

Role of type II macrophages in the treatment of pulmonary inflammations

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Abstract

Introduction: Pneumonia is a common acute respiratory infection that affects the alveoli and distal airways; it is a major health problem and associated with high morbidity and short-term and long-term mortality in all age groups worldwide. Pneumonia is broadly divided into community-acquired pneumonia or hospital-acquired pneumonia. A large variety of microorganisms can cause pneumonia, including bacteria, respiratory viruses and fungi, and there are great geographical variations in their prevalence. Pneumonia occurs more commonly in susceptible individuals, including children of <5 years of age and older adults with prior chronic conditions. Development of the disease largely depends on the host immune response, with pathogen characteristics having a less prominent role. Individuals with pneumonia often present with respiratory and systemic symptoms, and diagnosis is based on both clinical presentation and radiological findings. It is crucial to identify the causative pathogens, as delayed and inadequate antimicrobial therapy can lead to poor outcomes. New antibiotic and non-antibiotic therapies, in addition to rapid and accurate diagnostic tests that can detect pathogens and antibiotic resistance will improve the management of pneumonia. Macrophages represent the first line of anti-pathogen defense. they encounter invading pathogens to perform the phagocytic activity, to deliver the plethora of pro- and anti-inflammatory cytokines, and to shape the tissue microenvironment. Throughout pneumonia course, alveolar macrophages and infiltrated blood monocytes produce increasing cytokine amounts, which activates the antiviral/antibacterial immunity but can also provoke the risk of the so-called cytokine “storm” and normal tissue damage. The aim of this study is to investigate the effect of macrophages on lung inflammation.

Keywords: macrophages, pulmonary inflammations, Pneumonia.

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Introduction

Pneumonia, a prevalent acute respiratory infection, impacts the alveoli and distal bronchial tree of the lung.¹ Pneumonia, the leading cause of mortality among young children in developing nations and elderly individuals in developed regions, is linked with various microorganisms. Recently, there has been a growing recognition of the significance of viruses as causative agents in pneumonia.² Macrophages, the predominant immune cell type found in healthy lungs, can be categorized into two primary populations: alveolar macrophages (AMs) and interstitial

macrophages (IMs). AMs are located within the distal lung alveoli and inter-alveolar septum, often in close proximity to pneumocytes. Serving as the primary resident innate immune cells in the lungs, AMs play a pivotal role in maintaining tissue homeostasis. Their functions include recognizing and eliminating inhaled pathogens and debris, breaking down surfactant, and regulating the onset and resolution of inflammation.³ Similar to other tissue-resident macrophages, alveolar macrophages (AMs) are a self-renewing population that

arises from embryonic progenitors and typically require minimal contribution from peripheral blood monocytes under normal physiological conditions.⁴ Following lung injury, circulating monocytes extravasate from blood

vessels and infiltrate the tissue where they differentiate into Mo-AMs, further enriching the pool of resident AMs.⁵ (Figure 1)

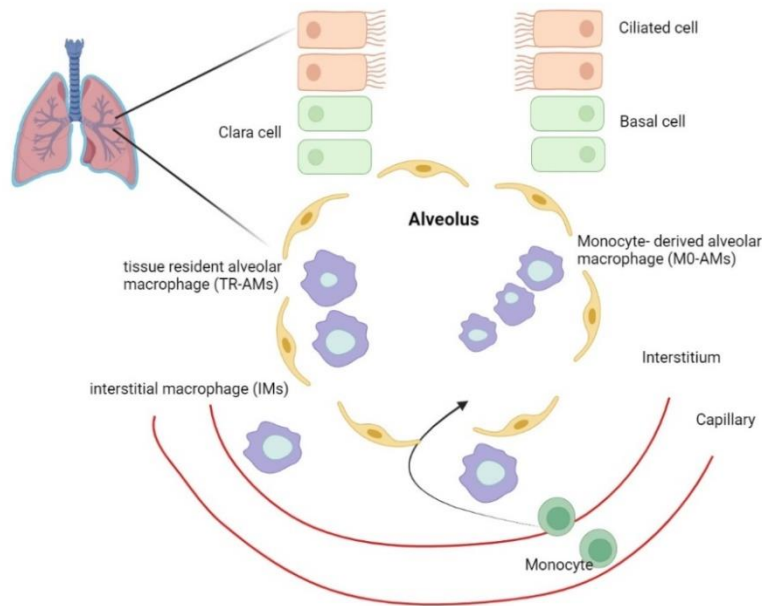


Figure 1. The macrophage population in the lung. Alveolar macrophages (AMs) and interstitial macrophages (IMs) reside in the lungs. AMs are in close contact with the epithelial cells of alveoli, and IMs reside in the parenchyma between the microvascular endothelium and alveolar epithelium. When AMs are damaged, circulating monocytes in the capillaries are then recruited to the lungs and transformed into AM-like cells.

