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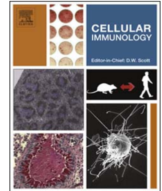

Review article

The interstitial macrophage: A long-neglected piece in the puzzle of lung immunity

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ABSTRACT

Lung macrophages have mostly been studied considering only their most accessible and well-defined representative, the alveolar macrophage (AM). In contrast, the identity and putative immune functions of their tissue counterpart, the interstitial macrophage (IM), have long remained much more elusive. Yet, recent evidence supports the notion that IMs perform important immune functions in the lung, notably in terms of innate immunoregulation. Here, we review current knowledge on the phenotype, ontogeny and function of IMs and propose strategies for the unambiguous identification and study of this important and dynamic lung innate immune cell population.

1. Introduction

Macrophages represent the most abundant immune cell population in the healthy lung. They are implicated, at least to some extent, in every immune and physiopathological process impacting the lung, including highly prevalent diseases such as asthma and chronic obstructive pulmonary disease (COPD) [1–3]. The best-studied type of lung macrophage is by far the alveolar macrophage (AM), a type of macrophage that populates the alveolar and airway lumen. Yet, macrophages also are present in the lung tissue interstitium and these cells have hence been coined “interstitial macrophages” (IMs) ([4] and references therein).

IMs long remained seldom studied, and we identify 2 main reasons for this. The first reason is purely technical. AMs are easily recovered from the lung of animal models and human patients through bronchoalveolar lavage and are easily discriminated from other luminal immune cells through their unique phenotype. AMs were therefore frequently used as the model lung macrophage. In contrast, the study of IMs requires lung resection (in animals) and biopsies or surgeries of lung tissue (in humans), followed by extensive tissue disaggregation and cell purification procedures for their isolation [5–7]. Technical hurdles hence biased the study of lung macrophages toward AMs. The second reason for overlooking IMs likely stems from the intuition that IMs represent a mere tissue-infiltrating transition state of circulating monocytes on their way to the airway lumen, where they would differentiate into AMs [8–12].

Interest in IMs was reignited by reports showing that mouse IMs may exert immunoregulatory activities in the lung and are hence immunologically relevant [6,13]. Since then, IMs have been the subject of increasing scrutiny. Here, we review current knowledge on the phenotype, ontogeny, population dynamics and immune function of IMs. We further argue that the histological definition of lung macrophages does not accurately account for the ontogeny, phenotype and immunological function of lung macrophage subsets, which can lead to misinterpretation. We therefore advocate that future research on lung macrophages should be assessed in light of unambiguous subset identification.

2. In search of the “real” lung interstitial macrophages

AMs and IMs have been primarily defined by their histologic localization, as their name indicates. Sensibly, one could argue that any macrophage present in the airway lumen is entitled to the denomination of “AM”, whereas any lung tissue-resident macrophage could be called “IM”. Clearly yet, this histologic definition of AMs and IMs may lead to undue confusion. Indeed, cells with a phenotype identical to AMs have been identified in the lung interstitium [5] and reciprocally, cells with a cell surface phenotype of IMs can infiltrate the airway lumen in response to specific immune stimuli [14]. Furthermore, IMs may easily be confused with blood and tissue-resident monocytes [6].

Abbreviations: AM, alveolar macrophage; COPD, chronic obstructive pulmonary disease; CpG-DNA, DNA containing non-methylated CpG motifs; HDM, house dust mite; IM, interstitial macrophage; LPS, lipopolysaccharide; TLR, toll-like receptor

