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HIGHLIGHTS

Basic

REVIEW

# Tissue-specific antigen-presenting cells contribute to distinct phenotypes of allergy

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**Antigen-presenting cells (APCs) are critical cells bridging innate and adaptive immune responses by taking up, processing, and presenting antigens to naïve T cells. At steady state, APCs thus control both tissue homeostasis and the induction of tolerance. In allergies however, APCs drive a Th2-biased immune response that is directed against otherwise harmless antigens from the environment. The main types of APCs involved in the induction of allergy are dendritic cells, monocytes, and macrophages. However, these cell types can be further divided into local, tissue-specific populations that differ in their phenotype, migratory capacity, T-cell activating potential, and production of effector molecules. Understanding if distinct populations of APCs contribute to either tissue-specific immune tolerance, allergen sensitization, or allergic inflammation will allow us to better understand disease pathology and develop targeted treatment options for different stages of allergic disease. Therefore, this review describes the main characteristics, phenotypes, and effector molecules of the APCs involved in the induction of allergen-specific Th2 responses in affected barrier sites, such as the skin, nose, lung, and gastrointestinal tract. Furthermore, we highlight open questions that remain to be addressed to fully understand the contribution of different APCs to allergic disease.**

**Keywords:** antigen presentation · allergy · dendritic cells · macrophages · monocytes

## Introduction

Antigen-presenting cells (APCs) are the critical link bridging innate and adaptive immune responses. To do so, APCs in barrier tissues constantly screen their surroundings for danger-associated molecular patterns and take up antigens which are intracellularly processed into short peptides and presented via MHC molecules to naïve T cells in the draining lymph nodes [1]. At the steady state, APCs maintain tissue homeostasis by presenting self and innocuous antigens in a tolerogenic context, while the activation of APCs under inflammatory conditions results in priming of distinct effector T-cell populations through co-stimulatory molecules on the cell surface, and soluble cytokine and chemokine signaling.

In the context of allergies, foreign antigens are recognized as pathogenic and elicit type 2 immune responses, which are locally modulated and affect allergen-specific T-cell activation, differentiation, and proliferation [2]. Many of these mechanisms are controlled by APCs, especially by dendritic cells (DCs), monocytes, and macrophages. These populations differ in their ontogeny, activation status, molecular phenotype, migratory capacity, as

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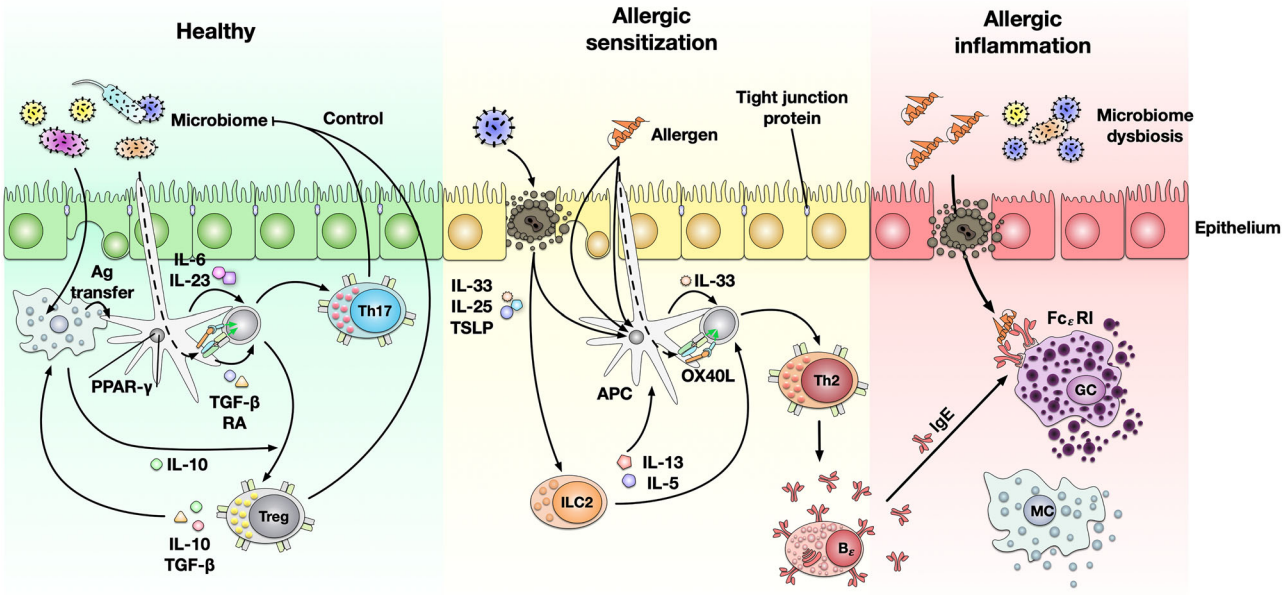


