

2. Dendritic cells as regulators of immunity and tolerance

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Dendritic cells (DCs) are antigen sampling sentinels of the peripheral tissue and specialists for antigen capture, processing, and presentation to T cells as well as T-cell priming. By virtue of their mission as antigen samplers, they populate the body surfaces that line the border of our organism with the environment such as the skin and the mucosa of the respiratory and the gastrointestinal tract. Although all DCs share some classic features, their individual organ-specific phenotype and function are ascertained by a complex, dynamic network of coregulatory factors provided by their microenvironment. DC subtypes might initiate novel inflammatory immune responses as well as accelerate or break down ongoing inflammatory immune reactions in the skin, the gut, and the respiratory tract. On the basis of the recognition of self-signals or nonself-signals in the presence or absence of danger signals, the interplay of DC antigen uptake and presentation leads into immunosilencing or immunoactivating properties, which designate the outcome of tolerance or defensive immunity within the skin, the gut, or the respiratory tree. (J Allergy Clin Immunol 2008;121:S370-4.)

Key words: Dendritic cells, immunity, tolerance, skin, mucosa

Dendritic cells (DCs) populate the skin, the respiratory tract, and the mucosa of the digestive system and are in essence situated at the front line of pathogen entry. Without a doubt, their function as antigen-presenting cells combined with their property to ascertain that inflammatory immune responses against commensals of the physiologic skin microflora, ingested food antigens, or inhaled airborne microorganisms are prevented while potent immune responses against harmful pathogens are sustained is essential for the maintenance of the intact immune homeostasis.¹ An emerging but still fragmented picture arises that DCs serve not only as gate keepers but also as key arbiters of immunity and tolerance having the ability to discriminate friend from foe. Although much knowledge has been gathered about organ-specific properties of DC

Abbreviations used

DC:	Dendritic cell
ICOS-L:	Inducible costimulatory molecule ligand
IDEC:	Inflammatory dendritic epidermal cell
LC:	Langerhans cell
PDC:	Plasmacytoid dendritic cell

subtypes,²⁻⁵ the fundamental question remains what organ specific strategies they use to elicit either tolerogenic or active defensive immune responses. Detailed answers to this question would provide important steps forward on our way to understanding which of these mechanisms might be dysregulated under pathological conditions. This is of particular relevance because abnormal immune responses toward virtually harmless antigens result in exaggerated, repeated tissue damage and inflammation and are regarded as the seat of the trigger of various chronic diseases.⁶⁻⁹

THE GENERAL NATURE OF ANTIGEN-PRESENTING DCs

Dendritic cells are the primary sensors of our immune system and can be subdivided into 2 types: myeloid DCs and plasmacytoid DCs (PDCs). PDCs express CD123 and the blood DCs antigen 4⁺ on their cell surfaces and turned out to be instrumental for the defense against viral infections through their production of type I IFNs.¹⁰ In addition, PDCs are able to take up allergens via the high-affinity receptor for IgE and have the capacity to cross-present allergens to CD8⁺ T cells.¹¹ Via a broad pattern of chemokine receptors such as CCR6 for allergic diseases and adhesion molecules on the surface of DCs, tissue-specific homing of DCs is induced.¹²⁻¹⁴ Recruitment of DCs to the peripheral organs is much more efficient in the case of inflammation, indicating that a pool of bystander DCs is present in the circulation, which can be rapidly recruited at the site of inflammation where antigen processing is required. After antigen sampling in the periphery, DCs either migrate to the peripheral lymph node, a process that is mainly dependent on the expression of CCR7, or might return to the circulation.^{13,14} Myeloid DCs in peripheral organs create a dense network by extending their characteristic dendriform cellular processes to cover a great area for effective antigen sensing. In the periphery, they occur in an immature state specialized for antigen uptake via receptor-mediated endocytosis by C-type lectins (langerin/CD207, dendritic cell-specific ICAM-3–grabbing non-integrin, dectin, dectin-205, or CD206) or in terms of allergen uptake via multivalent cross-linking of the high-affinity receptor for IgE (FcεRI), or internalization of fluids or soluble material through the actin skeleton via macropinocytosis. Last but not least, DCs have the capacity for phagocytotic incorporation of antigens. In addition, they are equipped with a tissue and compartment-specific

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repertoire of danger-sensing receptors, such as Toll-like receptors, which are capable of recognizing microbial as well as modified host structures.^{15,16} After cleavage of the uptaken antigens or allergens into peptides in the endocytic compartments, antigen loading on MHC molecules and migration to the T-cell area of the draining lymph nodes follow, accompanied by the maturation of DCs. During their journey to the lymph nodes, DCs, which are the only cells capable of priming naive T cells and initiating adaptive immune responses, downregulate their capacity to take up antigens and advance their stimulatory activity toward T cells and their capability to induce T_H1, T_H2 or undifferentiated T_H0 immune responses as well as tolerogenic T-cell subtypes.