Interstitial macrophages (IMs) are situated within the lung interstitium and typically exhibit a smaller size and morphology akin to blood monocytes. While their potential pro-inflammatory activities are not well elucidated, most studies have concentrated on their potential immunoregulatory properties. Both mouse and human IMs have been observed to express the immunosuppressive cytokine IL-10 under steady-state conditions.⁶ IMs are also engaged in tissue remodeling processes and contribute to barrier immunity by serving as antigen-presenting cells.⁷ An additional macrophage population known as intravascular macrophages, which are adherent to the capillary endothelium, has been identified in humans and other mammals. However, their specific role in immune function remains poorly understood.⁸ Macrophages are highly plastic cells, demonstrating a remarkable ability to transition from one phenotype to another.⁹ Beyond the AM/IM macrophage subtypes, polarized activation of macrophages distinguishes classically activated (M1) and alternatively activated (M2) macrophages, the latter being divided into M2a, M2b, M2c, and M2d subcategories.⁹ The central concept suggests that M1 macrophages inhibit fibrosis, whereas M2 macrophages promote fibrosis and contribute

to abnormal wound healing processes.¹⁰ M1 macrophage polarization occurs in response to inflammatory molecules such as T-helper (Th)1 cell-secreted cytokines like IFN- γ and tumor necrosis factor- α (TNF- α), as well as pathogen-associated molecular patterns and damage-associated molecular patterns. Conversely, M2 macrophages resolve inflammation by up-regulating anti-inflammatory mediators such as IL-10, TGF- β , IL-1R type II, and IL-1Ra. They also recruit Th2 cells, Tregs, eosinophils, and basophils through C-C Motif Chemokine Ligands (CCL17, CCL18, CCL22, and CCL24).¹¹ CD64, a high-affinity Fc- γ receptor, serves as a marker for M1 macrophages, while CD163 and CD206 are recognized as major markers of M2 macrophages.¹² The expression of these surface markers is closely associated with pathogen phagocytosis and inflammatory responses. Macrophages are abundantly present in the lung microenvironment, primarily as alveolar macrophages (AMs) and interstitial macrophages (IMs) (Figure 2).¹³ Circulating monocytes are recognized as a new source of macrophages when alveolar macrophages (AMs) are damaged.¹⁴ Alveolar macrophages (AMs) exhibit polarization into M1 and M2 phenotype macrophages. Macrophages play a crucial role in both pro-inflammatory and anti-inflammatory effects.

Increasing evidence indicates that the polarization of macrophages, governed by cytokines, chemokines, and transcription factors, is intricately linked to the onset and progression of pulmonary inflammatory diseases. These include acute lung injury (ALI), acute respiratory distress syndrome (ARDS), COVID-19-related ARDS, allergic asthma, chronic obstructive pulmonary disease (COPD), and idiopathic pulmonary fibrosis (IPF).^{16,17} Hence, modulating macrophage polarization and the associated

modulating macrophage polarization and the associated inflammatory molecules could serve as a promising therapeutic strategy for managing both acute and chronic inflammatory lung conditions. This review aims to explore the significance of M1/M2 macrophage functions in the pathogenesis of acute lung injury (ALI), acute respiratory distress syndrome (ARDS), allergic asthma, chronic obstructive pulmonary disease (COPD), and pulmonary fibrosis.¹⁸

Table 1. The type of macrophages and their role in ALI/ARDS

Subtypes	Production	Participation
M1	iNOS, TNF _α , IL-1β, IL-6, MCP-1	Pro-inflammatory, Reutrophilic inflammation, Tissue injury
M2	Arg1, IL-10, TGF-β	Anti-inflammatory, Phagocytosis, Tissue repair and remodeling

Table 2. The type of macrophages and their role in allergic asthma

Subtypes	Production	Participation
M2a	IL-10, IL-1ra, TGF-β	Allergic inflammation
M2b	IL-1, IL-6, IL-10, TNF _α	Tissue remodeling, Fibrosis
M2c	IL-10, TNF _β	Anti-inflammatory, Phagocytosis, Tissue remodeling, Fibrosis