**Figure 1.** APC involvement in tissue homeostasis and the development of allergies. The main types of professional APCs are DCs and macrophages. Upon antigen uptake (either direct uptake of antigen uptake via trans-epithelial sampling, or indirect antigen transport over the epithelial barrier via M-cells), APCs migrate to draining lymphoid organs to activate naïve, antigen-specific T cells. For the maintenance of antigen-specific tolerance, DCs contribute to the induction of Foxp3$^+$ Tregs via secretion of TGF-β and retinoic acid but are also able to drive Th17 responses via the secretion of IL-6 and IL-23. In the intestine, intestinal macrophages are highly phagocytic but only express low levels of TLRs and do not secrete pro-inflammatory cytokines after exposure to different bacterial signals. Instead, they locally promote the IL-10-dependent induction, maintenance, and expansion of Foxp3$^+$ Tregs. Furthermore, intestinal macrophages transfer gut lumen antigens (transported over the intestinal barrier via M cells) to migratory CD103$^+$ DC via a connexin 43-dependent mechanism that requires membrane transfer. Together Tregs and Th17 cells control the local microbiome and prevent detrimental immune responses against harmless microorganisms. During allergic sensitization, allergens can either directly disrupt epithelial integrity (e.g., by protease activity that degrades tight junction proteins), be taken up via trans-epithelial sampling of APCs, or enter the sterile inside of our body via damaged tissues. Epithelial cells are able to signal these events via the release of damage- and danger-associated molecules (IL-25, IL-33, TLSP) to recruit and activate local immune cells. Subsequent antigen uptake by local DCs results in the allergen-specific differentiation of Th2 cells via secretion of epithelial-derived IL-33 and the surface expression of OX40L. Allergen-specific Th2 cells in turn promote the activation and differentiation of allergen-specific IgE-producing plasma cells. The produced IgE binds to the high-affinity IgE receptor FcεRI on mast cells (and basophils). Upon allergen-contact IgE-sensitized mast cells are activated, degranulate, and promote allergic inflammation. Allergic inflammation then contributes to a disruption of epithelial integrity and structure, loss of tight junction proteins, nausea (intestine), itch (skin) and tightened airways (lung), and a dysbiosis of the local microbiome. Abbreviations: Ag: antigen, APC: antigen-presenting cell, FcεRI: high-affinity IgE receptor, GC: granulocyte, MC: macrophage, OX40L: OX40 ligand, PPAR-γ: peroxisome proliferator-activated receptor gamma, RA: retinoic acid, TGF-β: transforming growth factor beta, TIM-4: T-cell immunoglobulin and mucin 4, TSLP: thymic stromal lymphopoietin.

well as T-cell activation potential, and different developmental lineages and tissue-specific subsets have been defined [3, 4]. Tissue-specific APCs also play a role in allergen sensitization and have been implicated in the induction of allergen-specific Th2 responses in the skin, nose, lung, and gastrointestinal tract (GIT) (Fig. 1).

