Alveolar Macrophages in Resolution of Inflammation

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Abstract

Alveolar macrophages (AM) obtained by bronchoalveolar lavage (BAL) are widely used to study pulmonary macrophage-mediated immune responses. However, questions remain as to whether AM fully represents macrophage function in the lung. This study was performed to determine the contribution of lung tissue interstitial macrophages (IMs) to lung immunity that is absent in BAL sampling. In vivo BrdU injection was performed to assess kinetics and monocyte/tissue-macrophage turnover in Indian rhesus monkeys (Macaca mulatta). Pulmonary macrophage phenotypes and cell turnover were analyzed by fow cytometry and immunohistochemistry. Rhesus monkey lung AM and IM constituted approximately 70% of the immune response cells in the lung. AM represented the majority of macrophages (approximately 75-80%) and showed minimal turnover. Conversely, IMs exhibited a high turnover rate similar to blood monocytes during steady-state homeostasis. IMs also showed strong staining for TdT-mediated dUTP nick end labeling (TUNEL), indicating continued migration of blood monocytes displacing IMs undergoing apoptosis. Although AM appears static at steady-state homeostasis, an increased infux of new AM from monocytes/IMs was observed following the BAL procedure. Furthermore, treatment with ex vivo IFN-γ and LPS increased intracellular expression of TNF-α in IM, but not in AM. These results suggest that long-lived AMs obtained from BAL may not represent the full pulmonary spectrum of macrophage responses, and that short-lived IMs may function as an important subset of pulmonary mucosal macrophages and regulate homeostasis suggest that it may help maintain and protect against continued exposure.

Keywords: Bronchoalveolar; Pulmonary; Immunity; Monocytes

Introduction

Macrophages are blood monocyte-derived scavenger cells that play an important role in innate immunity and steady-state homeostasis [1]. Pulmonary macrophages are highly heterogeneous due to their anatomical location, specialized functions, and activation state [2, 3]. At least three types of macrophages have been identi ed in the lung, including alveolar macrophages (AM), interstitial macrophages (IM), and intravascular/limbic vascular macrophages, which di er in location and function [4]. In general, AM is thought to act to clear particles and microorganisms within the alveoli, and IM is thought to act in regulating tissue brosis, in ammation, and antigen presentation [5]. Perivascular macrophages appear to function by crosstalk between antigen-presenting cells in the lung stroma and recruit neutrophils or myeloid cell. e existence of subsets of pulmonary macrophages with distinct functional properties requires additional analyzes to better understand their contribution to lung disease pathogenesis.

Macrophages were recognized more than a century before Elie Metchniko rst described phagocytosis and de ned the role of these cells in in ammation in the 1880s, but monocyte/macrophage heterogeneity Questions remain about [6]. is is because macrophage classi cation is largely based on in vitro experiments and does not address the e ects of the tissue microenvironment in which monocytes/macrophages live. For example, alveolar macrophages are unable to develop resistance to endotoxin (LPS) at concentrations induced by mononuclear phagocytes or macrophages in other tissue compartments such as the peritoneal cavity, bone marrow, and spleen. is di erence is likely due to the rich GM-CSF microenvironment in the lung [7]. Moreover, species-speci c responses appear to reside in the expression of functional genes and homologous proteins, as well as unique markers of macrophage populations located in di erent tissues and hosts that contribute to the variability of the macrophage classi cation scheme.

Allergens such as house dust mites can cause apoptotic epithelial cell death and trigger the synthesis of IL-4 and IL-13 from mast cells and innate lymphoid type 2 cells (ILC2) [8, 9]. ese events lead to the production of insulin-like growth factor 1 from Aφ, which facilitates the uptake of macrophage-derived anti-in ammatory microvesicles by

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antigen-speci c CD4 T cells to generate Foxp3+ Treg cells. Both TGF-β and retinoic acid were required for Treg cell induction. us, migration of antigen-pulsed tissue macrophages into the airways prevented the development of asthmatic pneumonitis a er subsequent provocation with ovalbumin. However, other allergens such as Dermatophagoides pteronyssinus, Aspergillus fumigatus, or extracts from cat dander did not induce he Tregs due to signaling through proteases and her TLRs. Macrophages can also induce Tregs through an indirect pathway. Indeed, interleukin-6, a soluble mediator commonly associated with in ammation and elevated in people with severe respiratory infections, is important in promoting resolution of the host response to respiratory viral infections and limiting disease. Early but not late IL-6 signaling is required for resolution of immunopathology induced by respiratory syncytial virus.

Once in ammation is under control, tissue repair must occur to restore normal tissue architecture. In the lung, epithelial cells are the main cells damaged by infection and in ammation [15]. As long as the injury persists, the pro-in ammatory signals continue, further damaging the epithelium. Repair processes can therefore be considered an integral part of the resolution of in ammation.

e environment created by tissue damage control may favor pathogen persistence in the respiratory tract. Indeed, the immunosuppressive properties of Aφ in the process of tissue damage control are thought to be key leading to immune evasion. Bypassing immune surveillance is a key parameter leading to pathogen persistence. ese bacteria persist in the lower respiratory tract by surviving within Aφ. In vitro studies revealed that S. aureus persists and replicates within the mouse Aφ cell line [16]. We have previously stated that among the mediators used by Aφ to control tissue damage, PGE2 is produced a er e erocytosis and exerts anti-in ammatory e ects. PGE2 is known to suppress natural killer cell activity by increasing cellular cyclic adenosine monophosphate and downregulating MHC class II expression in dendritic cells, reducing antigen presentation. increase. Recently, it has been shown that the anti-in ammatory e ects of PGE2 in the lung are mediated exclusively through prostaglandin E receptor 4 (EP4). us, pathogens appear to be able to utilize PGE2 [17, 18]. In fact, PGE2 can block Aφ-induced bacterial killing by inhibiting her NADPH oxidase. In M. tuberculosis-infected macrophages, her PGE2 generated by TLR2 stimulation/p38 MAPK phosphorylation triggers her EP4 to increase PGE2 levels [19]. PGE2 then provides protection against necrosis via EP2. Host production of PGE2 is a protective mechanism against Mycobacterium tuberculosis by inhibiting IFN type I in macrophages and inducing apoptosis. Similarly, in uenza virus induces PGE2 to suppress type I IFNs, thereby weakening innate immunity [20]. Taken together, the pathogen appears to have evolved mechanisms that induce her PGE2 production by macrophages to suppress in ammation and better survive within the host. A recent studies show that dendritic cells and macrophages that develop in the lung a er resolution of severe infection acquire tolerogenicity that contributes to persistent immunosuppression and susceptibility to secondary infections.

Conclusion

Taken together, these studies suggest that Aφ is involved in (i) limiting lung tissue damage from potentially harmless stimuli, (ii) reducing immune surveillance, and (iii) harboring pathogens, thereby It has been shown to play a central role in pulmonary disease resistance. Pathogen persistence in the respiratory tract is a major concern, especially for diseases such as tuberculosis. In fact, the balance between eliminating pathogens and maintaining tissue integrity is the sword of Damocles for susceptible patients. , can o er treatment options. An important area that needs further investigation is to distinguish between the role of resident and recruited macrophages in the lung environment. It is of great interest how recruited macrophages interfere with various functions of resident Aφ to maintain lung homeostasis.

References

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