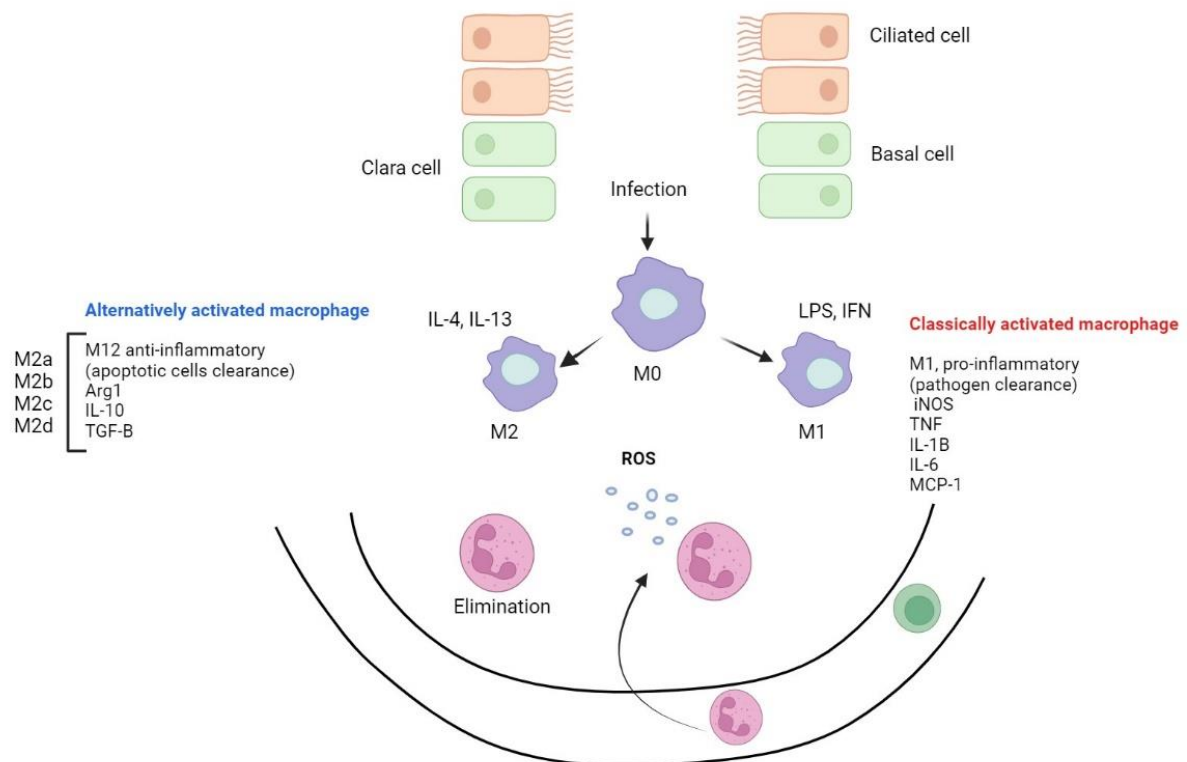


Figure 2. The role of macrophages in ALI/ARDS. Bacterial infection induces the development of ALI and ARDS. Under these conditions, AMs can be classified as M1 and M2 macrophages. Th1 cytokines, such as IFN-γ, and lipopolysaccharide (LPS), induce M1 phenotype macrophages, which produce iNOS, TNF-α, IL-6, and MCP-1, which are responsible for the pro-inflammatory, chemotaxis, radical formation, matrix degradation, and antimicrobial activities during the pathogenesis of ALI/ARDS. Th2 cytokines, such as IL-4 and IL-13, induce M2 phenotype macrophages (divided into M2a, M2b, M2c, and M2d), and these cells produce anti-inflammatory molecules, such as IL-10 and TGF-β, in ALI/ARDS.

Discussion and Conclusion

It's evident that macrophages play a crucial role in the pathogenesis of various pulmonary inflammatory diseases, including acute lung injury (ALI), acute respiratory distress syndrome (ARDS), allergic asthma, chronic obstructive pulmonary disease (COPD), and pulmonary fibrosis. Macrophages exist in different phenotypes, with M1 macrophages being associated with pro-inflammatory responses, while M2 macrophages contribute to anti-inflammatory reactions and tissue remodeling. The balance between these macrophage phenotypes is vital for maintaining lung homeostasis. The regulation of macrophage polarization and associated inflammatory molecules emerges as a promising therapeutic target for managing pulmonary inflammatory diseases. By modulating macrophage polarization, it may be possible to mitigate excessive inflammation and promote tissue repair, thus improving clinical outcomes in patients with these conditions. Overall, understanding the role of macrophages and their polarization in pulmonary inflammation provides valuable insights into the pathophysiology of these diseases and opens up avenues for the development of novel therapeutic interventions aimed at targeting macrophage function. Further research in this area is warranted to elucidate the underlying mechanisms and identify specific targets for intervention in different pulmonary inflammatory conditions.

Highlights

What Is Already Known?

Macrophages play a key role in the pathogenesis of pulmonary inflammatory diseases such as acute lung injury (ALI), acute respiratory distress syndrome (ARDS), allergic asthma, chronic obstructive pulmonary disease (COPD), and pulmonary fibrosis. Macrophages exist in different M1 (pro-inflammatory) and M2 (anti-inflammatory) phenotypes, and regulating this balance is critical for maintaining lung homeostasis.

What Does This Study Add?

Alveolar macrophages (AMs) and interstitial macrophages (IMs) are the two main macrophage subsets in the lung. AMs are involved in host defense and tissue homeostasis, while IMs participate in tissue remodeling and barrier immunity. Macrophage polarization into M1 and M2 phenotypes is a key mechanism in lung inflammation. Modulating macrophage polarization and associated inflammatory molecules could serve as a promising therapeutic target for managing both acute and chronic pulmonary inflammatory diseases. By tailoring macrophage polarization, it may be possible to mitigate excessive inflammation, promote tissue repair, and improve clinical outcomes in patients.

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All authors had an equal role in writing the article

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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