung parenchyma and may act as precursor of Mo-DCs or IMs [36,90]. In addition, small numbers of CCR2^{hi}CX3CR1^{lo}Ly6C^{+} classical monocytes are found in the parenchyma at steady state, have the ability to sample and transport antigens to the lymph nodes [91,92] and may also act as precursors of IMs [37,44]. Similar monocyte subsets are found in humans [90].

AMs are self-maintaining ResMacs that reside in the lumen of the alveoli. Their strategic positioning 'outside' the host arguably place them as early responders to lung insults. AMs are characterised by elevated expression of CD11c and Siglec-F in mice. Their development and maintenance require type 2 alveolar epithelial cell–derived GM-CSF and AM-intrinsic transforming growth factor-β, both instructive signals triggering sustained expression of peroxisome proliferator-activated receptor gamma (PPAR-γ) and imprinting a functional specification that allows efficient recycling of excess surfactant and cell debris [7,93–96]. While AMs arise almost completely from embryonically derived fetal monocytes in young adult mice [96], they are progressively replaced by bone marrow–derived cells as mice age [24,32].

Lung IMs populate the parenchyma and are less represented and less accessible than AMs. In adult mice, CD11b^{+}CD64^{+}CD88^{+}Siglec-F^{-} IMs are slowly replenished by classical monocytes [36,37,43,44], require MafB for their development [44] and encompass distinct subsets based on their origin, phenotype and localisation [35,36,43,97–99]. On the one hand, CD11c^{lo}Lyve1^{hi}CD206^{+} IMs represent a major source of the immunoregulatory cytokine IL-10 and preferentially associate with blood vessels and the bronchi, consistent with blood vessel–supportive and immunosuppressive functions [36,37,43,97]. On the other hand, CD11c$^{int/hi}$Lyve1^{lo}CD206^{-} IMs express high levels of MHC-II, can present soluble antigens to T cells and are located in the vicinity of nerve bundles [36,43,97,98,100]. Based on phenotypic similarities, CD206^{-} IMs might partially overlap with CD169^{+} NAM [35] and antigen-presenting CD11c^{+}Cx3cr1^{hi}MHC-II^{hi} bronchus-associated Macs [98].

