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REVIEW

Fungal-mediated lung allergic airway disease: The critical role of macrophages and dendritic cells

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Abstract

Fungi are abundant in the environment, causing our lungs to be constantly exposed to a diverse range of species. While the majority of these are cleared effectively in healthy individuals, constant exposure to spores (especially *Aspergillus* spp.) can lead to the development of allergic inflammation that underpins and worsen diseases such as asthma. Despite this, the precise mechanisms that underpin the development of fungal allergic disease are poorly understood. Innate immune cells, such as macrophages (MΦs) and dendritic cells (DCs), have been shown to be critical for mediating allergic inflammation to a range of different allergens. This review will focus on the crucial role of MΦ and DCs in mediating antifungal immunity, evaluating how these immune cells mediate allergic inflammation within the context of the lung environment. Ultimately, we aim to highlight important future research questions that will lead to novel therapeutic strategies for fungal allergic diseases.

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Introduction

Fungi are abundant in our environment, which leads to a large amount of fungal material being breathed into lungs on a daily basis [1]. Many individuals clear these fungi with no apparent sign of disease, but can trigger the development of allergic inflammatory diseases [2–4] such as severe fungal sensitised asthma [5–7] estimated to impact 10 million people worldwide [8]. Despite this, the underlying mechanism(s) that cause fungi to mediate these chronic diseases are poorly understood.

A variety of cell types in the lung have been shown to trigger responses to environmental allergens that causes allergic inflammation. In particular, myeloid innate immune cells such as macrophages (MΦ) and dendritic cells (DCs) have been shown to be essential [9–11]. However, these cells are also crucial for the clearance of fungal spores, to prevent tissue penetration leading to invasive disease [12]. The underlying events that cause MΦ and DCs to switch from orchestrating spore clearance (maintaining a "healthy environment"), to mediating diseases such as severe asthma are poorly defined.

Several excellent reviews have previously highlighted the clinical burden of fungal asthma and the general immune mechanism(s) that underpin the development of allergic inflammation to fungi [12–15]. Therefore, the aim of this review is to assess our current understanding

of the unique role MΦs and DCs play in directing and maintaining fungal allergic inflammation. We will reflect how this improves our appreciation of fungal allergic inflammation and highlight the challenges that remain.

The global health impact of fungal driven asthma

There are approximately 300 million people with asthma worldwide, and this is expected to rise to 400 million by 2025, placing a huge burden on global health [16,17]. Fungi such as *Aspergillus* spp. can trigger a spectrum of allergic airway inflammatory diseases, ranging from asthma, allergic fungal rhinosinusitis (AFRS), allergic bronchopulmonary aspergillosis (ABPA), and severe asthma with fungal sensitisation (SAFS) (Table 1) [3,18]. It is estimated that up to 10 million people globally suffer from severe asthma, as a direct result of hypersensitivity towards *Aspergillus fumigatus (Af)* [8]. Typically 1000s of spores are inhaled daily [19–21], and if spore clearance fails (typically in immunocompromised situations), fungi can grow and invade the lung tissue, causing invasive Aspergillosis [22,23]. Therefore, a delicate balance of appropriate responses to clear fungal spores, while avoiding hypersensitivity, is required to maintain a healthy lung barrier.

The fungal spores themselves are a crucial aspect in initiating host defence mechanisms. Ungerminated fungal spores are coated with a hydrophobic outer layer of rodlet proteins and melanin upon germination, disruption of this layer reveals numerous fungal motifs on the fungal cell wall (e.g., β-glucan and chitin) that can activate immune responses [24]. If they are not cleared from the airway, spores develop into hyphae secreting numerous components (e.g., glycans, proteases, metabolites, etc.) that aid fungal tissue invasion and can also stimulate immune responses [12]. Mouse models of repeat fungal exposure have shown that spore germination is a crucial factor in the development of allergic inflammatory responses [25,26], demonstrating that fungal motifs are crucial in actively mediating allergic inflammatory

Table 1. List of abbreviations and acronyms.

Abbreviation	Name
ABPA	Allergic bronchopulmonary aspergillosis
Af	*Aspergillus fumigatus*
AFRS	Allergic fungal rhinosinusitis
Alp 1	Alkaline protease 1
AlvMΦ	Alveolar macrophage
Aspf13	*Aspergillus* protease allergen
BATF(number)	Basic leucine zipper ATF-like transcription factor
Ca^{2+}	Calcium ion
CCR(number)	C-C motif chemokine receptor
CD(number)	Cluster of differentiation (number)
cDC	Conventional dendritic cells
CLC	Charcot–Leyden crystals
CLEC (number)	C-type lectin domain containing (number)
CLR	C-type lectin receptors
CXCL(number)	Chemokine (C-X-C motif) ligand
DAMP	Damage-associated molecular pattern
DC	Dendritic cell
DNGR (number)	CLEC9A
FAO	Fatty acid oxidation

(*Continued*)

Table 1. (Continued)