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Indeed, even after extensive perfusion of the lung vasculature to clear blood cells, classical and patrolling monocytes are massively retained in the lung [14–17]. Obviously, patrolling monocytes, which strongly adhere to the endothelium, cannot be eliminated by lung perfusion. Yet, by comparing wild-type mice with Nr4a1-deficient mice, which are devoid of patrolling monocytes [18], these cells were shown to account for 16% of all monocyte/macrophages in the perfused lung [14]. Similarly, by comparing wild-type mice with Ccr2-deficient mice, in which classical monocytes cannot egress from the bone marrow [19], classical blood monocytes were estimated to account for 26% of lung monocytes/macrophages. More surprisingly maybe, recent evidence indicates that cells closely resembling classical blood monocytes may reside transiently or for longer periods of time within the lung tissue [14,16]. Indeed, in wild-type or Ccr2-deficient mice treated with intravenous clodronate-loaded liposomes, which deplete blood monocytes, a subpopulation of monocytes closely resembling classical blood monocytes persists within the lung tissue. These extravascular, tissue resident monocytes have therefore been coined "lung monocytes" [14,16]. Lung monocytes account for 14% of all monocyte/macrophages in the perfused lung of mice [14].

With the exclusion of contaminating cells using a conservative definition of IMs as lung-resident interstitial macrophages expressing known differentiated macrophage markers, IMs were estimated to represent only 4% of lung monocytes/macrophages in the steady-state mouse lung [14]. An overview of the typical monocyte and macrophage populations that are present in the steady-state mouse lung is provided in Fig. 1. As a consequence of the above considerations, "IMs" isolated by lung digestion after lung perfusion are likely to also contain residual AMs along with a high proportion of blood and tissue monocytes if a correct set of discriminating markers is not used [14,16]. In addition to other classical subtypes of monocytes/macrophages, IMs may be confused with other immune cells such as eosinophils, conventional dendritic cells and different "monocyte-derived" macrophages and dendritic cells. Indeed it has recently been shown in mice that, even in the steady-state, the lung contains tissue resident eosinophils, which share some cell surface markers with IMs (e.g. F4/80 and CD11b) [20]. Like IMs, lung resident eosinophils may exert immunoregulatory activities and hence, could confound the study of IM function [20]. Contaminating eosinophils may however easily be excluded from IM preparations by flow cytometry using their distinctive granularity or their expression of SiglecF. A fraction of IMs express CD11c and MHCII [21], while lung type 2 conventional dendritic cells (cDC2s) express CD11b [22], so that both cell types may contaminate each other. Nevertheless, cDC2s differ from IMs by their low or absent surface expression of macrophage markers (e.g. CD64, Mertk, F4/80). Maybe of more concern is the potential confusion between IMs and as yet ill-defined types of immune cells often referred to as "monocyte-derived" macrophages and dendritic cells. For instance, the term "exudative macrophages" has been proposed to refer to CD11b^{+} non-AM monocytic/macrophage cell populations that increase in the lung in response to inflammatory stimuli or viruses [23–25]. Their expression of Ly6C and their partial dependence on Ccr2 suggest that exudative macrophages are closely related to lung resident monocytes and inflammatory monocytes [23–25]. Yet, the possibility remains that bona fide IMs are present within this particular population if it is only defined by its expression of CD11b. Likewise, IMs may be unwillingly included in inflammatory subtypes of monocytes/dendritic cells such as Tumor necrosis factor and inducible-nitric oxide synthase-producing dendritic cells (Tip-DCs) and monocyte-derived dendritic cells (mo-DCs), which also are ontogenically closely related to inflammatory monocytes and lung-resident monocytes [22]. IMs may nevertheless be discriminated from these types of monocyte-derived cells through their low expression of the inflammatory/classical monocyte marker Ly6C and their expression of the Mertk macrophage marker.