ANTIGEN UPTAKE AND PRESENTATION BY DCs IN THE SKIN

The skin, as one of the largest organs of our body, is much more than just a protective coat, and its barrier function is not simply composed of the bricks and mortar of the stratum corneum. In fact, immune cells within the epidermis and dermis form a complex network composed by CD1a⁺ DCs, which are responsible for the active cell-based defense against pathogens. The prototypes of DCs in the healthy epidermis are Langerhans cells (LCs).² LCs are derived from monocytes¹⁷ and reside in an immature state without renewal for months in mouse models. LCs constantly monitor the epidermal compartment for foreign antigens with the help of a cell type and disease-specific repertoire of pattern recognition receptors.¹⁸ Because human epidermal LCs express surface molecules involved in the inhibition of T-cell response like the inducible costimulatory molecule ligand (ICOS-L; B7-H2) or the immunoregulatory enzyme indoleamine 2,3-dioxygenase,¹⁹ LCs are regarded as “good guys” within the skin that are, to some degree, capable of maintaining a state of tolerance despite constant antigen exposure (Fig 1, A). This assumption is further supported by the observation that contact hypersensitivity reactions are much more pronounced in the absence of LCs in transgenic mice.²⁰ In diseased skin such as atopic dermatitis (AD), FcεRI amends the surface receptor repertoire of epidermal LCs. Most likely, their capability to undergo repetitive allergen challenge via FcεRI together with the invasion of various pathogens caused by the damaged skin barrier and the cumulative reception of danger signals sent out by other skin cells contribute to the breakdown of tolerance. Human LCs seem to produce only limited amounts of proinflammatory cytokines but release chemotactic signals that initiate the rapid invasion of proinflammatory cells such as inflammatory dendritic epidermal cells (IDECs) into the epidermis (Fig 1, B).²¹ IDECs overexpress FcεRI on their cell surface and are CD206⁺. In contrast with LCs, IDECs are regarded as “bad guys” on the level of skin DCs. IDECs are believed to aggravate the allergic inflammatory immune response by the release of proinflammatory mediators in response to allergens and other pathogens and by their strong stimulatory activities toward T cells leading to the exacerbation of the allergic inflammation in the skin. Looking at the composition of DC subtypes in inflammatory skin, the absence of human PDCs, which are crucial for the defense against viral infections, is believed to be a causative factor for the high susceptibility of patients with AD toward viral skin infections, which aggravates the course of AD in a subgroup of patients.¹¹

Taken together, epidermal LCs own some constitutive immune silencing functions in the skin. Both the repertoire of receptors

they are endowed with and the absence or presence of other DC subtypes ascertain the outcome of tolerance or active inflammatory immunity mediated by DCs in the skin.

ANTIGEN UPTAKE AND PRESENTATION BY MUCOSAL DCs

Compared with the skin, the situation in the gut appears to be much more complex, because the mucosal DC sentinels have to meet conflicting tasks. On the one hand, the continuous uptake of nutrients and fluids through the epithelial layer needs to be warranted, whereas on the other hand, the entry of harmful pathogens should be prevented and efficiently averted to avoid uncontrolled infections of the host. The main observers and coordinators within this flexible host defense apparatus are DCs, macrophages, and epithelial cells. A single layer of epithelial cells represents the protective barrier shield of the intestinal mucosa. Within this layer, M cells have turned out to represent a specialized epithelial cell type, localized mainly in the intestinal villi and follicle-associated epithelium. They are characterized by missing brush borders and by their unique capacity to capture, traffic, and transfer bacteria to DCs at their basolateral side. Murine DCs of the lamina propria and the Peyer patches are characterized by the expression of the CX₃ chemokine receptor (CR)1 (receptor for the chemokine fractalkine) and are derived from CX₃CR1^{high} granulocyte (Gr)1[−] monocytes, which migrate spontaneously into noninflamed tissue.²² Murine DCs of the subepithelial region of the Peyer patches are CD11c⁺CD11b⁺CD8a[−]CCR6⁺, whereas DCs in the mesenteric lymph or T-cell zones are CD11c⁺CD8a⁺CCR7⁺. Double-negative CD11b[−]/CD8a[−] murine DCs can be found at both of the Peyer patches, mesenteric lymph, and T-cell zones and inside the epithelium.²³