Abbreviation	Name
FCP	Fibrinogen cleavage products
FcεR(number)	Fc epsilon receptor (number)
FleA	*A. fumigatus* lectin
HDM	House dust mite
IFN-(type)	Interferon (type)
IFNAR	Interferon-α/β receptor
IgE	Immunoglobin E
IL-(number)	Interleukin-(number)
ILCs	Innate lymphoid cells
infDC	Inflammatory dendritic cell
IntMΦ	Interstitial macrophage
IRF(number)	Interferon regulatory factor (number)
KLF(number)	Kruppel-like factor
LN	Lymph node
LPS	Lipopolysaccharide
M. tuberculosis	*Mycobacterium tuberculosis*
MAC	Macrophage integrin
Mbd(number)	Methyl-CpG binding domain protein (number)
MelLEC	Clec1a
Mgl2/CD301b	Macrophage galactose N-acetyl-galactosamine specific lectin 2/Cluster of differentiation 301b
moDC	Monocyte-derived dendritic cell
Muc(number)	Mucin (number), oligomeric mucus/gel-forming
MΦ	Macrophage
NFAT	Nuclear factor of activated T cells
NK-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NLR	Nod-like receptor
Nlrx(number)	NLR family member X (number)
NOD(number)	Nucleotide-binding oligomerisation domain-containing protein (number)
Nos(number)	Nitric oxide synthase (number)
Nrf(number	Nuclear factor-erythroid factor (number)
OVA	Ovalbumin
OX40L	Tumour necrosis factor receptor superfamily, member 4/OX40 ligand
pDC	Plasmacytoid dendritic cells
PDL(number)	Programmed death ligand (number)
ROS	Reactive oxygen species
SAFS	Severe asthma with fungal sensitisation
scRNA-seq	Single-cell RNA sequencing
SP-(letter)	Surfactant protein (letter)
STAT (number)	Signal transducer and activator of transcription (number)
TAM	Tyro, Axl, MertK receptors
Tfh	T follicular helper cells
TGFβ	Transforming growth factor beta
TLR	Toll-like receptor
TNF	Tumour necrosis factor
TNFR (number)	Tumour necrosis factor receptor (number)
Treg	Regulatory T cell
TSLP	Thymic stromal lymphopoietin
Zeb (number)	Zinc finger e-box binding homeobox (number)

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responses. Despite this, the role of fungi are less studied in comparison to other allergens such as house dust mite (HDM) [27]. Indeed, murine models of allergic inflammation commonly utilise repeat doses of HDM or use of model antigens in the presence and absence of adjuvants (e.g., OVA and Alum [28]) rather than fungi. Interestingly, fungal components are an under-appreciated factor within HDM preparations and can further exacerbate allergic inflammation [29].

Upon sensitisation to allergens, the immune response and resultant cytokine environment mediates many of the features of chronic asthmatic disease [4]. Elevation of type 2 cytokines in the lung (e.g., IL-4, IL-5, and IL-13) is a feature of many asthmatic patients, which orchestrate increases of granulocytes in the airway (e.g., eosinophils and mast cells), activate B cell class switching to IgE and directly activate mucus overproduction, airway hyperresponsiveness and tissue remodelling/fibrosis [28]. However, some asthmatic patients have a lower type 2 response and instead have abundant levels of type 17 cytokines (IL-17 and IL-22) that mediate pathology [30]. Various cell types have been identified as being sources of these cytokines during asthma, including several innate cell populations, e.g., innate lymphoid cells (ILCs), granulocytes, and γδ T cells in addition to adaptive immune cells including $CD4^+$ and $CD8^+$ T cells [31]. The precise relationship between these responses and the role that MΦ and DCs have in mediating these processes upon fungal exposure are poorly understood, limiting our ability to improve therapeutic strategies.

Lung macrophages: Promotors or inhibitors of fungal allergic inflammation?

MΦ are widespread throughout the body and are essential for uptake/clearance of foreign pathogens while maintaining tissue homeostasis and development, through clearance of dead cells and debris/particles [32–34]. Upon activation, MΦs are capable of orchestrating downstream effector responses by secreting a wide array of inflammatory mediators (e.g., cytokines and chemokines) and even acting as antigen presenting cells [35]. However, the types of MΦ and their capabilities to elicit inflammatory responses varies depending on their tissue location. In the lung, there are 2 major populations; alveolar MΦs (AlvMΦ) located in the airway (particularly the alveolar sacs) and interstitial MΦs (IntMΦ), which reside within the tissue (Fig 1). These distinctions translate to differences of origin between these MΦ populations [36,37]. AlvMΦ are established by a distinct foetal monocyte population that colonise the lungs rapidly at birth, in steady state conditions these cells self-maintain and comprise the dominant macrophage population in the lung [38]. Conversely, several different populations within the Int MΦ have been identified, the origins of which are still debated, but have been reported to reside in different parts of the lung, e.g., close to lymphatic versus vascular vessels [39,40]. This section will discuss the role of these different macrophage populations in the context of fungal allergic inflammation.

One of the major roles of AlvMΦ populations is maintaining a "healthy" lung environment by removing foreign microbes, particles, and host secreted factors, e.g., MΦs catabolise surfactant secreted by epithelial cells, thus avoiding pulmonary alveolar proteinosis [41,42]. Therefore, AlvMΦ have been proposed to be the dominant cell type that acquires and clears *Af* spores inhaled into the airway [43,44]. There are several reported mechanisms that have been shown to be crucial for this process. Firstly, the spores are able to interact with secretory factors present in the airway which boost MΦ uptake. Melanin on the spore surface interacts with surfactant (particularly surfactant protein D), which boosts macrophage uptake of spores [45]. Furthermore, AlvMΦ express C-type Lectin receptors (CLRs) (e.g., Dectin-1 and 2), which recognise fungal motifs (e.g., β-glucan) revealed on germinating spores, triggering phagocytosis