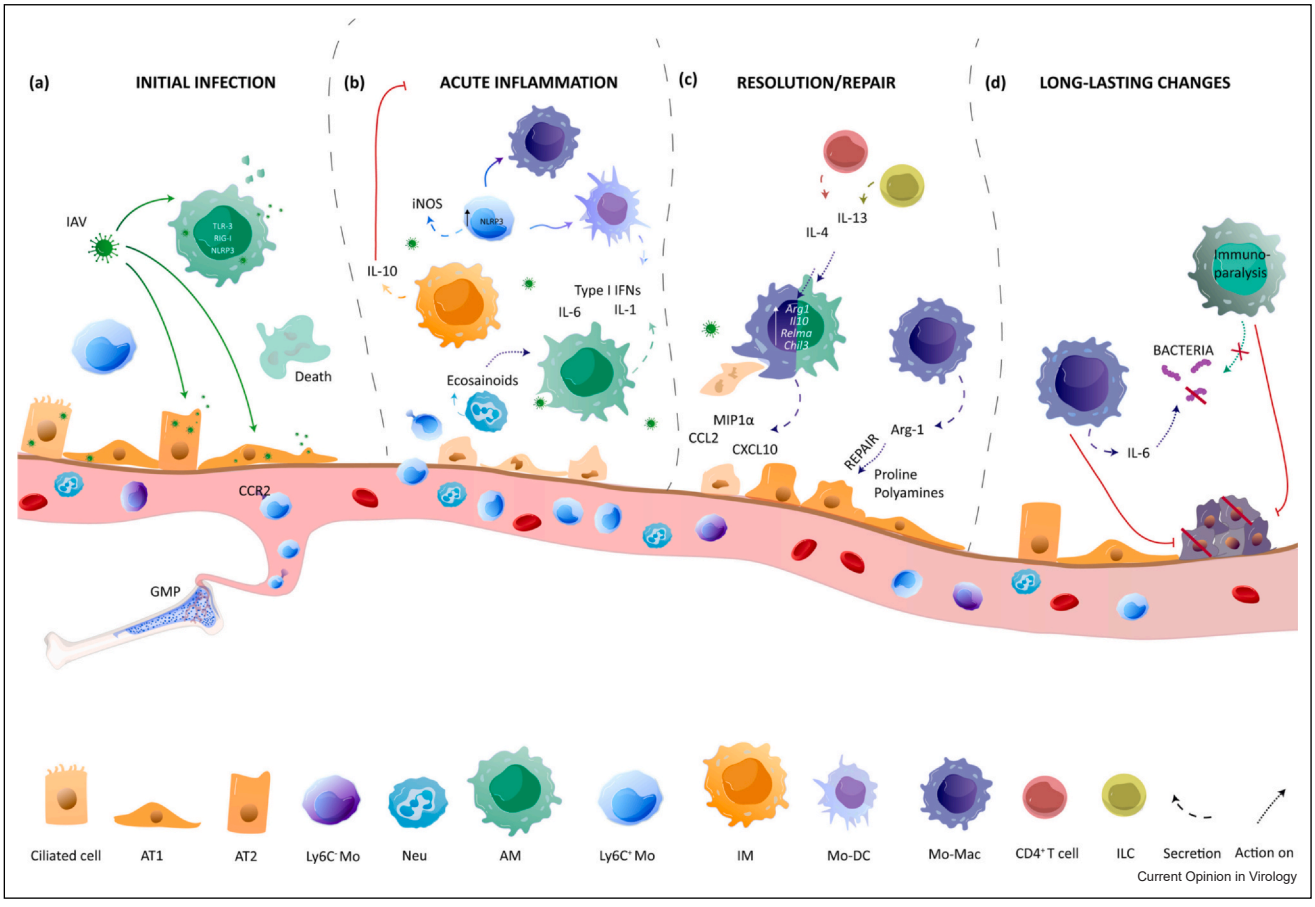
thought to contribute to limit viral spread [14–17]. Human AMs are less permissive and responsive to IAVs than Mo-Macs [14], which also produce larger amounts of tumour necrosis factor α [14,15], C-C motif chemokine ligand 5 (CCL5) and C-X-C motif chemokine ligand 10 (CXCL10) compared with AMs [15]. A recent report suggests that the inhibitory effects of AMs on viral replication could also be mediated by extracellular vesicles acting on epithelial cells [18].

Seminal reports showed that wild-type mice injected with supraphysiological doses of granulocyte–monocyte colony–stimulating factor (GM-CSF) [19] or mutant mice overexpressing GM-CSF in the lung [20] were protected from IAV infection. This protective effect was associated with improved lung functions, decreased protein exudates in the bronchoalveolar lavage (BAL), a better clinical recovery and a repolarisation of AMs from a M1-like to a M2-like phenotype [19–21]. Furthermore, the protective effects of GM-CSF were abrogated by airway administration of clodronate liposomes [20], suggesting a role for AMs in GM-CSF-mediated protection against IAV. Further supporting their beneficial roles, Schneider et al. showed that neonatal adoptive transfers of AM progenitors in *Csf2rb*$^{-/-}$ mice, lacking GM-CSF receptor, prevented severe disease post-IAV, while depletion of AM by clodronate liposomes in wild type mice before IAV infection exacerbated morbidity and mortality [11]. Recently, a study showed that an appropriate imprinting of AMs by their niche could contribute to host protection against IAV pathology. Indeed, the authors showed that *Alox15*$^{-/-}$ AMs, deficient in 12- and 15-lipoxygenase, were not properly instructed during the neonatal period by neutrophil-derived eicosanoids (Figure 1b) and were thus no longer able to control IAV replication later in life, which was associated with increased levels of C-C motif chemokine ligand 2 (CCL2), accumulation of monocytes and increased mortality of IAV-infected mice [22].