## APC populations shape allergic responses in the skin

The skin serves as a physical and immunological barrier against pathogen invasion. It is composed of an outer epithelial layer, the epidermis, which is formed by several layers of dead and differentiating keratinocytes, and an inner dermal layer comprising of stromal cells and fibroblasts. Within these layers of the skin, different populations of APCs serve as sentinels and a first line of defense against invading pathogens [5].

The epidermis is populated by Langerhans cells (LCs), a unique type of APCs that shares properties of both DCs and macrophages [6]. LCs control local immune tolerance and are locally maintained through TGFβ and IL-34 signaling [7, 8]. Upon activation, LCs migrate to the dermis and the draining LN [9]. Although LCs are poor APCs, recent data have shown that LCs can pass antigens to dermal DC populationsto indirectly influence T cell priming [10]. In the context of skin allergies, LCs display an activated phenotype in lesional skin of atopic dermatitis (AD) patients, but fail to activate T-cell responses *in situ* [11], a phenomenon also observed in murine models of skin allergy [12]. In the context of contact hypersensitivity, LCs have however shown a protective effect. Mice lacking epidermal LCs develop exaggerated contact-hypersensitivity responses and LC-derived IL-10 is necessary for the induction of regulatory T cells (Treg) and the suppression of inflammatory CD4 and CD8 T-cell responses [13].

In both mice and humans, the dermis contains conventional DCs, including IRF8-dependent DC1s and IRF4-dependent DC2s,

which in mice can further be distinguished into high- or low-expressing CD11b DC2 [14, 15]. DC2s are the most abundant DC populations in healthy skin of mice and humans [16], while monocytes increase in number during inflammation [17]. In healthy skin, topical antigens can reach the dermal layer via the hair follicles where, in the steady state, they are taken up by IRF4-dependent dermal DC2 populations to induce Treg responses and peripheral tolerance [18]. In disrupted skin particulate antigens can directly reach the dermis and are taken up by DC2s, which prime a variety of antigen-specific CD4 T-cell responses in the draining LN [19].

In the context of skin allergy and AD, DCs upregulate CCL17 and CCL18 [20]. Furthermore, TSLP-receptor is upregulated, which has been linked to allergic Th2 priming in several conditions [21]. DC2s, and in particular CD301b- and PDL2-expressing DC2 populations, are essential for priming Th2 responses in murine models of skin allergy [22, 23]. Dermal CD11b-low DC2s furthermore display extensive transcriptional changes after allergen immunization in murine Th2 models, including the upregulation of CCL17 and CCL22 [24, 25]. This skin-specific population of DC2 develops in response to homeostatic IL-13 signaling in healthy skin, depends on the transcription factors KLF4 and STAT6 expression [15, 26], and is highly responsive to TSLP signaling [27]. TLSP furthermore induces the expression of OX40L in murine and human DC2s, which is thought to promote Th2 and T follicular responses [28, 29]. Upregulation of Notch signaling pathways and the interaction with basophils have also been observed and linked to T-cell priming and Th2 responses [30, 31]. While similar molecular signatures are enriched in skin DCs from AD patients, other signatures are linked to a dysfunctional microbiome and an outgrowth of *Staphylococcus aureus* [32]. CCL18 expression by human DC has, for example, been linked to the exposure of *S. aureus* antigens and correlates with reduced IFN-γ receptor expression and attenuated IFN-γ responses by DC in patients with AD [33, 34].

During chronic AD, macrophages and monocytes also contribute to disease, although it is unclear if they are recruited by the type 2 inflammatory signature or by signals induced by the infiltrating microbiome. Monocytes are recruited to inflamed skin by keratinocytes expressing MCP-1, which interacts with CCR2 [35]. While this recruitment is usually restricted to the dermis, monocytes can also reach the epidermis during skin injury [36], but it remains unclear if this also occurs in AD. Monocyte- and fetal-derived macrophages, which reside in the dermis [37], further display an alternatively activated anti-inflammatory phenotype in AD, which contributes to itch, fibrosis, inflammation, and microbial dysbiosis [38].