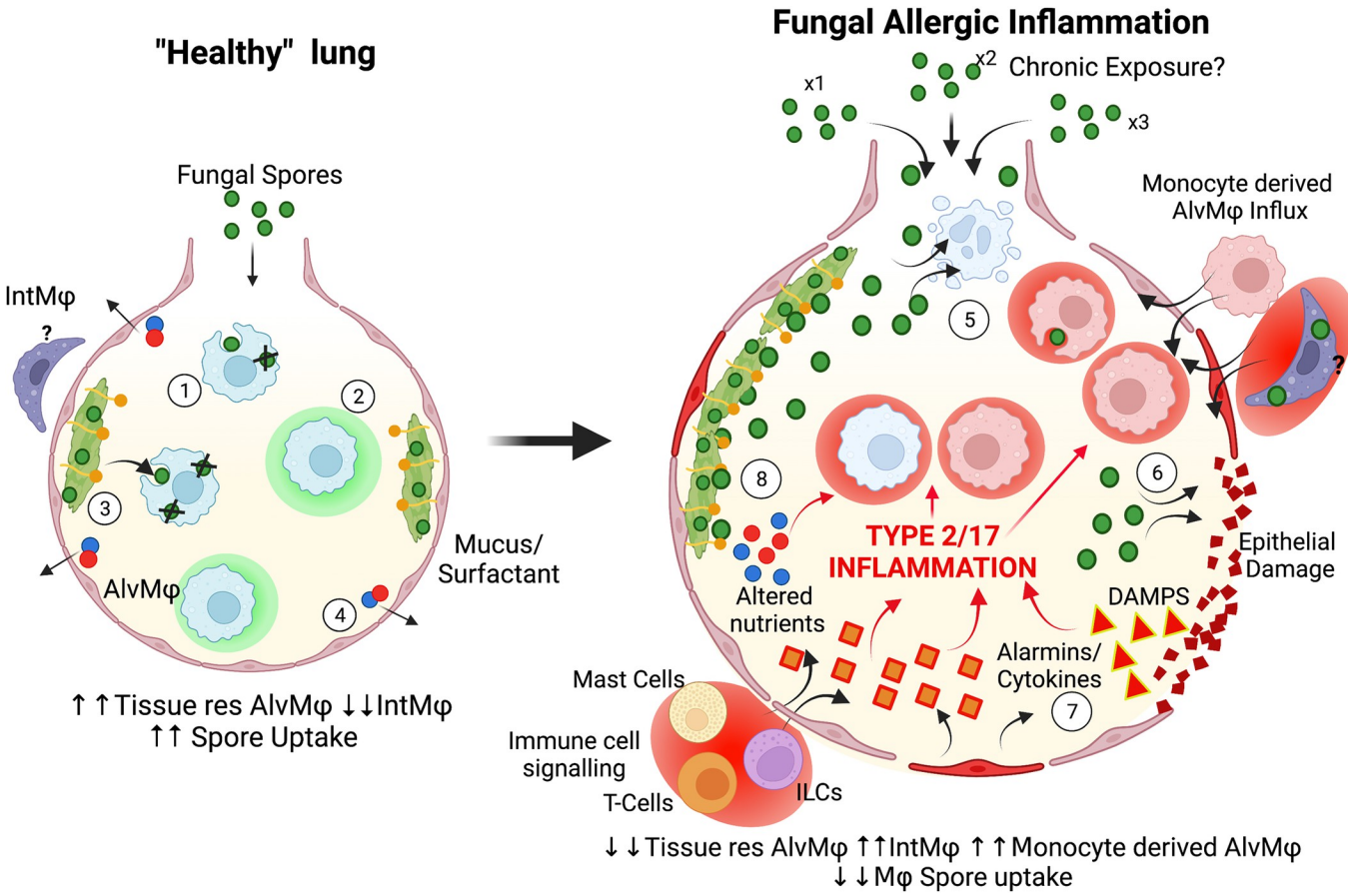

Fig 1. The influence of the lung environment and fungal spores on MΦ responses during allergic inflammation. In a "healthy lung environment" (**left**), (**1**) the majority of inhaled fungal spores are rapidly removed from the airways by AlvMΦ [43]. (**2**) Some AlvMΦ may not acquire spores and generate an anti-inflammatory environment [54]. (**3**) Spore uptake and killing, facilitated by the aid of components of the lung environment including epithelial cell secreted surfactants (SP-A, SP-D) and mucus (particularly the mucin glycoproteins, e.g., Muc5b) [45,159]. (**4**) Other features of the airway include a low nutrient airway environment (maintained by airway epithelial active transporters [170]) that maintain an immunoregulatory MΦ environment [144]. Upon allergic inflammation (**right**), (**5**) repeat spore exposure causes apoptosis or necrosis of resident AlvMΦ [183]. These are replaced by inflammatory IntMΦs [26] or recruited monocytes [37,76]. Both express altered inflammatory transcriptional and epigenetic profiles, leading to differential inflammatory responses upon subsequent spore exposure [71,73]. (**6**) Epithelial cell sensing of fungal material and/or damage to epithelial cell barrier (via fungal proteases), triggers the release of "alarmins" (e.g., TSLP, IL-33, IL-6, IL-22, and CCL2) [173–175]. (**7**) These epithelial signals can recruit and activate other immune cells such as mast cells, basophils and ILC2s inducing a type 2 cytokine environment directly impacting MΦ responses (potentially reducing spore killing) [135–138]. (**8**) Persistence of spores, disrupted epithelial barrier, immune cell infiltration (including $CD4^+$ T cells) leads to a type 2 and 17 cytokine environment, alteration of airway nutrient concentrations and hyper secretion of mucus (including Muc5ac) and surfactants [151,158]. These further promote pro-inflammatory MΦ antifungal responses, possibly sustaining allergic inflammation. Figures were created with BioRender.com. AlvMΦ, alveolar macrophage; CCL, chemokine ligand; DAMP, damage-associated molecular pattern; IL, interleukin; IntMΦ, interstitial macrophage; ILC, innate lymphoid cell; MΦ, macrophage; SP, surfactant protein; TSLP, thymic stromal lymphopoietin.

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of spores and antifungal immune-based killing [46–48] through phagolysosome acidification and production of reactive oxygen species (ROS) [43,49].

