

## Review article

## Antigen presenting cells: Professionals, amateurs, and spectators in the 'long game' of lung immunity

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## ABSTRACT

The lung is frequently and repeatedly exposed to invading pathogens and thus requires constant immunosurveillance. Professional antigen presenting cells (APCs), including dendritic cells, engulf invading pathogens and present their peptides via major histocompatibility complexes (MHC) I and II, to CD8 or CD4 T cells. Epithelial cells and stromal cells (including fibroblasts) provide more than structural support, they are increasingly recognised as key players in the immune response, acting as non-professional APCs through interactions with antigen experienced T cells that migrate to the lung. The importance of the contributions of non-professional and professional APCs to T cell function in vivo, is currently unclear. This review summarises the roles of professional and non-professional APCs in lung immunity, at the steady state and following viral insult, with particular emphasis on their ability to interact with and influence T cells.

## 1. Introduction

Diverse populations of antigen presenting cells (APCs) are found in the lung. These cells initiate innate responses following viral insult and shape local protective immunity. A substantial element of this role is via communication with T cells, driving T cell activation, differentiation, effector, and memory functions (Cabeza-Cabrero et al., 2021; Lo et al., 2008; Low et al., 2020).

Typically, T cells are divided into helper CD4 T cells that co-ordinate immune responses, and CD8 T cells that can kill infected cells and produce inflammatory cytokines to enhance anti-pathogen responses. Naïve CD4 and CD8 T cells migrate through lymph nodes and the spleen until they meet an APC presenting their cognate antigen. This leads to T cell activation, also known as T cell priming. While most activated T cells will die following pathogen clearance, some survive as memory T cells. These memory cells can be found in circulation (central memory T cells, T<sub>cm</sub>), migrating through peripheral tissues (effector memory T cells, T<sub>em</sub>), or residing within peripheral tissues (tissue resident memory T cell, T<sub>trm</sub>) to provide rapid immune responses following a reinfection (Mueller and Mackay, 2016).

Major histocompatibility complex (MHC) molecules are central to interactions between APCs and T cells. MHC class I (MHCI), expressed by all nucleated cells, presents peptides recognised by CD8 T cells. MHC class II (MHCII), in contrast, is found on so-called 'professional' APCs

and is required for antigen presentation to CD4 T cells. Traditionally, dendritic cells (DCs), macrophages and B cells are classed as professional APCs and expression of MHCII on other cell types is a consequence of local inflammation. However, several studies have identified MHCII expression by lung epithelial cells and fibroblasts at the steady state and in response to viral insult (Shenoy et al., 2021; Toulmin et al., 2021) or malignancy (Kerdidani et al., 2022).

A unique role of DCs is to prime naïve T cells. Three types of signals are required: peptide MHC-TCR; costimulatory molecules; and polarising cytokines. Macrophages and B cells can also provide these signals but are rarely located in the T cell zone of secondary lymphoid organs where T cell priming occurs. Non-professional APCs, such as epithelial cells and fibroblasts, do not express classical co-stimulatory molecules (such as CD80/86) to the same extent as professional APCs (Hutton et al., 2017; Lo et al., 2008; Shenoy et al., 2021). However, they can express CD40, ICAM1 and PDL1, molecules that can be important for memory T cell maintenance and activation (Ahmadvand et al., 2021; Hutton et al., 2017; Shenoy et al., 2021).

By enabling communication between the innate and adaptive arms of the immune system, APCs play central and distinct roles in ensuring protective immunity and the generation of immune memory. Here we will review how professional and non-professional APCs impact on the different stages of lung immune responses to provide local protection against respiratory pathogens.