## APC populations shaping allergic responses in the nose

The nose is the site of entry for virtually all inhaled antigens, including allergens. The nasal mucosa, therefore, serves as another important immunological barrier. Two main types of professional APCs (DCs and macrophages) are present in the nasal mucosa and are found in the subepithelium [39, 40], the lamina propria [41], and in nasal-associated lymphoid tissue (NALT) [42, 43].

In contrast to rodents, where DCs are the most abundant APCs within the nasal epithelium, a detailed confocal microscopic analysis of the human nasal mucosa revealed mature macrophages as the most dominant APCs [39]. Human resident APCs consist of MHC II$^+$ CD68$^+$ macrophages and DCs, which can further be divided into BDCA1$^+$ DC1s and BDCA3$^+$ DC2s, as well as a small number of plasmacytoid DC (pDC) [39, 44]. In the mouse, resident APCs include DC, pDC, and macrophages, and nasal DC can further be divided into three subpopulations based on their expression of CD103 and CD11b, which is similar to DC populations found in the intestine [43, 45].

Nasal epithelial APCs form dense subepithelial networks, similar to the LC network observed in the epidermis of the skin [39]. In early work, nasal resident DCs were indeed thought to be very similar to LC and characterized by their expression of CD1a, CD207/langerin, and Birbeck granules [46]. More recent findings, however, suggest that the majority of nasal epithelial DC express EpCAM, but only few co-express the LC-specific markers CD1a and CD207 [39]. E-cadherin and EpCAM expression are thought to support the interaction of DC with epithelial cells and facilitate the formation of long cytoplasmic protrusions that penetrate tight junctions and enable the sampling of antigens from the nasal lumen [43, 47]. Similarly, macrophages located at the basement membrane of the human nasal epithelium can also form long protrusions that penetrate the epithelium, suggesting a similar role in antigen sampling [39].

The majority of nasal DCs in mice can be found in the NALT, organized lymphoid structures located bilaterally between the upper soft palate and the opening of the nasopharyngeal duct [47, 48]. NALTs resemble intestinal Peyer's patches [49], contain distinct T cell areas and B cell follicles, and are lined by squamous epithelium with antigen-sampling microfold cells (M cells) [50]. Immunohistochemical staining demonstrates that different phenotypes of DCs are present in different NALT substructures. Nasal DCs in the crypt are immature and mainly make contact with B cells, squamous epithelial DC resemble LCs and might be involved in antigen-removal, while DCs in the T-cell zone have an activated phenotype [51]. Within the NALT vasculature, perivascular DCs have also been described and can enter the NALT via high endothelial venules [43], although it remains unclear if they belong to the DC or monocyte lineage [52].

Functionally, nasal DCs are essential and sufficient for priming CD4$^+$ T cells [53]. Apart from their role in allergic sensitization, nasal DCs also play a key role during recall responses against seasonal allergens. Upon inhalation of allergens, resting nasal DCs become activated and acquire a migratory phenotype. Activation of DCs can either occur directly via triggering of pattern recognition receptors by PAMPs and Damage associated molecular patterns (DAMPs) linked to allergen carriers, or indirectly, via alarmins secreted by activated epithelial cells. Mature nasal DCs migrate to the cervical lymph nodes via interaction of CCR7 with a CCL21 gradient and prime naïve T cells (allergic sensitization), or

migrate into the NALT and inflamed tissue by means of FLT3 ligand, PAMP, or chemokine signaling to interact with local effector cells (allergic effector phase) [43, 54].