While in health AlvMΦ clear spores without eliciting significant inflammatory responses, they can also mediate significant downstream antifungal pro-inflammatory responses, by secreting large amounts of cytokines/chemokines (e.g., IL-1α, IL-1β, IL-6, and TNFα) upon activation of CLR (e.g., Dectin-1), Toll-like receptor (TLR) (e.g., TLR4), and inflammasome signalling pathways [50–53]. The precise factors that govern whether AlvMΦs balance spore clearance, with minimal inflammation or significant inflammatory responses when required remains unclear. Recent evidence has shed some light by showing that *Af* spores can elicit differential AlvMΦ responses, measured through secretion of CXCL2 (a neutrophil

chemoattractant). This heterogeneity has functional relevance as $CXCL2^+$ AlvMΦs were the dominant population that acquired spores and exhibited higher levels of metabolic activity, compared to $CXCL2^-$ counterparts which displayed a more anti-inflammatory profile (characterised by expression of IL-10 and complement C1q component) [54]. The authors also observed plasticity between these AlvMΦ subsets, as instillation of bacterial ligands pushed all AlvMΦ towards a $CXCL2^+$ phenotype. This heterogeneity of AlvMΦ responses to fungi, and the impact on allergic inflammation upon frequent exposure to *Af* spores, is an important question for future studies.

In their steady-state role, AlvMΦs can also induce regulatory T cells (Treg) generating a regulatory cytokine milieu (e.g., IL-10 and TGFβ) in the lung [55–59] (Fig 1). This has been attributed as preventing, rather than promoting, the development of allergic inflammatory disease [60,61]. For example, in murine asthma models, depletion of AlvMΦ (via clodronate liposomes) exacerbated inflammation, while adoptive transfer of AlvMΦ from naive mice reduced airway hyperresponsiveness [62]. In contrast, others suggest a role for AlvMΦs in contributing to the development of allergic inflammation via pathogenic IL-17 signalling, as well as hypersecretion of pro-inflammatory cytokines (TNF, IL-6, IFN-β, and CXCL2) [56,63]. These conflicting results could reflect functional heterogeneity of lung AlvMΦs, and divergent outcomes are dependent on the context and timing of allergen exposure. Surprisingly, given its importance in anti-spore responses, it is unclear whether AlvMΦ CLR-signalling is important in triggering allergic inflammation. Studies have suggested that $Dectin1^{-/-}$ mice have disrupted allergic inflammation in response to *Af* spores, although the relative role of MΦs was not assessed [64]. In contrast, TLR signalling on lung MΦs has been proposed to instigate allergic inflammatory responses against spores. Fungal protease cleavage of host fibrinogen (generating fibrinogen cleavage products, FCPs) activate MΦ via TLR4 and the macrophage integrin (Mac-1), boosting macrophage fungistatic responses and triggering allergic inflammation [65,66]. These FCPs can also activate other cell types such as epithelial cells, mast cells, and DCs [67,68]. While it is clear that AlvMΦs are crucial for spore clearance, much remains unknown about how this role changes, and the relative contribution of AlvMΦ in development of allergic inflammation against fungi.

The role of IntMΦ, in mediating allergic inflammatory responses to inhaled fungi, is largely unexplored. In the context of bacterial lung infection and lung fibrosis, IntMΦ have been suggested to exhibit both pro- and anti-inflammatory capabilities [69]. A recent study utilised single-cell RNA sequencing (scRNA-seq) on lung MΦs from mice infected with transgenic *M. tuberculosis* to identify the fitness of the bacterial cells inside the MΦ population. This revealed 3 IntMΦ populations induce different bacterial responses; a monocyte origin MΦ subset (identified via Nos2) induced bacterial stress responses, and anti-inflammatory MΦ (expressing Nrf2) subset caused bacterial sensing of environmental stress and a Zeb2-expressing MΦ subset appear to be involved in resolving inflammation [70]. Whether these IntMΦ populations are present and mediating similar responses in the lung following fungal exposure is an important point to address with future studies. When considering MΦ responses in the lung, it is important to reflect that upon inflammation, the AlvMΦ and IntMΦ tissue niches can be repopulated with MΦ of monocyte origin with markedly altered functional capabilities [26] (Fig 1). In the context of bacterial infection or viral infection during asthma, the replacement of AlvMΦs with monocyte-derived AlvMΦs resulted in markedly altered function, with impaired phagocytosis and responsiveness reducing allergic inflammation [71,72]. Conversely, murine asthma models have demonstrated monocyte-derived AlvMΦs display a higher inflammatory potential, driving development of allergic inflammation [60,73]. This suggests monocyte replacement of AlvMΦs could be heavily influenced by the inflammatory environment of the lung. For example, LPS has been found to expand IL-10 secretion of IntMΦs

reducing DC-mediated induction of allergic responses [74]. In the context of invasive aspergillosis, recruitment of $CCR2^+$ monocytes have been shown to be crucial for orchestrating clearance of fungal spores [75,76]. The relative role of monocytes in replacing MΦ populations and the potential impact this has in the context of fungal allergic inflammation remains unclear.

The role of dendritic cells in mediating, sustaining, and dampening fungal allergic inflammation

DCs, which bridge innate and adaptive immune responses, are essential in eliciting, sustaining, and dampening lung allergic inflammation [10,77]. In the lung, DCs acquire potential allergens and migrate to the draining lymph nodes (LNs) activating antigen specific T cell responses [78,79]. However, DCs can also be "tolerogenic" and halt the progression of allergic inflammation, predominately via promoting Tregs [80]. In the context of anti-fungal allergic inflammation, earlier literature suggested that differential uptake of *Af* conidia versus hyphae mediates DCs to elicit type 1 (IFNγ mediated) anti-fungal immunity or type 2 associated allergic inflammation, respectively [81]. Also it has been suggested that fungal exposure can cause DCs to dampen allergic inflammation by driving tolerogenic responses [82]. Yet, the precise mechanisms that DCs employ to initiate and/or dampen chronic fungal allergic inflammation are poorly understood. This is partially due to the fact that the DC population is heterogeneous, consisting of multiple separate subsets and each with differing functional capabilities. It has proved technically challenging to definitively identify these subsets, making manipulation of these different populations difficult. This section will explore the role that different DC subsets have in mediating antifungal immunity and chronic allergic inflammation.