Mouse AMs have been reported to be depleted post-IAV [23,24]. The mechanisms driving AM depletion have been shown to be dependent on IFN-γ in BALB/c mice [23] and may involve AM apoptosis subsequent to a robust antiviral response [25], inhibition of AM self-renewal capacity by IAV-induced Wnt ligands [26] or modifications of the AM niche triggered by IAV infection of epithelial cells [5]. The extent of AM depletion is thought to be dependent on the host genetic background [23,24]. Indeed, employing a sublethal infection model with the H1N1 PR8 strain, Califano et al. reported a massive loss of AMs 7 and 9 days post-IAV in BALB/c mice, but not C57BL/6NCrl mice [23], while Li et al. recently showed that such infection also induced a rapid loss of resident AMs in C57BL/6J mice [24]. We also consistently observe AM depletion in PR8-infected C57BL/6J mice raised in our animal facilities (unpublished observations). The reasons for these discrepancies remain currently unclear and likely evolve a combination of genetic and environmental factors. In their study, Li et al. further showed that the AM pool was quickly replenished by Siglec-F^{hi} 'survivor' AMs (5–10% of original AMs) between day 4 and 15 post-IAV in mice [24]. After viral clearance, AMs were gradually replaced by proinflammatory monocyte-derived Siglec-F^{lo} Mo-Macs that would eventually outcompete embryonically derived AMs on a long-term basis [24,27]. Eventually, the alveolar niche can return to a homeostatic, noninflammatory state, and repopulated AMs can become similar to the native ones [7,28,29] (Figure 1d).

Ageing can affect AM microenvironment, ontogeny and functions, which might account for the enhanced mortality and morbidity post-IAV in the elderly [24,30–32]. The ageing microenvironment can confer resistance of AMs to GM-CSF responsiveness [33], which correlates with decreased AM numbers and proliferative abilities

Figure 1



Monocytes and macrophages after IAV infection. **(a)** IAV-derived HA proteins can bind to sialylated glycan receptors on lung epithelial cells from the airways and the alveoli. AMs are equipped with the viral RNA sensing machinery and are permissive to IAV, which results in an unproductive infection and a self-limiting disease and can lead to AM death. **(b)** IAV infection can trigger AM activation and production of cytokines, chemokines and type I IFNs, thereby controlling viral spread and coordinating the recruitment of additional immune cells. A proper AM imprinting by neutrophil-derived eicosanoids is essential for AM protective functions post-IAV. The role of IMs in the antiviral response is less clear, with IM-derived IL-10 playing a beneficial role in the downregulation of inflammation. Lung-recruited Ly6C$^+$ Mos can activate the NLRP3 pathway and produce elevated amount of iNOS, which can contribute to the acute inflammatory response and, sometimes, to undesirable tissue damage. Ly6C$^+$ Mos can differentiate into type I IFN–producing Mo-DCs or into proinflammatory Mo-Macs participating to efficient viral clearance. **(c)** Infected cells can release 'find me' signals and cytokines attracting Mo-Macs and inducing their engulfment. Efferocytosis limits viral spread and induces a reprogramming in efferocytic Mo-Macs toward a proresolving phenotype associated with upregulation of anti-inflammatory genes, such as *Arg1, Il10, Relma and Chil3*. Furthermore, during the resolution phase, T cells and ILC2s can produce type 2 cytokines (IL-4 and IL-13) triggering the production of Arginase-1 by Mo-Macs. Arg-1 metabolism results in production of polyamines et proline enhancing cell growth and collagen production and thereby contributing to tissue repair. **(d)** IAV infection leads to long-term consequences for lung immunity. Niche signals produced post-IAV infection induce an immunoparalysis in resident AMs, which exhibit impaired bacterial phagocytosis, thus enhancing the susceptibility to secondary bacterial infection. Mo-Macs replenishing the alveolar niche post-IAV maintain a proinflammatory phenotype conferring efficient IL-6-dependent protection against bacterial infection but leading to exacerbated lethal response in recurrent viral infection. IAV-instructed Macs can also contribute to protection against tumours by maintaining their phagocytic and cytotoxic potential despite tumour-induced immunosuppression. AT1/2, type 1/2 alveolar epithelial cell; Mo, monocyte; Neu, neutrophil.

[30]. Aged AMs have also been shown to be impaired in their ability to phagocyte neutrophils compared to young AMs, and high neutrophil counts might account for excessive tissue damage [30]. Finally, embryonically derived AMs are gradually replaced by bone marrow–derived AMs in aged mice, which can intrinsically contribute to disease severity post-IAV [24].