The current concept proposes that cross-talk between DCs and epithelial cells determines whether tolerance or active immunity is induced in the gut. In response to commensal bacterial signals, murine DCs produce mainly anti-inflammatory cytokines such as IL-6, IL-10, and TGF-β,²⁴ migrate to the mesenteric lymph nodes, prime T cells into T_H2, T_H3, and T-regulatory cells, and induce B-cell switch to local IgA production (Fig 1, C). When pathogenic bacteria attack the mucosa, DCs get a bacterial signal from their own sensing apparatus and a second danger signal sent out by infected epithelial cells. In response to this binary signal code, inflammatory cytokines and chemokines are released, leading to the recruitment of neutrophils and monocytes.^{24,25} As a consequence, DCs are highly activated and migrate to the mesenteric lymph nodes, where they prime T_H1 cells and induce IgG and IgA production by B cells,^{24,25} leading to gut inflammation (Fig 1, D).

The current model of the regulation of the immune homeostasis in the gut includes the concept that the type of the immune response conducted by DCs is closely associated with the fact that they get a single signal delivered by their own sensing machinery or a signal is accompanied by a second signal emitted by damaged epithelial cells to communicate a status of danger followed by the rapid mobilization of the inflammatory defense mechanism, which leads to immunity.

ANTIGEN UPTAKE AND PRESENTATION BY DCs IN THE LUNG

A high number of environmental pathogens, irritating particles as well as harmless and harmful antigens, is an integral part of the