Broadly, DCs are grouped into 2 major DC subsets, conventional DCs (cDCs) and plasmacytoid DCs (pDCs) [83]. Based on differences in development, marker expression and functional capabilities, cDCs can be further classified as cDC1s (dependent on BATF3 and IRF8) or cDC2s (dependent on IRF4 and KLF4) [84,85]. Lung resident cDC1s are potent at mediating $CD8^+$ T cell activation via cross presentation [86] and type 1 $CD4^+$ T cell responses against viral and bacterial pathogens [87,88]. In comparison, cDC2s have been proposed to directly mediate type 2 and type 17 $CD4^+$ T cell responses to a range of pathogens (including helminth parasites, fungi, and bacteria) [89,90]. Understanding the role of these subsets in inflammatory environments has proven challenging. For example during allergic inflammation, cDC2s can adopt an "inflammatory-like profile" (infDC2) and contribute to antiviral type 1 responses [91]. Others have proposed a presence of an "inflammatory" DC3 subset, which do not appear to express traditional markers of cDC1 and cDC2 cells but potentially can induce different types of T cell responses [92]. In addition to cDC subsets, recruited monocytes have been reported to develop into monocyte-derived DCs (moDCs) with capabilities of mediating inflammatory responses [93] (Fig 2). The complexity of accurately defining these subsets has made it difficult to understand the relative roles of these varying subsets in allergic inflammation.

Context-dependent role of pDCs in allergic inflammation. While pDCs are crucial for anti-viral immunity, they have also been proposed to have a protective role during invasive fungal disease [94]. CLR expression on human pDCs (e.g., Dectin-2) enables them to recognise *Af* and suppress hyphal growth through secretion of protective pro-inflammatory cytokines (IL-12, TNF-α, and IFN-α [95,96]) and release of extracellular traps [97]. This is underlined with a recent study that showed in response to *Af* spores, recruitment of pDCs via CXCL9 and CXCL10 enhances neutrophil spore killing [94].

On the observations in HDM- and OVA-induced asthma models, pDCs have been reported to dampen allergic inflammation (utilising depletion and cell transfer strategies) [98–100]. In