Enigmatic fate and function of resident interstitial macrophages post-influenza A virus

Lung interstitial macrophages (IMs) have been less studies than AMs (Box 1). To date, most of the studies aiming at addressing the contributions of IMs to disease physiopathology, including IAV-triggered pathology, have faced

two main challenges [34]. First, Mo-Macs recruited when homeostasis is broken often exhibit a phenotype that can largely overlap the one of IMs. Hence, while it is repeatedly reported that IMs 'expand' upon exposure to insults or pathogen-associated molecular patterns [35–42], the IM compartment arguably contains a mix of resident IMs and Mo-Macs, and the respective contributions of IMs versus Mo-Macs to disease physiopathology remain often unclear. Second, transgenic tools allowing a specific and efficient tracking or depletion of resident IMs while sparing AMs and Mo-Macs are difficult to obtain. To date, at least three models of diphtheria toxin (DT)–induced bolus IM depletion exist, namely, *Lyve1*$^{Cre/GFP}$ *Slco2b1*$^{LSL\text{-}DTR}$ [43], *Cd169*^{Cre} *Cx3cr1*$^{LSL\text{-}DTR}$ (NAM-DTR) [35] and *Tmem119*^{Cre} *Cx3cr1*$^{LSL\text{-}DTR}$ (IM^{DTR}) [44] mice. However, IM depletion is transient and rapidly followed by the recruitment of monocytes that refill the empty niche, and it remains to be determined whether DT treatment also targets Mo-Macs when such transgenic mice are subjected to disease models.

In the context of IAV infection, Ural et al. depleted nerve-associated IMs (NAMs) before IAV infection with the H1N1 PR8 strain in C57BL/6 NAM-DTR mice and found that depleted mice displayed increased morbidity at day 12 post-IAV compared with controls, even though the viral loads were unchanged [35]. As NAMs were the main producers of interleukin (IL)-10, the authors proposed that NAMs can downregulate IAV-triggered inflammatory responses. These data highlight potential beneficial, immunoregulatory functions of IMs after IAV, as shown in other contexts [37,43,45,46] (Figure 1b). Future investigations comparing different viral strains (e.g. H1N1, H3N2) and mouse strains (e.g. BALB/c, C57BL/6) and employing complementary models of IM-specific targeting along with additional cellular and molecular read-outs of inflammatory and repair responses will help deciphering their roles post-IAV. Along the same line, a model in which resident IMs could be tracked and discriminated from Mo-Macs post-IAV would open many opportunities for more comprehensive molecular, spatial and functional investigations.

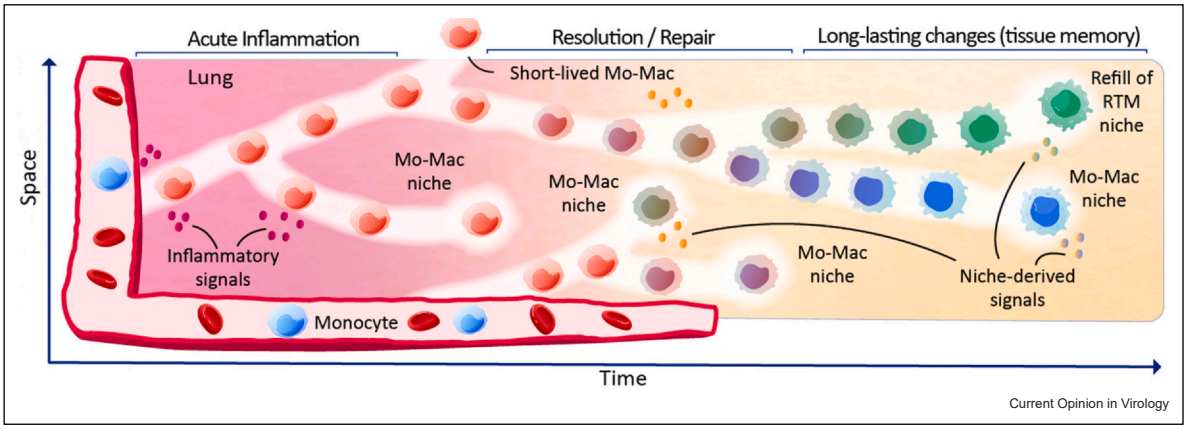
Monocytes and monocyte-derived Macs trajectories and functions post-influenza A virus