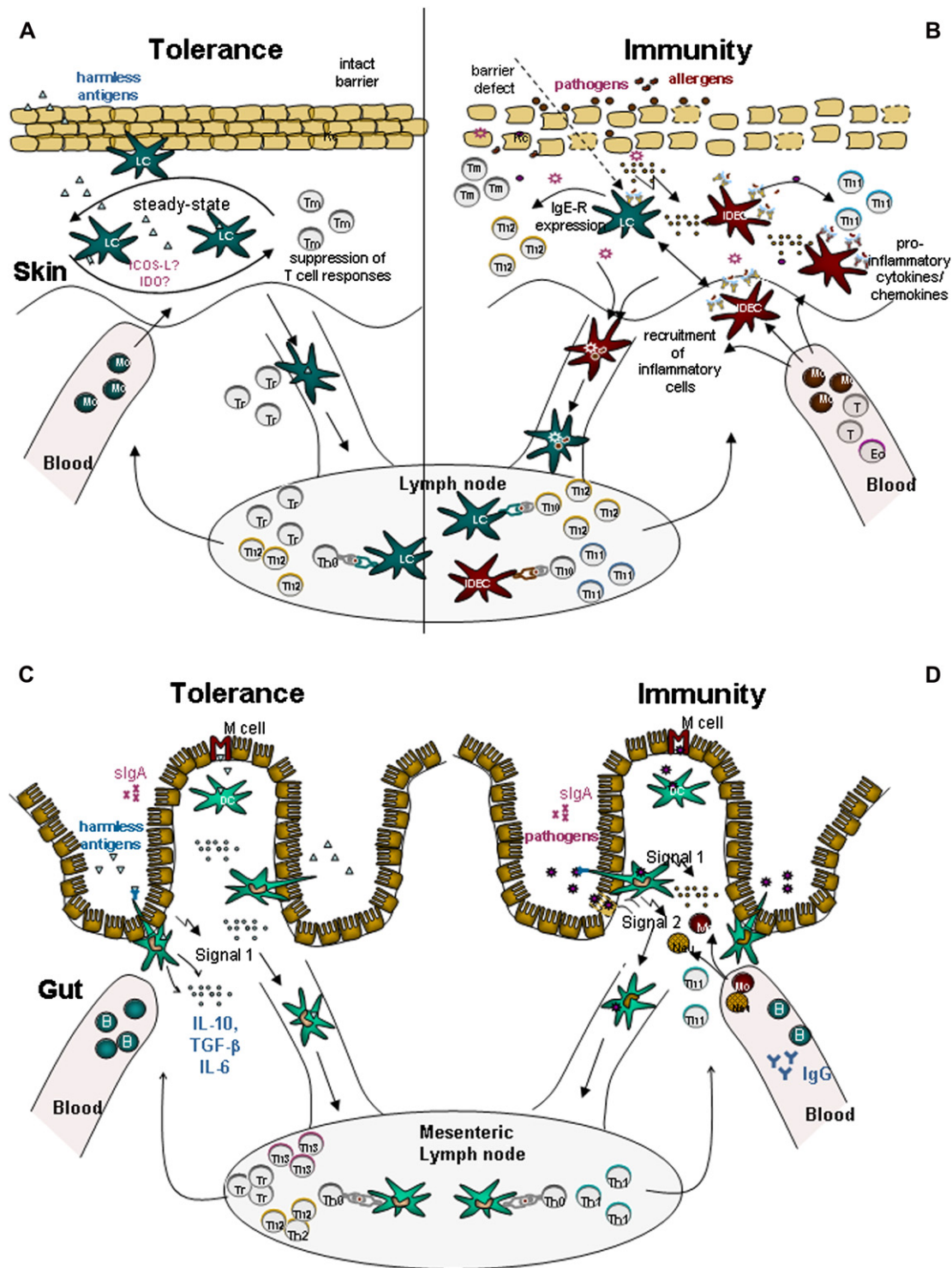


FIG 1. Model of the regulation of tolerogenic and immunogenic immune responses in the skin and the gut. Pathogen recognition by DCs in the skin leads either to tolerance (**A**) or to the outcome of an effective immune response (**B**). Recognition of harmless antigens by DCs leads to immunosilencing mechanisms (**C**), whereas the activation of DCs by pathogens induces effective immunity (**D**).

air we breathe. It is worth noting that only a thin layer of alveolar epithelial cells, 2 basement membranes, and a layer of epithelial cells separate antigens within the inhaled air from the blood capillaries. The regulation of the defense network within this sensitive barrier zone needs faithful control because any

excessive inflammation-related thickening of this junction would compromise the unobstructed gas exchange. DCs as main antigen-presenting cells of the lung populate the whole respiratory tree. Interstitial DCs, which can be found in the space between the alveolar epithelial cells and alveolar capillaries, are mainly

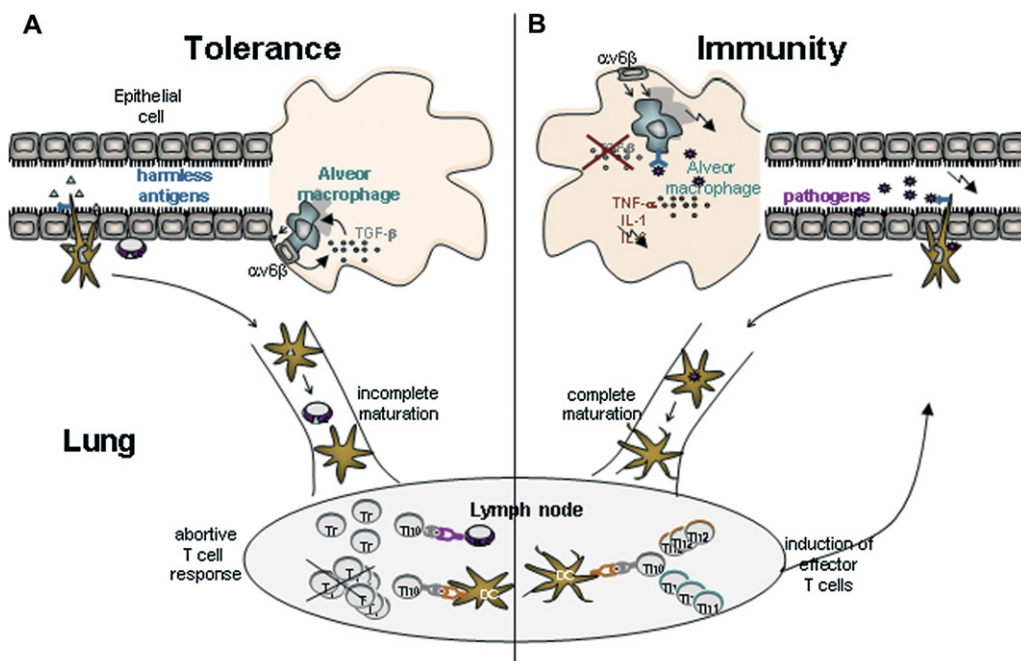


FIG 2. Model of the regulation of tolerogenic versus immunogenic immune responses in the lung. The contact of alveolar macrophages to epithelial cells keeps them in a quiescent immune state; recognition of harmless antigens leads to an incomplete, abortive T-cell response causing respiratory tolerance (A), whereas the loss of adhesion of alveolar macrophages together with the full maturation of DCs induces an active effector T-cell response, which results in respiratory immunity (B).