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## 2. Professional APCs

### 2.1. Dendritic cells

There are three distinct DC subsets in the lung: plasmacytoid DCs (pDCs), conventional DCs (cDCs) and monocyte-derived DCs (moDCs) (Naik et al., 2007). Conventional DCs prime naive T cells and are classified as either cDC1 (CD103<sup>+</sup>, XCR1<sup>+</sup>, IRF8<sup>+</sup> and Batf3<sup>+</sup>) or cDC2 (CD11b<sup>+</sup> and IRF4<sup>+</sup>). cDC1s sample the local airway lumen environment in the respiratory epithelium, whilst cDC2s are located in the lamina propria. A small number of pDCs may also reside in lymphoid follicles of the small airways in the lung (Lyons-Cohen et al., 2017; von Garnier et al., 2005). During homeostasis they play an immunoregulatory role while during viral infection, pDCs produce type I interferon (IFN) (Cella et al., 1999).

cDC1, cDC2 and moDCs express high levels of MHC I and II and key co-stimulatory molecules, CD80/CD86. Influenza A virus (IAV) is an important respiratory disease that causes thousands of deaths annually and is often used to investigate lung immunity in mouse models (Zens and Farber, 2015). During IAV infection, several subsets of DCs are recruited to and activated in the lung. Monocyte derived dendritic cells (moDCs) and pre-DCs are also rapidly recruited to the lung in a CCR2 dependent manner and are found at the foci of infection (Cabeza-Cabrero et al., 2021).

cDC1s are essential for CD8 and CD4 T cell priming (Kim and Bra-ciale, 2009; Kim et al., 2014) while cDC2s are able to polarise CD4 T cell responses and may be necessary to promote the development of memory CD4 and CD8 T cells (GeurtsvanKessel et al., 2008). The requirement for cDC2 in the generation of memory T cells is not restricted to viral infections as they are also required for the development of Thelper 2 Trm cells (Camacho et al., 2022).

Interestingly, Bosteels et al., identified an inflammatory cDC2 phenotype recruited to the lung upon respiratory viral infection (Bosteels et al., 2020). These cells made IL-12 and were able to activate CD4 and CD8 T cells in vivo. These inflammatory cDC2 shared gene expression, phenotype, and function with monocytes and cDC1s. This study also emphasised the relatively limited APC function of monocyte derived cells when separated from, and compared with, inflammatory-cDC2s (Bosteels et al., 2020).

### 2.2. Macrophages

There are two classes of resident macrophage populations in the lung, alveolar (AMs) and interstitial (IMs) macrophages. AMs (CD11c<sup>+</sup> SiglecF<sup>+</sup>CD11b<sup>+</sup>) are the most abundant immune cell in the lung. They are directly exposed to the environment acting as the first line of defence against IAV infection (Kulikauskaitė and Wack, 2020; Niec et al., 2021). Although AMs express low levels of MHCII, Ina et al., found that human AM may have antigen presenting capacity during tuberculosis infection (Ina et al., 1991). However, no comprehensive evidence for antigen presentation to CD4 T cells by AMs has been reported in further human studies. Rather, AMs are important sources of cytokines during IAV infections producing TGFβ, IL-6 and type I IFN. These cytokines enable communication with type I and II epithelial cells promoting viral and control tissue repair after pathogen infiltration (Aegerter et al., 2020).

IMs are categorised into three subpopulations depending on their expression of CD11c, MHCII and CD206 (Kawasaki et al., 2022). IMs reside in various locations throughout the lung. Compared to DCs, less is known about the antigen presenting capabilities of IMs. However, these cells express high levels of MHC I/II and single cell RNA sequencing analysis showed that they express genes involved in presenting antigen to CD4 T cells (Schyns et al., 2019).

### 2.3. B cells

B cell derived IAV-specific antibodies protect from future infections.

B cells can also secrete cytokines and can act as APCs, efficiently presenting antigen to T cells at later timepoints post infection. B cells also contribute to the formation of germinal centres (GC), ultimately leading to the production of B cell clones that bind viral antigen with high affinity. It is widely accepted that MHCII presentation by GC B cells to CD4 T cells, in particular follicular CD4 T cells, is necessary for GC B cell survival and proliferation (Gitlin et al., 2014).

IAV-specific B cells are also found in inducible bronchus-associated lymphoid tissues (iBALTs) in the lung at least 200 days post infection (Allie et al., 2019; MacLean et al., 2022). These B cells expressed genes associated with tissue residency in T cells (Tan et al., 2022). In comparison to GCs, iBALTs have variable morphologies, with a lack of distinct T and B cell zones and contain a mixed population of immune cells including DCs (MacLean et al., 2022; Tan et al., 2019). Cabeza-Cabrero et al., identified inflammation foci rich in DCs at day 5 post IAV infection (Cabeza-Cabrero et al., 2021), which potentially could be sites of iBALT formation. Future studies in this area should also address the discrepancies (if any) between inflammation foci and iBALTs at primary and memory timepoints post IAV infection, the identity of APC types present within these areas, and their roles in presenting antigen to T cells.