Monocytes are, along with neutrophils, the first innate cells recruited to the infected lung. Type I IFNs produced early post-IAV can trigger an emergency monopoiesis in the bone marrow, associated with the proliferation of granulocyte—monocyte progenitors, their upregulation of the M-CSF receptor and the egress of Ly6C$^+$ monocytes exhibiting increased expression of stem cell antigen-1 at the expense of dendritic cell differentiation [47–49]. Type I IFN signalling also promotes the differentiation and lung recruitment of CCL2-producing Ly6C$^+$ monocytes, which further facilitates the influx of CCR2$^+$Ly6C$^+$ monocytes into the lung [24,50,51] (Figure 1b). Type II IFNs have also been shown to regulate inflammatory monocyte recruitment post-IAV [52]. Along with AMs, recruited monocytes orchestrate the acute inflammatory response in part via the activation of nucleotide oligomerization domain (NOD)-like receptor family pyrin domain–containing 3 (NLRP3) inflammasome [53]. In lethal models of IAV infection, early NLRP3 inflammasome activity is thought to be protective [54], while an excess of activation may worsen lung damage and increase mortality [55]. Several reports support that the global outcome of CCR2$^+$ monocyte accumulation is detrimental and associated with increased morbidity and mortality [4,24,56,57]. Deleterious effects of CCR2$^+$ monocytes may be related to an elevated production of induced nitric oxide synthase (iNOS), which, unlike for other pathogens, does not display antiviral activity against IAV but rather inhibits an effective adaptive immune response [58].

Upon recruitment, a portion of monocytes can differentiate into monocyte-derived dendritic cells (Mo-DCs), peaking in the lung at days 7–10 post-IAV [57]. Type I IFN–producing Mo-DCs have been shown to contribute to the antiviral response [59] (Figure 1b) and ensure appropriate virus-specific CD8$^+$ T cell memory responses [60]. Recruited monocytes can also develop into Mo-Macs that are either short lived or can establish in particular niches with functional consequences for lung immunity [7,8,27,28,61]. While Mo-Macs have long been considered as detrimental and pathogenic cells after IAV infection [24,57], their functional specification is arguably much more complex than previously thought.

During the acute inflammatory phase, IFN-γ-induced Mo-Macs with a proinflammatory profile are thought to contribute to efficient viral clearance. They are progressively replaced by proresolving Mo-Macs, thereby facilitating tissue healing [25,62,63] (Figure 1c). The phagocytosis of dying cells, called efferocytosis, is an integral part of the resolution of inflammation [64]. Before cell death, infected cells can release 'find me' signals and cytokines such as macrophage inflammatory protein-1α, CCL2, CXCL10, able to direct Mo-Macs towards apoptotic cells for engulfment [25,63]. This process contributes to limit the progression of IAV infection in mice by clearing infected cells and promoting a proresolving phenotype in efferocytic Mo-Macs [65–67]. Degradation of engulfed cells induces a substantial metabolic shift from proinflammatory glycolytic pathways towards oxidative phosphorylation pathways associated with anti-inflammatory functions [64,68,69] (Figure 1c). After H1N1 infection in mice, genes related to anti-inflammatory functions, such as *Arg1*, *Il10*, *Relma* and *Chil3*, are upregulated in macrophages as soon as 7 days post-IAV [70]. Of note, the resolution phase post-IAV is characterised by a local type 2 profile, including elevated levels of IL-13$^+$ type 2 helper T cells, innate lymphoid type 2 (ILC2s) cells, IL-4 and IL-13 [70,71], which participate to macrophage reprogramming towards a wound-healing phenotype [72,73]. The receptor for IL-4 and IL-13 (IL4R) starts to be expressed on

Figure 2



Updated view on the determinants of Mo-Mac identities and functions after lung injury. Upon IAV infection or exposure to other pathogens or insults, the diversity of lung macrophages increases as monocytes are recruited and differentiate into Mo-Macs that join the pool of macrophages. As opposed to ResMacs, Mo-Macs are highly plastic and exhibit a higher potential for imprinting by inflammation and by tissue cues. Hence, they can adopt distinct identities that are regulated spatiotemporally and can also refill homeostatic ResMac niches if space is available and homeostatic cues are present. The origin, the differentiation trajectories, the stress-derived and microanatomical niche-derived cues they encounter, the time spent in the tissue and their localisation are increasingly thought to be essential determinants of Mo-Mac identities and functions.