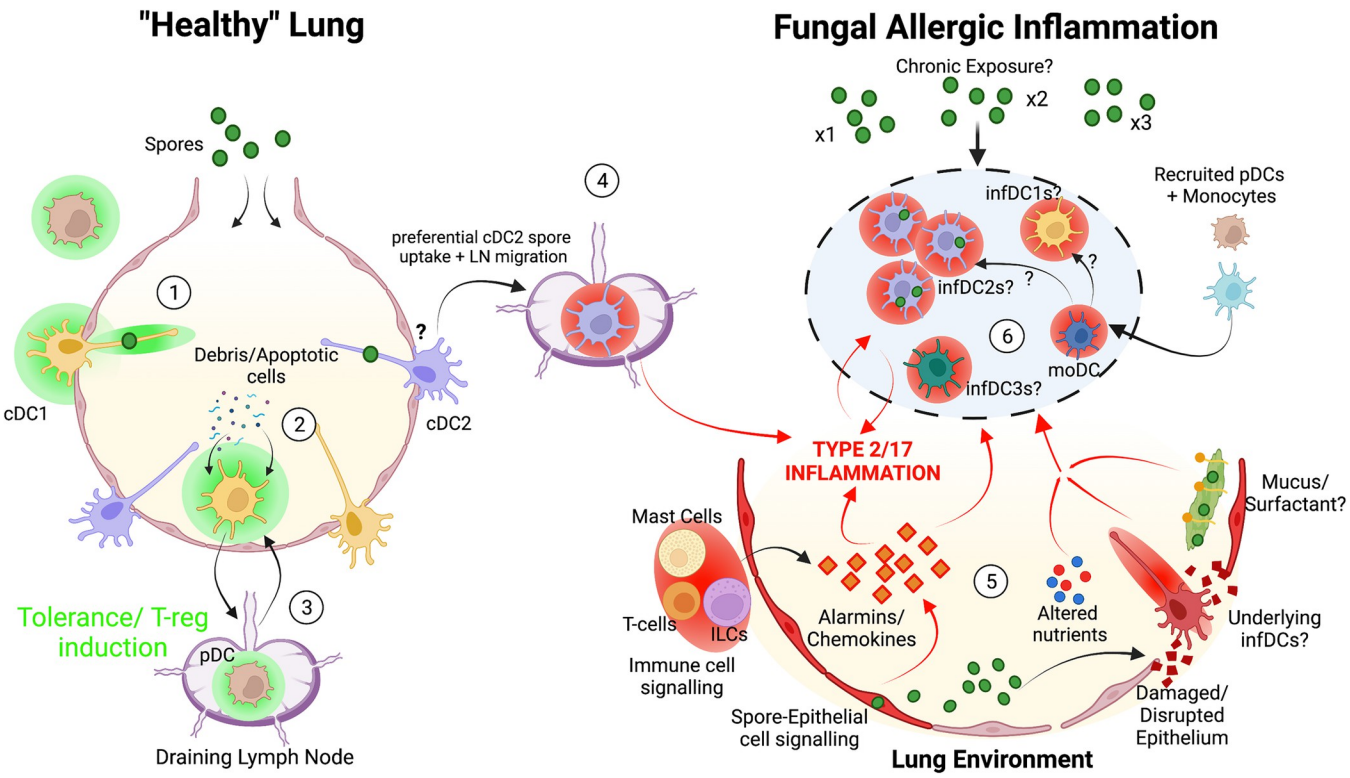

Fig 2. Understanding how DC induction of fungal allergic inflammation is shaped by the lung environment. In health (**left**), DCs predominantly reside in the tissue but can project dendrites into the airway to sample antigen. (**1**) As AlvMΦs predominantly clear inhaled spores [43], exposure of DCs to fungal antigen is minimal reducing potential for inflammatory responses. (**2**) DC subsets, especially cDC1s, assume housekeeping duties (e.g., clearance of apoptotic cells) maintaining a tolerogenic phenotype. (**3**) Upon migration to draining LN lung DCs, in concert with other subsets such as pDCs, induce T-reg generation further maintaining an immuno-regulatory lung environment. (**4**) Fungal allergic inflammation is initiated upon cDC2 acquisition of *Af* spores and migration to the draining LN where they can prime adaptive $CD4^+$ T cell responses (**right**). (**5**) While the precise mechanisms by which cDC2 mediate these responses to spores is unclear, the lung environment is known to directly influence this process. Fungal secretory products (including proteases) in the airway lumen can not only activate DCs directly, but also damage the epithelial barrier. This allows spores to move beyond the epithelial barrier and potentially activate cDC2s in the deeper underlying tissue. Furthermore, epithelial cell responses to fungi and/or barrier damage triggers the release of alarmins, chemokines, cytokines, and DAMPs (e.g., CCL2, IL-6, IL-33, and TSLP[173,] [174,175]), which can further activate DCs to promote allergic response. In addition, ILCs and mast cells (which can be activated by epithelial signals) further promote type 2 and type 17 cytokine which further conditions DCs to exacerbate allergic inflammation [68,145,180,184]. Other lung environmental factors such as altered nutrient availability and increased surfactant/ mucus concentrations [45,158] can further shape DC responses. (**6**) These features can lead to the formation of several inflammatory DC states (infDC1, infDC2, and infDC3) and possibly DCs differentiated from monocytes (moDCs) which further amplify and sustain fungal allergic inflammatory disease. Figures were created with BioRender.com. AlvMΦ, alveolar macrophage; CCL, chemokine ligand; DC, dendritic cell; IL, interleukin; moDC, monocyte-derived dendritic cell TSLP, thymic stromal lymphopoietin.

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the context of fungi, transfer of pDCs from *Af* sensitised mice successfully suppressed allergic inflammation via IL-10 secretion in recipient mice [101]. Furthermore, pDCs can mediate Treg generation leading to dampening of airway hyperreactivity [102]. In contrast, other studies have observed that pDC may exacerbate allergic inflammation [103]. For example, complement C3a component reduces pDC expression of PDL1 and PDL2 leading to the promotion of fungal allergic inflammation [104]. These discrepancies may suggest that the timing of pDC recruitment and activation, as well as subsequent signals from the lung environment upon their arrival govern their ability to direct fungal allergic disease.

Are cDC1s important in fungal allergic inflammation?. The cDC1 subset is crucial for initiating type 1 protective immune responses (e.g., targeting pathogens and cancer) and tissue homeostasis, via uptake and clearance of apoptotic cell antigens (e.g., via the CLR and DNGR1) [105,106]. In the context of allergic inflammation, the majority of studies suggest that cDC1s appear to dampen, rather than initiate, these responses [10,92] (Fig 2). This is

based on the fact that cDC1 deficient mice (e.g., CD103$^{-/-}$ and *Batf3*$^{-/-}$) mount greater allergic inflammation in both OVA and HDM based models [107,108]. This restraining allergic airway inflammation is mediated via cDC1 secretion of IL12 limiting type 2 inflammation [107].

In the context of fungal infection, there is limited research into the potential role of cDC1s in shaping allergic inflammation. Upon invasive fungal disease, cDC1s secrete IL-2 upon recognition of germinated fungi via the $Ca2^{+}$ calcineurin-NFAT pathway which is crucial for protective (not pathogenic) type 17 responses [109]. A recent study has highlighted that cDC1s expression of Nlrx1 (NOD9, a negative regulator of downstream NK-kB–mediated responses) limits ability to induce type 2 inflammation during invasive fungal disease [110]. In the context of other fungi, cDC1s can be dispensable (e.g., against *Candida albicans* in the intestine) [111] or essential (e.g., mediating type 1 protective responses to the dimorphic fungus *Histoplasma*) [112]. Therefore, these studies suggest that cDC1 have the potential to play some role in shaping type 1, 2, and 17 anti-*Af* responses (Fig 2). However, more investigations are needed to define the specific role of pulmonary cDC1s in a setting of chronic exposure to fungal spores and the ensuing allergic inflammation.

The role of cDC2 subsets in fungal allergic inflammation. Numerous studies have highlighted that cDC2s are crucial in mediating allergic inflammation [85,89]. Indeed, they are the major DC subset to acquire allergens from the airway (following HDM or OVA administration) and subsequently migrate to draining LNs [88,89]. Upon arrival, cDC2 can mediate type 2 [85,89], type 17 [113,114], and follicular (Tfh) CD4^{+} T cells [115] responses to allergens (e.g., HDM). This was established via transfers of cDC2s and use of cDC2 deficient mice (*Irf4*$^{fl/fl}$*Cd11c*^{cre} mice [85,116]) (Fig 2). In addition to the resident cDC2s during sensitisation, repeated allergen exposure can also mediate significant expansion and/or recruitment of lung cDC2s [117]. In the context of fungi elicited allergy, similar to MΦs, DCs (likely cDC2s, although not determined in study) have been shown to respond to FCPs and type 2 cytokine (IL-13) via up-regulation of PDL2, boosting their ability to mediate type 2 inflammation [68]). Interestingly, cDC2 were found to be crucial in mediating protective type 2 responses against *Cryptococcus* infection [118], while cDC2s have also been identified in eliciting protective type 17 responses in response to invasive *Af* infection [90]. Whether the same cDC2 population is important in driving over exuberant type 17 inflammation, in addition to type 2 responses, to fungi during allergic inflammation has not been fully explored.

