Dendritic Cells—The Link Between Innate and Adaptive Immunity in Allergy

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Introduction

The primary site of antigen/allergen exposure of the body is the epithelium of skin and mucosal surfaces. These epithelial tissues are populated by highly specialized antigen-presenting cells (APCs), termed "dendritic cells," that act as sentinels of the immune system [1]. The migratory capacity of dendritic cells allows them to transport ingested antigen/allergen from sites of primary exposure to regional lymph nodes, where they can initiate systemic immune responses. Dendritic cells differ from other APCs in that they display a unique capacity to activate naïve T cells and induce the polarization of the ensuing immune response toward a T helper 1 (T_H1) or a T_H2 phenotype. Since T_H2 effector lymphocytes play a critical role in orchestrating allergic inflammation, allergists have become increasingly interested in the mechanisms that regulate dendritic cell biology and the factors that control the dendritic cells–mediated induction of T_H2–dominated immune responses.

Allergen Uptake and Processing

At the interface of environment and organism, resident dendritic cells are in a functional immature state that is specialized to capture and process antigen. Antigen uptake is mediated via a number of mechanisms, including macro-pinocytosis, phagocytosis, and receptor-mediated endo-cytosis involving clathrin-coated pits. Immature dendritic cells display a large panel of cell receptors for patterns associated with foreign antigens, such as the C-lectin carbohydrate receptors (*eg*, mannose, Langerin, DEC205, DC-SIGN). These pattern recognition receptors facilitate antigen capture and uptake and lead to an increased effectiveness in antigen presentation. In addition, dendritic cells express complement and Fc receptors that mediate capture of opsonized or antibody-bound antigens during primary and secondary antigen exposure. Ingested antigen is cleaved into peptides by proteolytic enzymes within the endocytic compartment and loaded onto newly synthesized major histocompatibility complex class II (MHC II) molecules within the acidic MHC II compartment or onto preformed MHC II molecules that have been internalized from the cell surface into less acidic endosomal vesicles. Recent reports indicate that, at least in vitro, some of the antigen processing by dendritic cells may also occur extracellularly through secretory proteases. Our current understanding is mostly based on studies using model antigens, while there is still very little data available on the mechanisms involved in uptake and processing of allergens. Recent in vitro data indicate that recombinant allergens, such as rPhl p1 or rBet v1, are primarily ingested via macropinocytosis, a mechanism that may be of particular relevance during primary sensitization. In already sensitized individuals, uptake is most likely mediated by receptor-mediated endocytosis, *eg*, internalization of IgE-bound allergen via the high-affinity IgE receptor that targets the allergen to the MHC II compartment.

Activation, Migration, and Maturation of Dendritic Cells

A key event in the induction of primary immune responses is the migration of allergen-loaded dendritic cells from the periphery to the regional lymph nodes. Local activation of dendritic cells (*eg*, during allergen exposure) leads to a dramatic change in their chemokine receptor profile that allows the directed migration from the epithelium to the regional lymph nodes [2]. Local activation of immature dendritic cells is best understood in the context of pathogen-induced responses. Dendritic cells are equipped with pattern recognition receptors (PRRs), such as the TOLL-like receptors (TLRs), that discriminate and are triggered by different pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS), lipoteichoic acid, flagellin, or bacterial DNA. While other receptors primarily mediate

pathogen uptake (*eg*, lectins), ligation of TLRs leads to signaling that results in the activation and maturation of dendritic cells. Many PAMPs still remain to be characterized, and it is not clear whether allergens or allergen carriers, such as pollen grains, contain similar molecular patterns that can trigger TLRs or other PRRs. It is well conceivable that at the site of allergen exposure, such allergen- or allergen carrier–associated molecular patterns (AAMPs) could directly induce the activation and maturation of dendritic cells. Alternatively, some allergens may have direct dendritic cell–activating potential because of their intrinsic enzymatic activity, as it was recently reported for one of the major house dust mite allergens—the cystein protease Der p1 [3]. Finally, immature dendritic cells may also get activated indirectly. Perturbation of the epithelial homeostasis by allergen exposure may lead to the local release of inflammatory mediators, such as interleukin 1 (IL-1) or tumor necrosis factor-α (TNF-α), which are known agonists of dendritic cell maturation. In this context, consideration of the natural exposure conditions is of particular relevance. For many aeroallergens, the bioavailability depends on the allergen liberation from internal binding sites within the allergen carrier, such as pollen grains. In addition, we recently demonstrated that pollen grains are a rich source of bioactive mediators that get rapidly released upon pollen contact with the aqueous phase [4]. Among others, eicosanoid-like lipid mediators are released within minutes, clearly preceding the liberation of protein allergens. Even though in vivo effects of these mediators are still somewhat uncertain, it seems very likely that they may act as adjuvants, leading to the activation and modulation of dendritic cell function at the site of allergen exposure.

