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Review Article

# Particle engineering to enhance or lessen particle uptake by alveolar macrophages and to influence the therapeutic outcome

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ABSTRACT

The alveolar macrophages defend the lung against airborne pollutants and infectious microorganisms. Recent advances in the understanding of the role of macrophages in generation of immunological and inflammatory responses have established that alveolar macrophages could be used as targets for drug delivery. Enhanced uptake of particulate drug carriers by macrophages could be beneficial in pathological conditions such as tuberculosis and HIV where infectious microorganisms utilize macrophages as a safe haven and a vehicle to further infections. In contrary, to achieve prolonged residence time, extended drug release and in desired situations, increased systemic absorption, drug carrying particles that can avoid recognition and uptake by alveolar macrophages may prove to be significantly advantageous. Drug targeting to macrophages can achieve superior therapeutic efficacy for the treatment of medical conditions that involve tumorigenesis, inflammation and infections. Various particulate carriers containing therapeutic agents have been used to deliver drugs to the macrophages residing in the lung. Particulate systems have also been engineered to facilitate or avoid uptake by macrophages. But pathological conditions to be treated and drug delivery goals dictate the engineering approach for reducing or enhancing uptake by macrophages. In this review, we have summarized the influence of various physicochemical properties – composition, size, shape, pegylation and presence or absence of surface ligands – of particulate carriers on their uptake by macrophages. We have also described the macrophage biology and strategies that have been used to influence uptake and avoidance of particulate carriers by macrophages.



## 1. Introduction

The human lung has a very complex but highly coordinated mechanism to remove inhaled particulate matters and airborne infectious agents. Contact of foreign substances with the physiological environment of the lung can lead to potential health risks and hence their prompt and complete elimination is important for normal functioning of the respiratory system. Natural defense mechanisms against the assaults of pollutants and pathogens present in the inspired air are complex and involve a number of processes such as mucociliary clearance, secretion of endogenous anti-pathogenic proteins and timely response from leukocytes residing in the lungs [1–3]. The mononuclear phagocytic system (MPS), especially macrophages in the alveolar region, plays a critical role in immune reconnaissance, initiation and regulation of the inflammatory response toward invading particles and organisms, and their subsequent removal by phagocytosis. Macrophages, monocytes and dendritic cells of the lungs defend the respiratory system by engulfing and eliminating apoptotic cells, organisms and foreign substances [4].

In addition to exposure to the environmental pollutants and pathogens, the lung is also exposed to drug formulations that are administered for the treatment of respiratory disorders. Recent advancements in the technology for drug delivery have spurred a growth in inhalational drug formulations with superior therapeutic outcomes [5]. The success of this route of drug delivery depends on the optimization of key pharmaceutical factors such as design of controlled release formulations with efficient regional deposition and increased residence time. Currently available inhalable formulations, which are mainly fine liquid mist and dry powder particles, deposit in the lungs in the form of particulate matters. Macrophages, the first-line of defense for the lungs, act against inhaled particulate formulation in an unbiased fashion and eliminate them

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by phagocytosis and thus reduce the pharmacological efficacy of drug formulations. In this review article, we have discussed two opposing scenarios: (i) situations when formulation uptake by lung macrophages is desirable and the strategies that facilitate particle recognition and engulfment by resident macrophages; (ii) conditions when avoidance of uptake by alveolar macrophages is preferred to achieve continuous drug release and prolonged residence time; and formulation approaches to avoid macrophage uptake. However, to design inhalable drug delivery systems that favor or prevent macrophage uptake, a good understanding of the physiology of lung macrophages and the process of phagocytosis – which we have discussed below – is important.

## 2. Lung macrophages

### 2.1. Origin of lung macrophages

In the classical view, undifferentiated heterogeneous and self-renewing pluripotent hematopoietic stem cells (HSC) in the bone marrow are the precursors of mononuclear phagocytes including macrophages (Fig. 1). These precursor cells reach the circulation after differentiation into monocytes in the bone marrow. Circulatory monocytes migrate into various organs by extravasation and the microenvironment of resident organs directs the monocytes to develop into mature macrophages and dendritic cells with different but organ-specific phenotypes [6]. Depending on the residing organ, macrophages are classified into various subtypes: Kupffer cells in the liver, osteoclasts in the bone, alveolar macrophages in the lungs and histiocytes in connective tissue [7]. Differentiation of monocytes into mature alveolar macrophages is influenced by various factors such as alveolar and bronchial epithelial cells, cytokines and surfactants. Matured macrophages express multiple surface receptors for detection, binding and phagocytosis of pathogens, cell debris and inhaled particles. However, this classical view of development of tissue-specific macrophages from HSC has been evolved based on recent observations that suggest that in specific tissue environment, macrophages could self-renew by locally proliferating mature differentiated cells [8].