Despite a demonstrated role for cDC2s in mediating allergic inflammation, the mechanism (s) that they utilise to orchestrate downstream inflammation is unclear. A range of cell surface molecules (e.g., CD40, CD86, Dectin-2, IFNAR, Mgl2, OX40L, PDL1, and PDL2), intracellular mediators (e.g., Mbd2 and Stat5) and secreted cytokines and chemokines (e.g., IL-10, IL-33, CCL17, and CCL22) have been suggested [10,68,113,119,120]. In particular, a recent study proposed that cDC2s expression of IFNAR1 and TNFR2 enables them to generate Tregs in steady state conditions and type 2 responses upon HDM challenge [121]. Further work suggested that IFNβ signalling can render cDC2s tolerogenic, ameliorating HDM allergic inflammation [122]. This suggests that, similar to the other DC subsets, the timing of stimuli may influence the mechanisms that cDC2 employ to mediate allergic inflammation.

In addition to cDC2s, moDCs (defined as CD64^{+}FcεR1^{+}) have been proposed to be important to induce pulmonary allergic inflammation. This was shown as moDCs were able to initiate allergic inflammation in the absence of lung cDC subsets [89]. Additionally, transfer of moDCs induced type 2 allergic inflammation [123], indicating moDCs are important to induce pulmonary allergic inflammation Others have proposed that moDCs are the main mediators of the "effector" stage of the allergic response by producing the chemokine milieu responsible for recruiting eosinophils, effector T cells and mononuclear cells (via secretion of CCL2, CCL4, CCL9, and CCL24) to the lungs [89]. In response to invasive disease, moDCs

have been reported to mediate fungal killing as well as secreting TNF and IL12p70 stimulating neutrophil-mediated fungal clearance [75]. Also, moDC secretion of CXCL9/10 appears important to the recruitment of pDCs, with this crosstalk crucial in mediating immunity to invasive aspergillus infection [124]. Importantly, moDC secretion of TNFα has been proposed to mediate type 17 inflammation following chronic *Af* exposure [125]. This suggests that moDCs may play a crucial role either directly, or in collaboration with other DC subsets, to mediate fungal allergic inflammation (Fig 2). However, when considering the potential role of moDCs, it is important to reflect on recent studies that have identified previously unrecognised subsets like infDC2s and DC3s [126,127]. Indeed, formation of these subsets are likely dependent on the inflammatory context [91,128,129]. Definitively, separating these populations from cDC2 and moDC subsets is challenging. Indeed, scRNA-seq studies suggest that previous strategies to identify moDCs actually contain infDC2s that also express higher levels of CCR2 [91,130] and its these and not "moDCs" that mediate allergic inflammation[91]. Therefore, the relative role for infDC2s, DC3s and moDCs, and the mechanism(s) they employ in mediating fungal allergic inflammation is an important question for future studies to tackle.

How the lung environment governs myeloid cells in mediating fungal allergic disease

It has become clear that tissue microenvironments are critical in shaping the development and functional capacity of MΦs and DCs. Indeed, the role of the lung environment on shaping MΦ function has been well explored [34,37,131,132], and recent work is now underlining the importance of the environmental influence on shaping DC responses [36,133]. Moreover, many aspects of the lung environment change during chronic lung inflammation, and it is important to consider the differing impacts these may have on governing how MΦs and DCs mediate antifungal allergic disease.

Alteration of secretory mediators in the lung environment. One of the major changes in the lung environment upon the onset of allergic inflammation is the increase in type 2 cytokines. These can trigger "alternative" M(IL-4) activation of MΦ, associated with enhancing fibrosis through aberrant wound repair responses [134]. These MΦ display elevated expression of arginase-1 (diverting L-arginine metabolism away from nitric oxide production) and chitinase-like proteins [135–138]. In addition to type 2 cytokine, others have suggested that surfactant protein A, uptake of apoptotic cells via TAM receptors, and chitin (a crucial constituent of the fungal cell wall) can mediate M(IL-4) activity [139–141] (Fig 1). The functional impact of these M(IL-4) MΦ on fungal allergic inflammation is unclear, but it has been proposed to boost MΦ ability to clear *Af* spores while others have suggested these exacerbate responses [142,143]. Furthermore, AlvMΦ in the lung airway are less able to respond to type 2 cytokine compared to IntMΦ, which reside in the tissue [144]. The impact of these environmental cytokine and fungal signals on MΦ subset function during allergic inflammation is unknown.

Type 2 cytokine signals are also known to be crucial in shaping DC maturation and functional capabilities (Fig 2), e.g., IL-13 and IL-33 released by ILC2s has been proposed to enhance cDC2 generation of type 2 responses in the lung and skin [145,146]. A recent study has further highlighted this by demonstrating that IL-13 in the skin environment shapes cDC2s to mediate type 2 responses, and if absent DCs, elicit a type 17 response instead [147]. The impact that differing lung cytokine environments, induced during allergic inflammation, have on governing DC subset development and capacity to respond in the context of antifungal inflammation is an important question for further research.