Tissue alarmins, such as TSLP [55] and IL-33 [56], ILC2-derived IL-13 [57], and Notch ligands [58], shape the phenotype of allergen-activated nasal DCs and lead to the induction of allergen-specific Th2 and Th17 cells [59]. Similar to mechanisms in the skin, TSLP acts by increasing the expression of OX40L in DCs, which favors Th2 priming [60], while indolamine-2,3-dioxygenase (IDO)-expressing, tolerogenic DCs are potent inducers of Tregs [61]. PPAR-y-signaling can also have a tolerogenic effect, which has been observed in allergic rhinitis patients [62], although PPAR-y-signaling might also act independently of APCs [63, 64]. In contrast, TLR4 engagement on DCs preceding an allergen exposure is presumed to limit Th2 differentiation by skewing the T-cell differentiation toward Th1 [65], with TLR-agonistic adjuvants now being used in clinical trials [66]. Chronic allergen exposure, however, can induce autophagy of nasal DCs, which in murine models promotes excessive Th2-mediated inflammation and can be reversed by using autophagy inhibitors [67].

## APC populations shaping allergic responses in the lung

Within the lung, DCs and macrophages play important roles in the maintenance of tolerance to innocuous environmental antigens and the sensitization of allergic responses [68]. In steady-state conditions, both DC1 and DC2 are found in close proximity to the airways and sample antigens via probing through the epithelial layer [69–71]. Alveolar macrophages, in contrast to interstitial macrophages, have a limited role in antigen presentation and mostly maintain homeostasis and protection of the lung lumen [72, 73].

Three different populations of DCs have been implicated in the induction of pulmonary Th2 responses. $CD103^+$ DCs have been shown to initiate Th2 responses [74], but also restrain allergic airway inflammation through the production of IL-12 [75] and the de novo differentiation of Tregs through mechanisms controlled by the transcription factor PPAR-$\gamma$ and the production of retinoic acid [76, 77]. While $CD103^+$ DCs are mostly associated with the DC1 lineage, CD103 expression has also been reported on DC2 [78], making the use of DC1- and DC2-specific markers (such as XCR1 and Sirpa, respectively) necessary to correctly interpret DC subset specific functions [4]. Additional levels of heterogeneity within these DC populations have been described using single-cell RNA sequencing tools, opening new possibilities to discover additional tissue-specific populations and novel functional mechanisms [79–81].

In the lung, human and murine DC2 are essential for allergen-induced Th2 and Th17 responses [82–84], which can be mediated by dectin-2-dependent mechanisms [85]. Lung DC2 function is enhanced by CSF-2 and TSLP, which promotes DCs recruitment to the lung and the expression of Th2-promoting OX40L, respectively [60, 77]. While additional subsets of lung DC2 have recently been described in mice and humans [86], their contribution toward allergen-induced Th2 and Th17 responses remains to be investigated.

In addition, monocyte-derived DCs (also known as moDC or inflammatory DC) expressing Ly6C, CD64, FcεR, and C5aR1 are recruited to the murine lung in large numbers after allergen exposure, which requires CCL2/CCR2 signaling and the formyl peptide receptor 2 [83]. Recent studies have found that murine DC2s acquire a similar moDC phenotype, but in contrast to moDC in the lung are the sole contributors to T-cell priming in the mediastinal LN [80]. Therefore, a regional distribution of type 2 associated APCs could be observed, with moDC supporting the activation of T cells, eosinophils, and monocytes within the lung via cytokines and chemokines such as CCL2, CCL4, CCL7, CCL9, CCL12, and CCL24 [83], while DC2 primed de novo Th2 cells in the LN [80]. Interestingly, murine monocytes can also differentiate into pro-inflammatory COX-2-expressing $MHCII^+$ interstitial macrophages in the lung, which further contribute to allergic inflammation [73, 87], suggesting that monocytes can influence allergic responses both in the short and long term.