### 2.2. Types of lung macrophages

In the lungs, macrophages not only reside in the alveolar space but also in other locations including intravascular, pleural and interstitial spaces. Based on the anatomical location in the lungs and functional phenotypes, lung macrophages are further divided into four classes: pulmonary intravascular macrophages (PIMs), pleural macrophages (PMs), interstitial macrophages (IMs) and alveolar macrophages (AMs) (Fig. 2).

#### 2.2.1. Pulmonary intravascular macrophages (PIMs)

PIMs are large cells with 20–80 μm in size and exhibit the same phagocytic potential as that of Kupffer cells. They reside around the pulmonary vascular endothelium and stay in direct contact with the circulating blood. The total population of PIMs in pulmonary capillaries varies depending on the species. For example, compared with human and rodents, horses, sheep, cats and pigs have a greater number of PIMs in the lungs [9]. PIMs have high phagocytic and retention capacity for circulating foreign particles in the blood and subsequent propagation of acute inflammatory response. The impact of PIMs on the lung vascular physiology is prominent due to their high secretory and pro-inflammatory functions [10].

#### 2.2.2. Pleural macrophages (PMs)

Pleural space, a fluid filled zone between the visceral and the parietal pleura, contains various cells, 50% of which are macrophages [11]. PMs are differentiated monocytes, express cluster of differentiation (CD) markers, $CD14^{++}$ and $CD14^{+}/CD16^{+}$, that they play a vital role in the defense of the pleural compartment. Due to higher expression of interleukin (IL)-10, PMs are categorized as moderately phagocytic and reasonably anti-inflammatory. Further, PMs can recognize changes to the surrounding microenvironment and propagate appropriate inflammatory response by recruiting neutrophils [12].

#### 2.2.3. Interstitial macrophages (IMs)

IMs are typically localized within the thin compartment between the vascular and alveolar epithelial layers in the lung connective tissues. They are considered obligatory intermediate between blood monocytes and alveolar macrophages [13,14]. A large number of IMs are present in the lungs and that accounts for ~40% of the total macrophages in the lung [15]. Since they are in direct contact with the surrounding interstitial tissue, mediators released by IMs may exhibit a higher influence on the pathophysiology of the lungs compared with the macrophages residing in the alveolar compartment [16]. IMs also play a prominent regulatory role in specific immune response and have

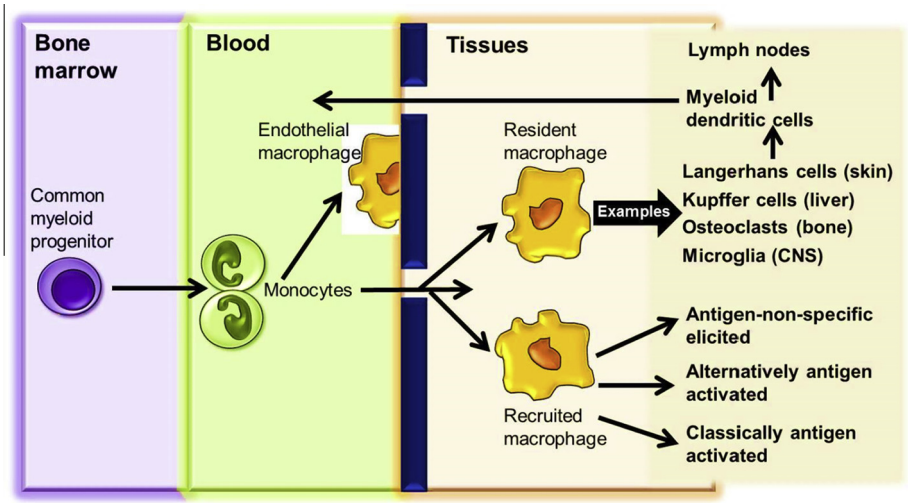


**Fig. 1.** Flow diagram depicting growth and differentiation of common myeloid progenitor cells into various tissue macrophage populations with organ-specific phenotypes depending on cell microenvironment (reproduced with permission from Ref. [7]). (For the interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)