Review

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*Series: Tissue-resident immune cells*

# Alveolar macrophages and type I IFN in airway homeostasis and immunity

**Maziar Divangahi[1,2], Irah L. King[2], and Erwan Pernet[1]**

[1] Department of Medicine, Department of Pathology, McGill International TB Centre, McGill University Health Centre, Meakins-Christie Laboratories, Montreal, QC, Canada
[2] Department of Microbiology and Immunology, Microbiome and Disease Tolerance Centre, McGill University, Montreal, QC, Canada

**Globally, respiratory infections cause more than 4 million deaths per year, with influenza and tuberculosis (TB) in particular being major causes of mortality and morbidity. Although immune cell activation is critical for killing respiratory pathogens, this response must be tightly regulated to effectively control and eliminate invading microorganisms while minimizing immunopathology and maintaining pulmonary function. The distinct microenvironment of the lung is constantly patrolled by alveolar macrophages (Mφ), which are essential for tissue homeostasis, early pathogen recognition, initiation of the local immune response, and resolution of inflammation. Here, we focus on recent advances that have provided insight into the relation between pulmonary Mφ, type I interferon (IFN) signaling, and the delicate balance between protective and pathological immune responses in the lung.**

## Alveolar Mφ and tissue homeostasis

Mφ are an ancient cellular compartment of innate immunity found in all tissues, where they have an essential role in tissue homeostasis and host defense. Alveolar Mφ (AMφ) occupy a unique environmental niche, taking up extracellular residence in the lung, where they directly contact the external atmosphere, sense the high partial pressure of oxygen, and bath in a surfactant-rich fluid, all essential components of respiratory gas exchange and pulmonary homeostasis. Being constantly and directly exposed to the environment, the pulmonary immune response must be tightly regulated to effectively recognize and eliminate invading microorganisms with minimal immunopathology to maintain optimal gas exchange. For this reason, the primary defense mechanisms of the lungs involve multiple mechanical components, including cilia, mucus production, and the cough reflex, all preventing the access of pathogens to the lower airways and avoiding a full-scale inflammatory response. In fact, the success of many respiratory pathogens is directly linked with their ability to reach the lower airways and activate AMφ.

During the steady state and in the absence of infection, alveolar Mφ exhibit a relatively quiescent state, produce low levels of cytokines, and suppress the induction of innate and adaptive immunity [1]. Nevertheless, AMφ retain high phagocytic activity to clear particulate antigens and short-lived epithelial cells from the airways. Given their unique microenvironment, it is not surprising that local environmental cues epigenetically modify gene transcription programs to confer functional specification on the AMφ population [2].

AMφ homeostasis is regulated in part by granulocyte macrophage-colony stimulating factor (GM-CSF) [3]. One of the best examples for a central role of alveolar Mφ in pulmonary homeostasis occurs in humans carrying mutations in the GM-CSF receptor or spontaneously developing autoantibodies against GM-CSF. These individuals develop pulmonary alveolar proteinosis (PAP), a condition associated with reduced number and function of AMφ, and are more prone to pulmonary infections [4,5]. A major area of current investigation involves understanding the source of AMφ during development and throughout life. Recent studies using genetic fate-mapping strategies demonstrate remarkable differences in the origin and maintenance of this cell type in the lung [6,7]. Studies by Ginhoux and others suggest that a pre-existing population of yolk sac-derived lung Mφ is markedly diluted following generation of monocyte-derived Mφ expanded from the fetal liver [8–10]. However, Schulz and colleagues provided evidence that yolk sac Mφ are the major source of tissue Mφ, including in adult lungs [7]. In addition to embryonically derived Mφ, adult bone marrow-derived monocytes can give rise to Mφ, but this may be limited to settings of inflammation or sites of chronic microbial exposure, such as the intestine [11,12] (Box 1). How these different progenitors contribute to the persistence of the AMφ compartment, and how developmental origin relates to effector function during acute and chronic infection are important areas of investigation.

Besides their important phagocytic function during homeostasis, Mφ are encoded with a variety of pattern recognition receptors (PRR), which are critical for sensing pathogens and tissue damage [13–16]. The extensive

*Corresponding author:* Divangahi, M. (maziar.divangahi@mcgill.ca).
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## Box 1. Macrophage origins

The appearance of single-cell microorganisms on Earth is dated to more than 3.5 billion years ago, ultimately leading to the development of multicellular organisms approximately 3 billion years later. The evolutionary burst of species diversity and 'struggle for existence' [79] generated a complex host system of defense, with the innate immune system first developing in single-celled eukaryotes, such as amoeba, followed by the appearance of adaptive immunity in cartilaginous fish and all jawed vertebrates [80]. The importance of innate immune mechanisms is reflected by their remarkable diversity at almost every level of the evolutionary tree of life. The first demonstration of innate immunity was during the late 19th century by Elie Metchnikoff. He introduced the term 'macrophage' (meaning 'large eater') after inserting a thorn into a translucent starfish larva and observing large cells engulfing the foreign body [81]. Although initially it was hypothesized that Mφ originated from the reticuloendothelial system (phagocytes and endothelial cells), emerging morphological and functional differences between these cells refute this hypothesis [82]. In fact, recent studies provide evidence that most tissue-resident Mφ are seeded before birth and have self-renewal capacity (Figure I) [8,83].