## APC populations shaping allergic responses in the Gastrointestinal tract

In intestinal homeostasis, DCs and macrophages establish a delicate balance between tolerance toward molecules derived from food, the commensal microbiome and appropriate responsiveness toward invading pathogens. Intestinal DCs can be classified into $CD103^+$ DC1, $CD103^+$ DC2, and $CD103^-$ DC2 [88], while macrophages can be identified as $F4/80^+CD103^-CX3CR1^+CD64^+$ cells that do not migrate upon stimulation [89, 90]. At the steady state, murine intestinal macrophages are highly phagocytic but only express low levels of TLRs and do not secrete pro-inflammatory cytokines such as IL-1β, IL-6, IL-12, IL-23, or TNF-α after exposure to different bacterial signals [91, 92]. Instead, they promote the IL-10-dependent induction, maintenance, and expansion of $Foxp3^+$ Tregs both *in vitro* and *in vivo* [93]. Moreover, murine $CX3CR1^+$ macrophages contribute to Treg-generation and oral tolerance by transferring gut lumen antigens to migratory $CD103^+$ DC via a connexin 43-dependent mechanism requiring membrane transfer [94]. During chronic intestinal inflammation, macrophages change their profile and express high levels of TLRs, co-stimulatory molecules, and inflammatory receptors [95, 96]. Intestinal macrophages from patients with inflammatory bowel disease also produce large quantities of TNF-α and other proinflammatory cytokines [73, 97, 98], indicating that intestinal macrophages can possess anti- or pro-inflammatory phenotypes. However, the relevance of either of these phenotypes in the induction and maintenance of allergic inflammation in the GIT remain largely unclear (reviewed in [99]).

In contrast, murine DCs have clearly been linked to intestinal allergy. Intestinal DCs express CCR7 and are highly migratory