### 2.4. Professional APCs and memory T cells

Dendritic cells, B cells (and some macrophage subsets) present antigen to CD4 and CD8 T cells during IAV infection. It is believed that the division of labour between these different APCs effectively induces the adaptive immune response, clearing the pathogen and generating protective memory.

The presumption that memory T cells do not require professional APCs for their reactivation was brought into question by Zammit et al., (Zammit et al., 2005) who found that memory CD8 T cells are dependent on DCs for their reactivation (Zammit et al., 2005). In contrast, Low et al., elegantly demonstrated that lung Trm cells can be reactivated by a diverse array of professional and non-professional APCs (Low et al., 2020). Restricting antigen presentation to non-haematopoietic cells reduced the expression of cell cycle genes in reactivated T cells but increased their interferon stimulated genes (ISGs). In contrast, T cell production of inflammatory cytokines production was increased when only professional (CD45<sup>+</sup>) cells could directly re-activate the Trm CD8 T cells (Low et al., 2020). These data suggest that cell fate may be intimately linked to which APC reactivates a Trm cell.

## 3. Non-professional APCs

### 3.1. Epithelial cells

Following IAV re-infection, CD8 Trm cells migrate from the interstitium into the airways facilitated by epithelial derived chemokine gradients (e.g., CXCL16-CXCR6) (Wein et al., 2019). While the majority of studies have focused on interactions between epithelial cells and CD8 Trm cells (Low et al., 2020; Wein et al., 2019), recent studies have shed new light on interactions between epithelial cells and CD4 T cells.

In the distal lung, the alveolus contains two morphologically and functionally distinct populations of epithelial cells, alveolar type I (ATI) and type II (ATII) epithelial cells. The surfactant producing ATII cells maintain the alveolar epithelium during homeostasis and promote regeneration after lung injury. ATII cells are capable of self-renewal and can also differentiate into ATI cells, specialised for gas exchange (Rock et al., 2011).

Toulmin et al., demonstrated that ATII epithelial cells can act as antigen presenting cells to CD4 T cells in a mouse model of IAV infection (Toulmin et al., 2021). *Ex vivo* antigen presentation assays showed ATII cells were capable of presenting antigen to CD4 T cells, though to a lesser extent than DCs. Interferon-gamma (IFNγ) levels in the lung micro-environment can regulate exogenous antigen presentation by

non-professional APCs and subsequent T cell interactions (Hutton et al., 2017; Reith et al., 2005). However, constitutive MHCII expression by ATII was IFN $\gamma$  independent and did not influence viral replication (Toulmin et al., 2021).

Studies using mice with an ATII specific depletion of MHCII (SPC $\Delta^{Ab1}$ ) have demonstrated the importance of MHCII on these cells. In naïve animals, loss of MHCII on ATII cells reduced lung T cell numbers and proportions of CD4 T cells expressing PD-1 (Ahmadvand et al., 2021). More dramatically, after IAV infection, SPC $\Delta^{Ab1}$  animals have a 2-fold higher mortality rate compared to control animals (Toulmin et al., 2021). This highlights a survival advantage conferred by MHCII+ ATII cells. Intriguingly, Shenoy et al., found that specific deletion of MHCII in lung epithelial cells resulted in reduced PDL1 expression by alveolar epithelial cells, during both homeostasis and bacteria-driven pneumonia (Shenoy et al., 2021). Following re-infection, antigen presenting ATII cells may re-activate effector T cells or initiate recruitment of regulatory T cells to promote epithelial regeneration (Mock et al., 2014).

Shenoy et al., also found that MHCII was expressed on multiple lung epithelial subsets, including upper airway (club, ciliated and progenitor cells) and lower airway (ATII) subsets in mice (Shenoy et al., 2021). These findings are consistent with previous studies using primary human lung tissue that also highlighted diversity of MHCII and co-stimulatory molecule expression in the upper and lower respiratory tracts (Kalb et al., 1991; Rossi et al., 1990). Shenoy et al., directly showed that a mixed population of upper and lower respiratory lung epithelial could present antigen in an *ex vivo* assay with co-cultured CD4 T cells. In a model of bacterial infection (*S. Pneumoniae*), airway epithelial cells supported CD4 Trm cell maintenance around airways (Shenoy et al., 2021). However, only the effect on total T cells was investigated and not antigen-specific T cells.