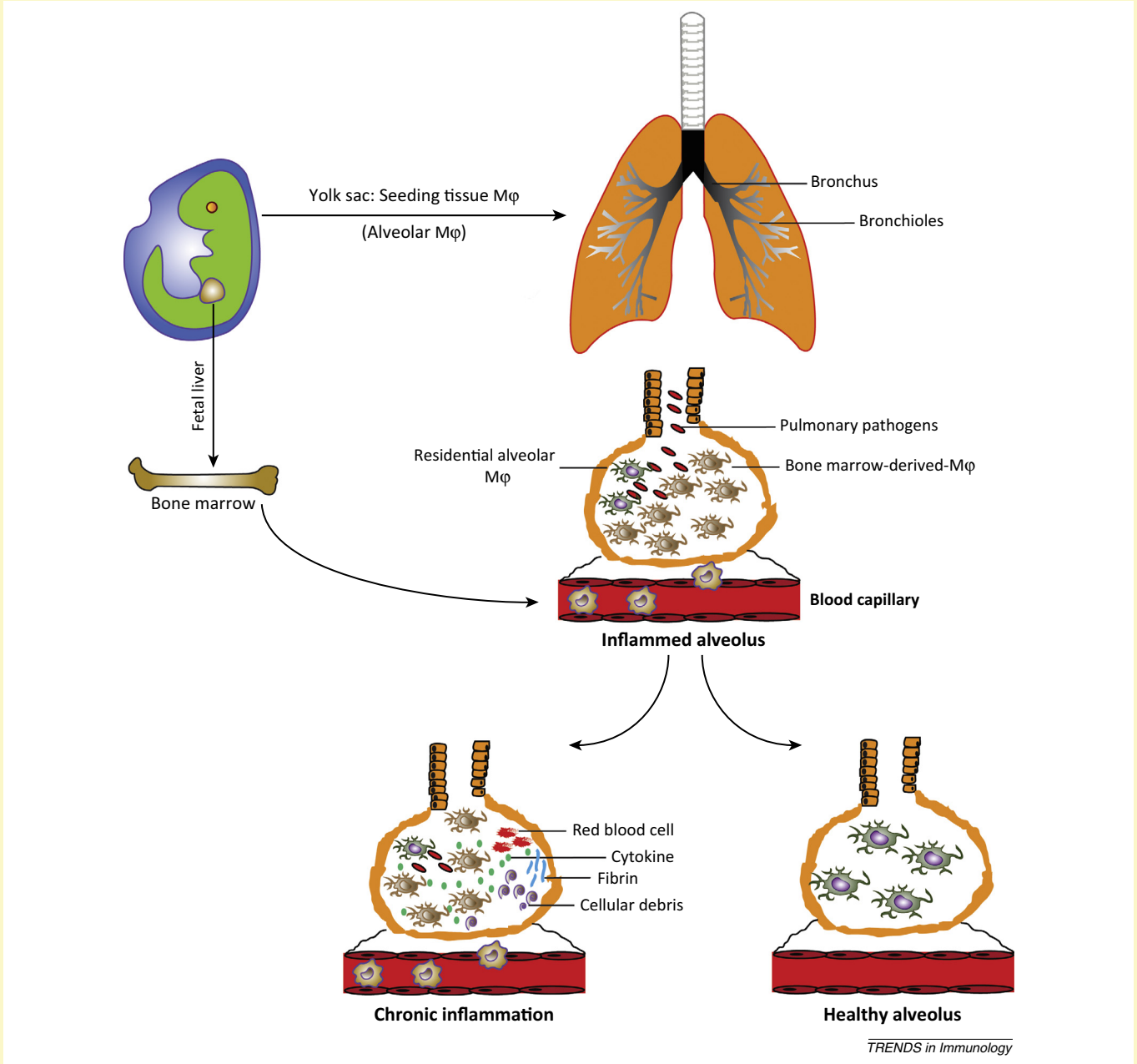


**Figure I**. Origin of tissue macrophages (Mφ) and their contribution to pulmonary infection. Specific fate-mapping studies indicate that pulmonary Mφ are derived from the yolk sac during early embryogenesis. However, during infection, bone marrow-derived monocytes recruited to the inflamed lung in a C-C chemokine receptor type 2 (CCR2)-dependent manner differentiate into inflammatory Mφ. As the infection is cleared, bone marrow-derived Mφ contract and lung-resident Mφ, which have self-renewal capacity, repopulate the airways and contribute to the resolution phase of inflammation. The exact contribution of bone marrow-derived Mφ to residential alveolar Mφ remains ill defined. The inability of bone marrow-derived Mφ to contract due to persistent infection or a cell-intrinsic defect can lead to immunopathology and lung dysfunction.