CD11c⁺ and remain in an immature state mirrored by low expression of costimulatory molecules but high expression of receptors for proinflammatory chemokines and endocytotic antigen uptake.⁵ In addition, it has been shown very recently in the murine system that B220⁺Gr1⁺ plasmacytoid DCs occur in the interstitium as well.²⁶ Murine alveolar DCs are CD11c⁺ and HLA-DR⁺ and rest in an immature state in the alveolar epithelia. In regards to the critical balance between tolerogenic and immunogenic immune responses, it is assumed that harmless antigens or self-antigens from dying epithelial cells encountered by lung DCs under noninflammatory conditions do not lead to full activation and maturation of DCs, so that effective T-cell activation by these incompletely matured DCs in the lymph nodes is avoided. Consequently, an abortive proliferative response of T cells, which are finally deleted, results in respiratory tolerance (Fig 2, A). In this context, it has been shown in a mouse model that a subset of murine DCs exposed to respiratory antigens produces transiently the anti-inflammatory cytokine IL-10 and induces regulatory T cells via the ICOS-ICOS-L pathway leading to peripheral tolerance and effective prevention of lung inflammation.⁶ This suggests that ICOS-L expression by DCs might play a critical role as an additional feature of respiratory tolerance. Respiratory tolerance also appears to depend on the presence of PDCs in the lung, which have the capacity to drive tolerogenic functions.²⁶ Within the concert of APCs, alveolar macrophages, which adhere to alveolar epithelial cells, assume a prominent role. The interplay of macrophages with DCs and their capacity to switch their immune silencing functions into an immune activating state seems to be partially regulated by the adherence of alveolar macrophages to alveolar epithelial cells and the consecutive cell-cell contact-dependent expression of the $\alpha v \beta 6$ integrin.²⁷ Further, in *in vitro* experiments, alveolar macrophages mixed with lung DCs are able to suppress

the activation of T cells via the release of nitric oxide, prostaglandins, TGF- β , and IL-10.

In view of this complex network, a picture emerges that the maturation stage of lung DCs that reach the lymph node together with the nature of other DC subtypes such as PDCs in their surroundings and the ongoing immune function of alveolar macrophages profoundly govern a state of tolerance or immunity in the lung.

Conclusion

The plethora of functions of DCs in the skin, the respiratory tree, and the gut nicely illustrates the versatile character of DCs. Moreover, the selected concepts about the organ-specific regulatory missions of DCs introduced here provide several exciting ideas about how DCs might govern the fragile balance between tolerance and immunity and supplement stepwise our picture that DCs act not only as gate keepers but also as important arbiters of health and disease.

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Dendritic cells as regulators of immunity and tolerance

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Learning objectives: "Dendritic cells as regulators of immunity and tolerance"

1. To identify the functions of antigen-presenting cells in the skin, gut, and respiratory mucosa.
 2. To compare the ways in which antigen-presenting cells are capable of inducing either iatrogenic or immunogenic immune mechanisms.
-

CME items

Question 1. Which of the following is characteristic for human epidermal Langerhans cells?

- A. the expression of the marker for langerin (CD207)
- B. the expression of the mannose receptor (CD206)
- C. a low antigen-presenting capacity
- D. the absence of CD1a expression

Question 2. Typical for antigen-presenting cells in the gut is that —

- A. dendritic cells (DCs) in the lamina propria are derived from CX₃CR1^{high} Gr1[−] monocytes, which migrate spontaneously into inflamed tissue.
- B. double-negative CD11b[−]/CD8a[−] DCs occur only inside the epithelium.
- C. DCs produce mainly proinflammatory cytokines in response to commensal bacterial signals.
- D. a cross-talk between DCs and epithelial cells determines whether tolerance or active immunity is induced.

Question 3. The capacity to capture, traffic, and transfer bacteria to gut DCs is a feature of which of the following?

- A. plasmacytoid DCs
- B. alveolar macrophages
- C. M cells
- D. CD11c⁺ interstitial DCs

Question 4. Respiratorial tolerance in the lung is partially mediated by —

- A. inducible costimulator–inducible costimulator ligand.
- B. CX₃CR1.
- C. CCR7.
- D. IgA production.