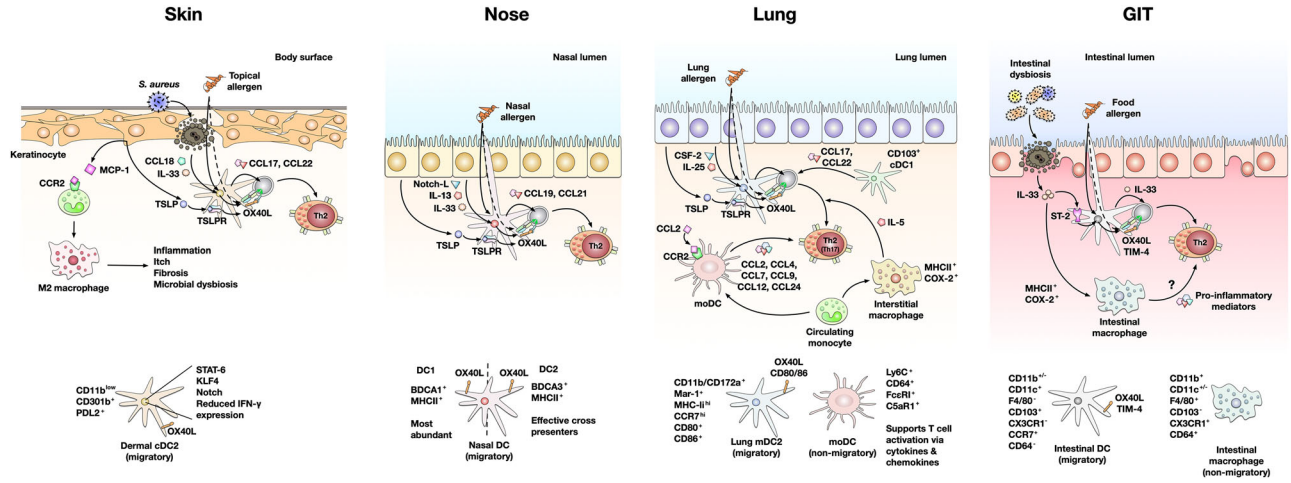


**Figure 2.** Tissue-specific mechanisms involved in the local induction of allergen-specific Th2 responses. In the skin, allergen uptake by dermal DC2s (including skin specific CD11b-low DC2) in the context of polarizing cytokines and chemokines (CCL-18, IL-33, TSLP) results in the activation of allergen-specific T cells via CCL17, CCL22, and OX40L. Furthermore, MCP-1 released from keratinocytes promotes the differentiation of M2 macrophages from monocytes, which in turn contribute to allergic inflammation, itching, fibrosis, and microbial dysbiosis. In the nose, nasal allergens are either taken up by trans-epithelial sampling of nasal migratory DC1 and DC2 or cross the epithelial barrier independently. In the presence of epithelial-derived factors such as Notch-L, IL-13, IL-33, or TSLP, these cells promote the activation of allergen-specific T cells via CCL19, CCL21, and OX40L. Effector T cells homing to the lung via the chemokines CCL17 and CCL22 (produced by $CD103^+$ DC1s) are activated by $CD11c^+$ DC2 subsets that express OX40L and the costimulatory molecules CD80/86. After allergen exposure, moDCs are CCL2/CCR2-dependently recruited to the lung in large numbers to orchestrate local inflammatory responses. While being dispensable for allergic sensitization, moDCs support activation of the recruited T cells, eosinophils, and monocytes via secretion of cytokines and chemokines. Also, interstitial macrophages differentiating from circulating monocytes contribute to allergic inflammation via the secretion of IL-5. Finally, in the gastrointestinal tract, allergen sampling by intestinal DC or direct crossing of allergens through a damaged epithelial barrier promotes the IL33-, OX40L-, and TIM-4-dependent differentiation of allergen-specific Th2 cells. Intestinal dysbiosis further contributes to the activation of Th2-promoting APCs in the GIT. Currently, the contribution of intestinal macrophages to the activation of allergen-specific Th2 cells is not clear. The phenotypes, transcription factors, surface molecules, and main characteristics of the different tissue-specific APCs relevant in the induction of Th2 responses are indicated in the lower half of the figure. Abbreviations: BDCA(1/3): blood dendritic cell antigen (1/3), CCL: C-C chemokine ligand, CCR2: C-C motif chemokine receptor type 2, moDC: monocyte derived DC, OX40L: OX40 ligand, GIT: gastrointestinal tract, KLF4: Krüppel-like factor 4, Mar-1: maresin 1, MCP-1: mast cell chemotactic protein 1, Notch-l: Notch ligand, PDL2: programmed cell death 1 ligand 2, STAT-3: signal transducer and activator of transcription 3, TSLP: thymic stromal lymphopoietin, TSLPR: TSLP receptor, TIM-4 T-cell immunoglobulin and mucin 4, Xcr1: X-C motif chemokine receptor 1.

[100]. At steady state, they contribute to $Foxp3^+$ Treg-induction via TGF-β and retinoic acid secretion [101], but are also able to respond to pathogens and can drive Th17 responses in the lamina propria via the secretion of IL-6 and IL-23 [102]. While CD103-expression clearly distinguishes two distinct populations of murine DC2 in the intestine and mesenteric LN [103], further subsets of $CD103^+CD11b^+$ DCs have recently been identified within the epithelium [104].

Within the GIT, food allergy is the most common allergic phenotype and arises from a failure of tolerance toward ingested food antigens resulting in IgE-mediated, local inflammation in the GIT with symptoms like nausea, regurgitation, and diarrhea. In food allergic patients, Treg induction is compromised, resulting in the generation of antigen-specific Th2 cells that drive both IgE class switching and expansion of allergic effector cells [105]. Sensitization toward food allergens can occur via the GIT, skin, and less commonly via the respiratory tract [106, 107]. Intestinal DCs either directly sample antigens from the intestinal lumen or via M cells within Peyer's patches and present those antigens to naive T cells within the Peyer's patches or the mesenteric LN [108].

Changes among intestinal DCs are readily observed during GIT allergic models (such as peanut extract and cholera toxin treatment) and result in increased numbers of inflammatory $CD11b^+$ DCs and reduced numbers of immune-regulatory $CD103^+$ DCs [109]. In addition, different populations of murine $CD11b^+$ DC2 and ILC have been described throughout the GIT [4, 110, 111], which might impact local Th2 induction and a distinct pathology between the small intestine and colon. The mechanisms of GIT allergy induction follow similar pathways as those observed in the lung and skin. Oral feeding of peanut or mite allergen plus cholera toxin was shown to trigger IL-33 release from epithelial cells, which induced OX40L expression on $CD103^+$ DCs, leading to Th2 priming [112]. Moreover, in murine models of food allergy, oral feeding of cholera toxin induced both DC maturation and Th2 differentiation via upregulation of OX40L in mesenteric LN [113]. TIM-4 expression on intestinal DCs was upregulated in food allergy models driven by staphylococcal enterotoxin B [114] or cholera toxin [115] and might represent a specialized molecular pathway that enhances Th2 polarization within the intestine (Fig. 2).