Once activated, dendritic cells undergo a functional maturation during which the capacity of antigen uptake and processing is shut down and the signals for optimal antigen presentation are acquired. This involves increased surface expression of peptide/MHC complexes (signal 1); upregulation of costimulatory molecules, such as CD40, CD80, and CD86 (signal 2); and the production of cytokines, such as IL-12, IL-18, and IL-10 (signal 3), which can polarize T cell responses (TCRs).

T Cell Activation and Polarization of the T Cell Response

T cells interact with dendritic cells in a highly dynamic environment where they have to compete to achieve a level of T cell receptor (TCR) stimulation sufficient to drive their activation and differentiation. A sustained TCR stimulation is not only required for naïve T cells to proliferate but also for proliferating T cells to differentiate into effector cells. Signals that drive this activation are generated during the cognate interaction of T cells and dendritic cells in specialized areas of the cell membrane—the immunological synapse—and critically determine the polarization of T helper cell responses toward a T_H1 or a T_H2 pheno-

type. A number of regulatory mechanisms seem to be operative. Initially, it was suggested that the preferential induction of either T_H1 or T_H2 responses is determined by the lineage of dendritic cells utilized for antigen presentation. According to this concept, dendritic cells of myeloid origin (designated as DC1) induced IL-12–dependent T_H1 responses, while dendritic cells derived from plasmocytoid precursor cells of lymphoid origin (plasmocytoid dendritic cells, DC2) preferentially induced T_H2 responses. However, follow-up studies demonstrated that depending on the type of stimulus present during dendritic cell activation, both types of dendritic cells can be induced to polarize either toward a T_H1 or a T_H2 response. The resulting T_H polarization seems to be predominantly regulated at the level of cytokines present during antigen presentation (signal 3) with dendritic cell–derived IL-12 favoring T_H1 and dendritic cell–derived IL-10 favoring T_H2 development. The degree and type of costimulation (signal 2) also modulates the outcome of TCR with CD40 and CD80 favoring T_H1, while CD86, OX40L, and ICOS-L have more of a T_H2-promoting effect. In addition, polarization may be regulated at the level of duration and affinity of TCR-MHC interaction (with sustained or low-affinity interactions favoring T_H2 induction, while short or high-affinity interactions preferably induce T_H1 responses) and at the ratio of dendritic cells to responder T cells (with low stimulator/responder ratios promoting T_H2, while high ratios favor the T_H1 development). To add to the level of complexity, the timing at which naïve T cells get to interact with dendritic cells may also be of relevance. Early after LPS-mediated activation, dendritic cells produce transiently large amounts of IL-12 and induce T_H1 responses, while at later time points, the same dendritic cells lose the capacity to produce IL-12 and preferentially prime T_H2 responses. Taken together, it seems that there exists an enormous plasticity in the response profile of dendritic cells to different activation signals and that multiple factors need to be integrated that determine the outcome of the ensuing T_H response.

It is still a matter of debate whether allergens by themselves can lead to a dendritic cell activation that preferentially induces T_H2 priming. A recent report suggested that the enzymatic activity of Der p1, a cystein protease, can induce dendritic cell activation with a selective upregulation of CD86—a T_H2-promoting costimulatory molecule [3]. It remains to be determined whether other allergens with enzymatic activity have a similar impact on dendritic cell maturation and on T_H polarization. A different level at which allergens may modulate the outcome of T_H polarization is the degree of dendritic cell activation under natural exposure conditions. In contrast to pathogens that induce profound dendritic cell activation via triggering of PRRs, allergens may just lack this capacity and induce activation in only a small subset of dendritic cells. Mobilization of low numbers of dendritic cells from the site of allergen exposure would lead to a low stimulator/

responder ratio in the regional lymph node, which, at least in vitro, would promote the development of T_H2 responses. Finally, under natural conditions, organisms are rarely exposed to isolated allergens but rather to a complex mixture of multiple allergens in conjunction with potential adjuvants. Our recent observation that bioactive eicosanoid-like lipid mediators are rapidly released from allergen carriers, such as grass pollen [4], suggests that these mediators may exert direct or indirect effects on dendritic cell function at the site of allergen exposure. In this context, prostglandin E–like phytoprostanes seem to be prime candidates that, like prostaglandin E_2, may inhibit dendritic cell IL-12 production and result in a propensity to induce T_H2, rather than T_H1, immune responses.

Conclusions

During the past years, a large number of studies have provided compelling evidence that dendritic cells are the principal APCs involved in the polarization of T helper cell responses, not only in the T_H1 but also in the T_H2 direction. Although in vitro studies have improved our understanding of the various factors that effect dendritic cell function, we are only beginning to comprehend the complex interactions of environmental and local factors that modulate dendritic cells under natural allergen exposure conditions. Identification and characterization of factors relevant for the T_H2-promoting capacity of dendritic cells in vivo will advance our understanding of the pathogenesis of allergic diseases and possibly provide novel targets for therapeutic or preventive intervention.

References

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