proinflammatory Mo-Macs [74] and its activation triggers expression of Arginase-1, an enzyme competing with IFN-γ-induced iNos for the common substrate L-Arginine [75]. The Arg-1 product L-ornithine can be further converted into polyamines and proline that can contribute to tissue repair via enhancement of efferocytosis, regulation of cell growth and collagen production [76–78]. GM-CSF, overexpressed by infected alveolar epithelial cells, is also involved in macrophage reprogramming from a proinflammatory to a proresolving state [19,79] and has been shown to confer protection against lethal IAV infection in mice [20,21]. Whether GM-CSF acts on homeostatic AMs, Mo-Macs, or both, would require further investigations.

Consequences of influenza A virus–shaped macrophages for lung immunity

The shaping of the alveolar niche by respiratory infections and the long-term consequences for lung immunity have been reviewed recently [8]. We will focus here on studies supporting the idea that IAV-induced changes in macrophages are associated with short- and long-term modifications in the ability of the host to respond to subsequent insults and stimuli (Figure 1d). IAV-triggered AM depletion can increase susceptibility to secondary bacterial pneumonia [80]. Moreover, IFN-γ produced by T cells after IAV infection can impair AM antibacterial properties and increase the risk of secondary bacterial infections [81,82]. Such impaired capacity of resident AMs to capture bacteria has been shown to last for months and to rely on signal regulatory protein alpha (SIRPα)-dependent immunosuppressive signals released in the local environment, leading to immunoparalysis after IAV infection [83]. Influenza-trained AMs have recently been proposed to confer antitumour immunity [84]. Indeed, in a model of B16 melanoma, IAV-trained AM could maintain their phagocytic and cytotoxic potential despite tumour-induced immunosuppression, thereby enabling enhanced antitumour function [84]. However, concerns have been raised as to whether these effects might rather be mediated by recruited Mo-Macs resembling AMs [85]. Mo-Macs replenishing the alveolar spaces post-IAV have been shown to exhibit a more proinflammatory phenotype associated with higher glycolytic activity [24] and IL-6 production [27] compared with AMs, which can confer protection against secondary bacterial infection 1 month post-IAV [27] but can also be responsible for increased mortality in recurrent viral infection [24].

Conclusions and future directions

Substantial progress has been made to understand the roles of monocytes and macrophages during and after IAV infection. Yet, recruitment of monocytes and Mo-Macs induces a highly dynamic and complex response in the lung, and such cells can no longer be considered as a single entity based on their origin. Indeed, they are thought to be highly plastic, and as they navigate through the infected lung and interact with other immune cells, structural cells and extracellular matrix components, they undergo a spectrum of activation states and phenotypic changes and can adopt distinct functional identities that depend on their differentiation trajectory, the diseased tissue microenvironment and the extent and phase of inflammation [6,7,28,29] (Figure 2). Therefore, we believe that resolving IAV-triggered macrophage adaptations and the complexity of the macrophage compartment after IAV, including the

investigation of the stress-related and tissue-instructive signals integrated by Mo-Macs and of the intrinsic molecular programmes that mediate distinct spatiotemporal trajectories and functions, is still in its infancy and represents an exciting challenge for future research. Single-cell and spatial transcriptomic analyses arguably represent the first important step in such investigations [86,87], which will be critical to fully understand myeloid cell contributions to IAV-triggered immunopathology, to understand why they become dysregulated in the elderly or in severe and chronic diseases, and to ultimately be able to manipulate their fate and functions for medically relevant conditions such as severe respiratory viral infections and ARDS. To succeed, it will be important to undertake a systems biology approach in order to connect single-cell gene expression and regulation within structural and immune cells to cell identity, functions, cell–cell interactions, and ultimately disease physiopathology.

Accordingly, efforts should be made to employ clinically relevant human samples and preclinical models that better reflect the human disease, along with top-notch multi-omic and spatial technologies that are currently revolutionising research in life sciences.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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