When viral load is high, antigen presentation by ATII cells may be important, enabling professional APC populations to rapidly acquire antigens from infected epithelial cells. For example, MHCII from epithelial cells may be 'passed' onto immune cells (Stephens et al., 2021). Professional APCs may acquire subviral material from infected ATII cells, which is more easily presented via the exogenous pathway compared to whole viral virions (Miller et al., 2015). PDL1 expression by epithelial cells may contribute to CD4 T cell suppression by preventing overly exuberant and potentially damaging responses (Lo et al., 2008).

### 3.2. Fibroblasts

Fibroblasts are often found in close proximity to lung epithelial cells; although they are less likely to become infected with IAV (Steuerman et al., 2018). In models of adenoviral infection, lung stromal cells alter the lung microenvironment and organise lymphoid structures to provide a supportive niche for inflating memory CD8 T cells. Cupovic et al., showed that immunisation with adenovirus vectors led to changes in lung stromal cell populations, accompanied by increased IL-33 production by lung fibroblasts (Cupovic et al., 2021). Loss of these infected fibroblasts, or IL-33 production by these cells, led to a reduction in the fitness and functionality of virus-reactive memory lung CD8 T cells (Cupovic et al., 2021).

Recently, Kerdidani et al., identified MHCII+ lung fibroblasts in both the steady state and in mouse models of lung cancer, located next to areas of high CD4 T cell density (Kerdidani et al., 2022). In the IAV infected lung, Denton et al., identified CXCL13 + lung fibroblasts that supported the formation of lung germinal centres by promoting B cell recruitment (Denton et al., 2019). These fibroblasts were MHCII+ and were not detected in the naïve lung. These data suggest it may be feasible for MHCII+ lung fibroblasts to come into contact with antigen experienced lung T cells and promote protective immune responses (Silva-Sanchez and Randall, 2020).

Multiple *in vitro* studies in mice have demonstrated the ability of fibroblasts to present antigen to CD4 T cells (Davidson et al., 2021; Kerdidani et al., 2022; Ngwenyama et al., 2022). Ngwenyama et al.,

investigated cross talk between fibroblasts and T cells in a mouse model of heart failure (Ngwenyama et al., 2022). They found that cardiac fibroblasts take up and process antigens for presentation to CD4 T cells via MHCII that is induced by IFN- $\gamma$ . In the lung, Kerdidani et al., showed that antigen presenting cancer-associated fibroblasts (ApCAFs) induced expression of effector cytokines by cancer-specific CD4 T cells (Kerdidani et al., 2022).

IAV infection of lung endothelial cells, for example, capillary endothelial cells, might induce viral antigen presentation and contribute to a rapid recall response of intravascular or perivascular memory T cells (Anderson et al., 2012). Further information can be found about the immunomodulatory role and antigen presentation capabilities of endothelial cells as reviewed by (Amersfoort et al., 2022).

## 4. Therapeutic targeting

Prolonged consequences of lung viral infection include airway tissue damage, fibrosis, and long-term sequelae. Current seasonal IAV vaccines provide protection by generating strain specific antibodies against the outer regions of inactive viral preparations or as attenuated virus in live vaccines targeted at children. However, targeting the activation of CD4 and/or CD8 memory T cells that respond to peptides from the core of the virus may provide better protection against infections with different IAV strains (Sridhar et al., 2013; Wilkinson et al., 2012). Miller et al., propose that a robust IAV CD4 T cell response in mice requires presentation of endogenous IAV antigens via MHCII (Miller et al., 2015). The infectivity of DCs by IAV seems to be dependent on the HA protein (H1 and H5) in the virus (Liu et al., 2010). Thus, APC subtypes (immune, epithelial or stromal cells) that are more likely to become infected may promote better CD4 T cell responses.