Another critical change to the lung environment during allergic inflammation is increased secretion of mucus and surfactant into the airway [148–154]. Indeed, mucus plugging is

prominent in cases of severe asthma [155,156]. A major constituent of mucus are polymeric mucin glycoproteins (e.g., Muc5b and Muc5ac) that can directly interact with immune cells as evident by the fact that Muc5b-deficient mice are susceptible to bacterial infection due to impaired MΦ responses [157]. Furthermore, Muc5ac has been proposed to be important for mediating allergic airway hyperreactivity against *Af* extract [158]. Strikingly, FleA protein expression on *Af* spore surface readily binds with mucin glycoproteins enhancing MΦ spore uptake [159], while surfactant protein D, (elevated in allergic diseases) boosts fungal spore uptake by MΦs [45] (Fig 1). Recent work demonstrates that intestinal mucin proteins (Muc2) shape DC activation and cDC2 development [160,161] (Fig 2). Additionally, seminal work has shown that spontaneous protein crystallisation (Charcot–Leyden crystals, CLCs), which can form in the airways of asthma patients, have the potential to drive cDC2s to mediate allergic inflammatory responses [162]. The relative role of mucus and surfactant in shaping MΦ and DC allergic inflammation in response to fungi remains poorly understood.

Metabolic activity within the lung environment. The metabolic state of MΦ and DC populations greatly influences their functional capabilities. Both cell types can utilise distinct metabolic pathways for energy production which governs their downstream activity, impacting chronic lung disease [163,164]. For example, tolerogenic DCs and M(IL-4) MΦs rely on mitochondrial respiratory chain and fatty acid oxidation, whereas inflammatory DCs and MΦs rapidly up-regulate glycolytic activity [163,165,166]. Indeed, fungal stimulation of both MΦ and DCs can lead to a rapid transition from utilising one metabolic pathway to another (e.g., from fatty acid oxidation to glycolysis) as the main energy source for cellular activity [167–169]. This can also be regulated by the tissue environment, with AlvMΦs or transferred MΦs that reside in the airway exhibiting dampened glycolytic activity reducing their potential to respond to type 2 inflammation [144]. While the precise factors in the airway that cause this are unclear, an important aspect could be the amount and/or type of nutrients in the lung which are altered in many chronic inflammatory lung disease [170]. Therefore, DC and MΦ metabolic activity that is possibly regulated by nutrient availability maybe critical in governing the downstream fungal allergic inflammation (Figs 1 and 2).

Lung epithelial and innate cell crosstalk. The airway epithelial barrier itself has a crucial role in governing MΦ and DCs responses [10]. Proteases secreted from germinating *Af* spores (e.g., Aspf13 and Alp-1) disrupts the epithelial barrier, increasing permeability [171,172]. This enables fungal allergens to cross the disrupted epithelial barrier into the lung tissue and stimulates calcium flux (via calcineurin) within epithelial cells further activating DCs and IntMΦs [173]. This suggests that fungi are more likely to be exposed to pro-inflammatory cells (e.g., IntMΦ and inflammatory DCs) rather than normal regulatory AlvMΦs and DCs, which reside in the airway, and may trigger and sustain allergic inflammation (Figs 1 and 2). In addition to this, epithelial cells can release various pro-allergy mediators such as IL-33, TSLP, IL-17, IL-6, IL-8, IL-25, and CCL2 [73,174–176] and damage-associated molecules such as uric acid, calcium, and calcineurin [173,177], all of which facilitates crosstalk that can trigger the activation of lung resident MΦ [73,178] and DCs [146,179] to promote allergic inflammatory responses (Figs 1 and 2). These epithelial-mediated signals (e.g., IL-33) can boost ILC2-mediated responses, leading to the secretion of type 2 cytokines and triggering both MΦ and DC to induce allergic inflammation [180,181] (Figs 1 and 2). Despite the evidence of epithelial crosstalk with lung MΦs, DCs and ILCs, the relative importance of these interactions in governing fungal allergic inflammation is yet to be fully explored. In addition to epithelial cells, endothelial cell recognition of *Af*, via the CLR MelLEC, has been shown to promote allergic inflammation. Although what impact endothelial cell recognition of spores has on MΦ and DC induction of fungal allergic inflammation is unclear. Fungal material can also promote a type 2 cytokine environment by inducing mast cells to secrete IL-13 [68] and activated mast cells can

trigger AlvMΦs to promote allergic inflammation [63]. Therefore, it is clear that numerous cell types in the lung can "interact" with MΦ and DC populations and alter downstream inflammatory responses in response to fungi. Yet, in order to build an accurate model of on the pathogenesis of allergic bronchopulmonary mycoses, further work is needed to understand which of these cellular interactions are critical in governing MΦ and DC antifungal activity.

Concluding remarks

In summary, the recent advances in single cell approaches have resulted in vast improvements in our understanding of how MΦ and DC subsets govern inflammation that underpins allergic disease. This review has discussed the roles of MΦ and DC subsets in fungal allergic inflammation and highlighted several areas where our current understanding is limited. Future important questions remain unanswered. For example, this review has mainly considered the impact of *Af* spore exposure only on MΦ and DC responses. Whereas in the majority of cases, individuals will be exposed to *Af* in combination with other well-known allergens (e.g., HDM) and even other fungi which can promote allergic inflammation [182]. Understanding this complexity and defining the dominant allergen signals could greatly inform future diagnostic approaches. Finally, in addition to considering the host lung environmental factors we highlighted, it is clear that the micro- and myco-biome in the airways and distal sites can profoundly influence immune responses (e.g., the gut–lung and skin–lung axis). How these wider diverse microbial interactions fit with intrinsic cues and epithelial innate immune cell crosstalk in the lung microenvironment, and how they together influence MΦ and DC responses upon fungal spore exposure, is an additional challenge for future research. Ultimately a better understanding of how MΦs and DCs respond upon fungal exposure in the wider context of the lung environment may yield novel therapeutic strategies to combat the growing problem of fungal allergic disease.

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