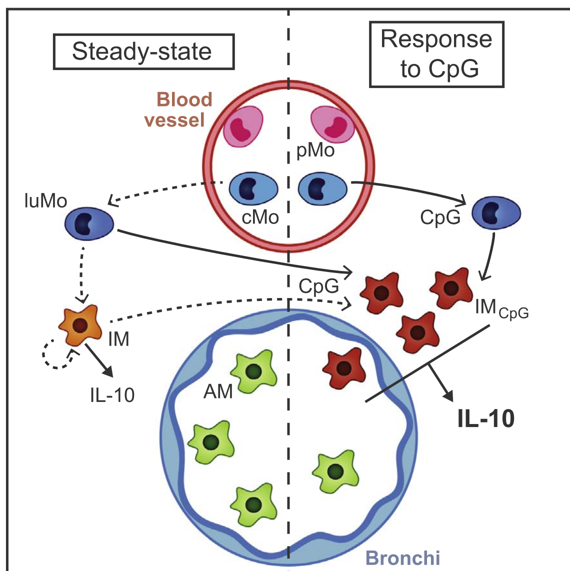

Fig. 1. Lung interstitial macrophages in the steady-state and following exposure to CpG-DNA. In the steady-state (left), interstitial macrophages (IMs) are located in the lung interstitium, where they produce interleukin-10 (IL-10). Steady-state IMs probably derive part from the recruitment of classical blood monocytes (cMo) through a lung-resident monocyte (luMo) intermediate, and part from local maintenance. Following exposure to CpG-DNA (CpG, right), luMo and possibly IMs, along with classical monocytes derived from the splenic reservoir, differentiate into IMs that produce high quantities of IL-10 (IM$_{CpG}$), thereby exerting potent anti-allergic immunoregulation. IM$_{CpG}$ may also infiltrate the airway lumen (AM: alveolar macrophage, pMo: patrolling monocyte).

The elements above stress out the need for a sufficient understanding of the ontogeny and immune surface phenotype of lung monocytes/macrophages if the field is to avoid undue lexical complexity and misinterpretation [22]. For the same reasons, we argue that caution should be taken when interpreting older studies on "IMs" and that a clear immunophenotypic definition of IMs is required. Toward this goal, different markers have been identified at the surface of murine IMs that can help discriminating them from AMs and blood or lung monocytes (Table 1). These markers are also helpful to discriminate IMs from monocyte-derived inflammatory cell types, as mentioned above. In this line of thought, we recently proposed a simplified flow cytometric procedure to identify all lung macrophage and monocyte subsets in mice with a minimal marker set [14]. Using this phenotypic definition, AMs may be identified as highly autofluorescent CD45^{+} F4/80^{+} cells, blood patrolling monocytes as SSC^{lo} CD45^{+} F4/80^{+} Ly6C^{lo} CD64^{int} cells, blood classical and lung monocytes as SSC^{lo} CD45^{+} F4/80^{+} Ly6C^{hi} CD64^{int} cells, and "true" IMs as lowly-autofluorescent SSC^{lo} CD45^{+} F4/80^{+} Ly6C^{lo} CD64^{hi} cells.

In the absence of discriminating markers, some studies on human lung macrophages relied on lung tissue dissociation followed by culture to isolate "IMs" [7]. The macrophages that would adhere to the plastic of the culture dishes were considered as IMs and were shown to have at least some features that distinguish them from AMs, including higher expression of HLA-DR and differential expression of specific Toll-like receptors (TLRs) [7]. It is worth noting however that monocytes easily differentiate into macrophages following culture on plastic. Hence, it is not clear whether lung macrophages obtained through cell culture represent resident lung macrophage populations or rather the product of in vitro (lung or blood) monocyte differentiation. More recent studies aimed at identifying surface markers to discriminate IMs from other lung monocyte/macrophages in resected human pulmonary tissue (Table 1). Sensibly, human IMs must be a component on the "non-AM, non-monocyte" pool of lung monocyte/macrophages. In humans, AMs and monocytes may be identified as highly autofluorescent SSC^{hi} CD169^{hi} CD206^{hi} cells and SSC^{lo} CD169^{-} CD206^{-} CD14^{+} CD16$^{lo/hi}$ cells, respectively [15,17,26]. Three recent studies reported on the existence in the human lung of HLA-DR^{+} CD169^{lo} CD206^{int} cells, which

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