## Conclusions and future perspectives

APCs are a highly diverse population of cells that share certain functional and molecular properties, but also fulfill highly

specialized functions in their respective tissues. Distinct populations of APCs thus impact allergic sensitization and chronic allergic inflammation. In most contexts, DC2s promote Th2 priming and allergen sensitization. However, unique signals from the microenvironment are necessary to activate DC2 in a Th2-promoting manner, and together with responses from other APCs lead to highly context- and tissue-specific allergic phenotypes.

In the murine skin, two unique populations of DCs exist, which differentially contribute to allergies. Epidermal LCs, which usually promote tolerance, display an activated phenotype and an impaired tolerogenic ability during skin allergy in both mice and humans, while dermal CD11b-low DC2 promote enhanced type 2 immune responses, strongly respond to TSLP and produce high amounts of CCL17. Within the airways, nasal EpCAM+ DCs can be activated by allergy-associated alarmins, ILC2-derived IL-13, or Notch ligands and prime local $CD4^+$ T cells against seasonal allergens via OX40L. In the lung, DC2s are essential for allergen-induced Th2 and Th17 responses via dectin-2-dependent mechanisms, while moDCs are recruited to the murine lung in large numbers after allergen exposure to orchestrate local inflammatory responses via the secretion of cytokines and chemokines [83]. While in the intestine, $CD103^+$ DC2 are involved in the induction of Th2 responses via TIM-4 and OX40L.

Regardless of tissue, epithelial cell-derived DAMPs and alarmins are of critical importance in allergic sensitization and lead to the upregulation of OX40L and other cytokines and chemokines by DCs that facilitate the priming of Th2 cells. Interestingly, dermal CD11b-low DC2 are particularly responsive to IL-13 and alarmin signaling [26, 27], providing a potential explanation for the skin-specific bias toward type 2 immune responses, which not only affects the local immune environment but can also lead to food and lung allergies [116]. In addition to these classical activators, immune cell metabolism has become a prominent field of study in the context of allergies [117]. While activated DCs and proinflammatory macrophages have a glycolytic profile [118, 119], lipid metabolism has been associated with APCs that induce type 2 immunity [120]. It has, for example, been observed that the inhibition of fatty acid metabolism in murine DC results in an altered T-cell polarization profile that favors proinflammatory Th1 responses [121]. Similarly, murine $CD11b^+$ DCs displayed disrupted fatty acid oxidation upon mTOR deficiency, which results in the preferential induction of proinflammatory neutrophilic Th17 responses instead of eosinophilic Th2 inflammation upon intranasal challenge with house dust mite [122]. These metabolic mechanisms might also explain the epidemiological link between obesity and allergy, which has been associated with epigenetic reprogramming and an increased heritable susceptibility to develop allergies [123]. Modulating the immune cell metabolome might therefore represent a promising new therapeutic avenue. Several approaches to interfere with immune cell metabolism are being studied and include studies of APCs. High levels of IDO activity in DCs lead to increased tryptophan catabolism and have been consistently linked to a regulatory DC phenotype with an enhanced propensity to induce Treg differentiation and the suppression of allergic responses [61, 124]. Increasing the expression of IDO has already been tested in models of autoimmunity and contact sensitivity [125] and highlights the potential the immune cell metabolism holds in controlling disease.

Future studies characterizing the heterogeneity of APCs in the context of allergies should therefore not only focus on the responses of chemokines and cytokines but also assess the immune-metabolic profile as an important mediator of disease.

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