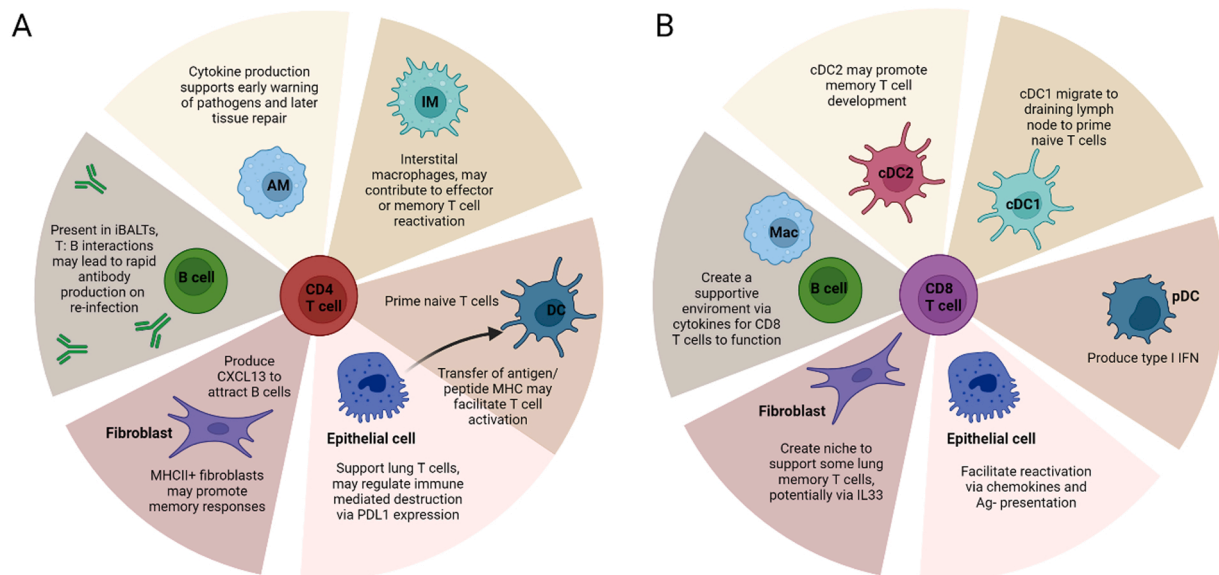
Specific interactions between professional and non-professional APCs and lung T cells are summarised in Fig. 1. Modifying these APC-T cell interactions may represent a potential avenue to generate protective immunity. This could prevent future disease, particularly if the continued presence of certain APC sub-populations following infection facilitates memory T cell maintenance. Future vaccines could be designed to boost the functions of 'IAV altered' structural cells or myeloid cells by using an adjuvant. Interestingly, Denton et al. found that targeting TLR4 using adjuvants improved the MAdCAM-1 + stromal cell response to immunisation and facilitated longer term protection post vaccination (Denton et al., 2022). Development of other novel therapies that target specific DC subsets that home to a particular location (lung versus draining lymph node) or enhance their interactions with T cells, could be beneficial. Conversely, inflammatory (or other) mediators present in the micro-environment may promote exogenous antigen presentation by APCs. It is plausible, in both scenarios, that retention of these signals would make the Trm compartment less transient, thereby sustaining protective immunity.

## 5. Conclusion

Limited APC-T cell interactions occur during pulmonary homeostasis. Conversely, following viral insult, local T cell interactions with both professional and non-professional APCs are much more diverse. The potential to skew functional responses of reactivated memory T cells, using distinct subsets of APCs, may prolong protective immune responses, informing future vaccine design. Promoting longevity of interactions between the 'right' APC subset(s) with memory T cells at the 'precise' time in the 'correct' location may provide an opportunity to enhance vaccine efficacy.

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**Fig. 1.** Schematic showing how professional and non-professional antigen presenting cells interact with (A) CD4 and (B) CD8 T cells in the lung following viral and bacterial infection. Abbreviations: AM (alveolar macrophage), IM (interstitial macrophage), DC (dendritic cell), iBALT (inducible bronchus associated lymphoid tissue), Mac (macrophage), cDC1 (conventional dendritic cell 1), cDC2 (conventional dendritic cell 2), pDC (plasmacytoid dendritic cell), IFN (interferon).

### Conflict of interest

The authors have declared that no conflict of interest exists.

### Data availability

No data was used for the research described in the article.

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