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ALLERGY

Review article

The role of antigen presenting cells at distinct anatomic sites: they accelerate and they slow down allergies

It has been repeatedly demonstrated that allergic reactions are driven by the continuous flow of antigen uptake and presentation processes, which are perpetuated mainly by dendritic cells (DC). The ability of allergens to cause allergic inflammation is contingent upon the presence of an immunological milieu and microenvironment that either privileges Th2 responses or prohibits these reactions by the induction of contraregulatory anti-inflammatory activities of the immune system. In the light of recent developments it appears that DC have to manage two opposing tasks: on the one hand they can favor pro-inflammatory reactions and actively induce a T-cell response, yet on the other hand they serve an important function as 'silencers' in the immune system by sending out anti-inflammatory, tolerance inducing signals. This unique capacity of DC has opened several exciting possibilities for a role of DC in both – accelerating and slowing down allergic reactions. It is therefore a challenge to understand in which way DC subtypes located at distinct anatomic sites with frequent allergen exposure, such as the skin, the nasal mucosa, the respiratory tree or the mucosa of the intestinal tract can have an impact on mechanisms involved in tolerance induction or effective immunity.

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Antigen presenting cells of the skin

Dendritic cell (DC) subpopulations throughout the body often occur at the interface with the environment. They reside in the skin, the airways and the gut and because of their function as antigen presenting cells (APC) they have a wide range of features in common. As primary sentinels of the immune system APC traffic from the blood to the peripheral tissue to capture foreign antigens (1, 2). Thereafter, they migrate to the draining lymphoid organs in order to prime naïve T-cells and gear their development into Th1 or Th2 effector cells. In the human immune system, two functionally different subsets of DC have been found: myeloid DC, which preferentially drive naïve T-cell differentiation toward Th1 cells and are therefore called DC1 and plasmacytoid DC which represent the type 2 DC, namely plasmacytoid dendritic cells (pDC) and have a Th2 polarizing profile (1, 2). The oldest members of the DC1 system are the classical epidermal Langerhans cells (LC), which are characterized by their primary ultrastructural marker, the tennis-racket shaped *Birbeck* granules in combination with their surface expression of CD1a (3). The LC reside in the basal and suprabasal layers of the epidermis and are present even in normal, uninflamed skin. Marker and functional studies have provided strong support for a concept in which LC represent a resident population of the human epidermis (4). Their primary function in uninflamed skin is to maintain a state of tolerance against invading antigens and allergens under immunological steady state condition (5). By contrast, in response to arriving danger signals such as inflammation multiple changes occur. Among these is the release of monocyte-chemoattractant protein (MCP)-chemokines by skin cells which induce the recruitment of LC progenitors from the bone marrow. Other factors initiate LC migration to the peripheral lymphnode. Altogether, this leads to the break down of tolerance and the rapid induction of an immune response at this site. In this manner in the acute phase of allergic and inflammatory diseases, LC precursors and other DC subtypes are immediately recruited by chemotactic signals to the site of inflammation. Compelling evidence is now available that in the exacerbation state of Atopic Dermatitis (AD) (6), the so-called 'Inflammatory Dendritic Epidermal Cells' (IDEC) are recruited from

Abbreviations: APC, antigen presenting cells; DC, dendritic cells; LC, Langerhans cells; IDEC, inflammatory dendritic epidermal cells; pDC, plasmacytoid dendritic cells; AD, atopic dermatitis; FcεRI, high affinity receptor for IgE; IgE, immunoglobulin E; TSLP, thymic stromal lymphopoetin; MDC, macrophage-derived chemokine; TARC, thymus and activation-regulated chemokine; RANTES, regulated upon activation normal T-cell expressed and secreted; MHC, major histocompatibility complex; IDO, indoleamine 2,3-dioxygenase; IL, interleukin.

monocytes of the peripheral blood into the inflammatory skin lesions (7–12). A hallmark of both, epidermal LC and IDEC in the skin lesions of AD patients is the elevated expression of the high affinity receptor for immunoglobulin (IgE) (FcεRI) (Table 1) (13–17). Evidence suggests that allergens, which penetrate the epidermis due to the reduced skin barrier of AD patients, are taken up by FcεRI-bound IgE molecules of epidermal DC, are internalized and processed in major histocompatibility class (MHC) II containing compartments within these cells (Fig. 1). This mechanism is referred to as antigen focusing and leads to a more efficient antigen presentation toward T-cells (12–18). Furthermore, mRNA for IL-16, the natural soluble ligand of the CD4 molecule that induces chemotactic response of $CD4^+$ cells, monocytes and eosinophils is enhanced in active AD (18, 19). Recent findings suggest that LC are a major cellular source for the production of Interleukin (IL)-16 in AD, which can be induced by the aggregation of FcεRI on LC of atopic donors *in vitro*. It is therefore likely that IL-16 plays a major role in the initiation phase of AD (18, 19). Based on recent evidence thymic stromal lymphopoetin (TSLP), which is an IL-7 like cytokine, is produced in high amounts by keratinocytes in AD and seems to contribute to the initiation of the allergic cascade and the induction of LC migration into the lymph nodes (20). The TSLP stimulated DC prime naïve T-cells to produce

Table 1. Summary of the phenotype and function of dendritic cells at distinct anatomic sites

Anatomic site	Dendritic cell type	Phenotype	Function	Reference
Skin	Langerhans cells	CD1a+++ FcεRI++ IgE+ CD206– CD207+ MHCII+	Antigen-uptake Antigen-presentation Priming of naïve T-cells Inflammation Cell recruitment Inflammation Therapeutic Target Cells	3–11, 13–17, 22, 23, 46
	Inflammatory dendritic epidermal cells	CD1a++ FcεRI+++ FcεRII+ IgE+ CD206+ CD207– CD11b+ CD1b+ MHCII+		
Nasal Mucosa	Dendritic cells	CD1a+ CD11c+ FcεRI+ FcεRII– IgE+ MHCII+ CD80+ CD86+	Antigen-uptake Antigen-presentation Priming of naïve T-cells Cell recruitment Therapeutic Target Cells Tolerance ?	31, 32, 35–39, 46
	Plasmacytoid dendritic cells	CD4+ CD123+ (IL-3R+) MHCII+ CD11c–		
Lower respiratory tract	Dendritic cells	CD1a+ FcεRI+ CD11c+ MHCII+ ICOS-L(+)	Antigen-uptake Antigen-presentation Priming of naïve T-cells Cell recruitment Therapeutic Target Cells Tolerance	46–49, 52, 58–60
Gastrointestinal mucosa	Dendritic cells	CD1a+ CD11c+ MHCII+	Antigen up-take and presentation Priming of naïve T-cells Induction of regulatory T-cells Tolerance	61;63–68
Oral Mucosa	Langerhans Cells	CD1a+ FcεRI+ CD11b+ CD207+	Antigen up-take and presentation Priming of naïve T-cells Tolerance	61, 66, 74

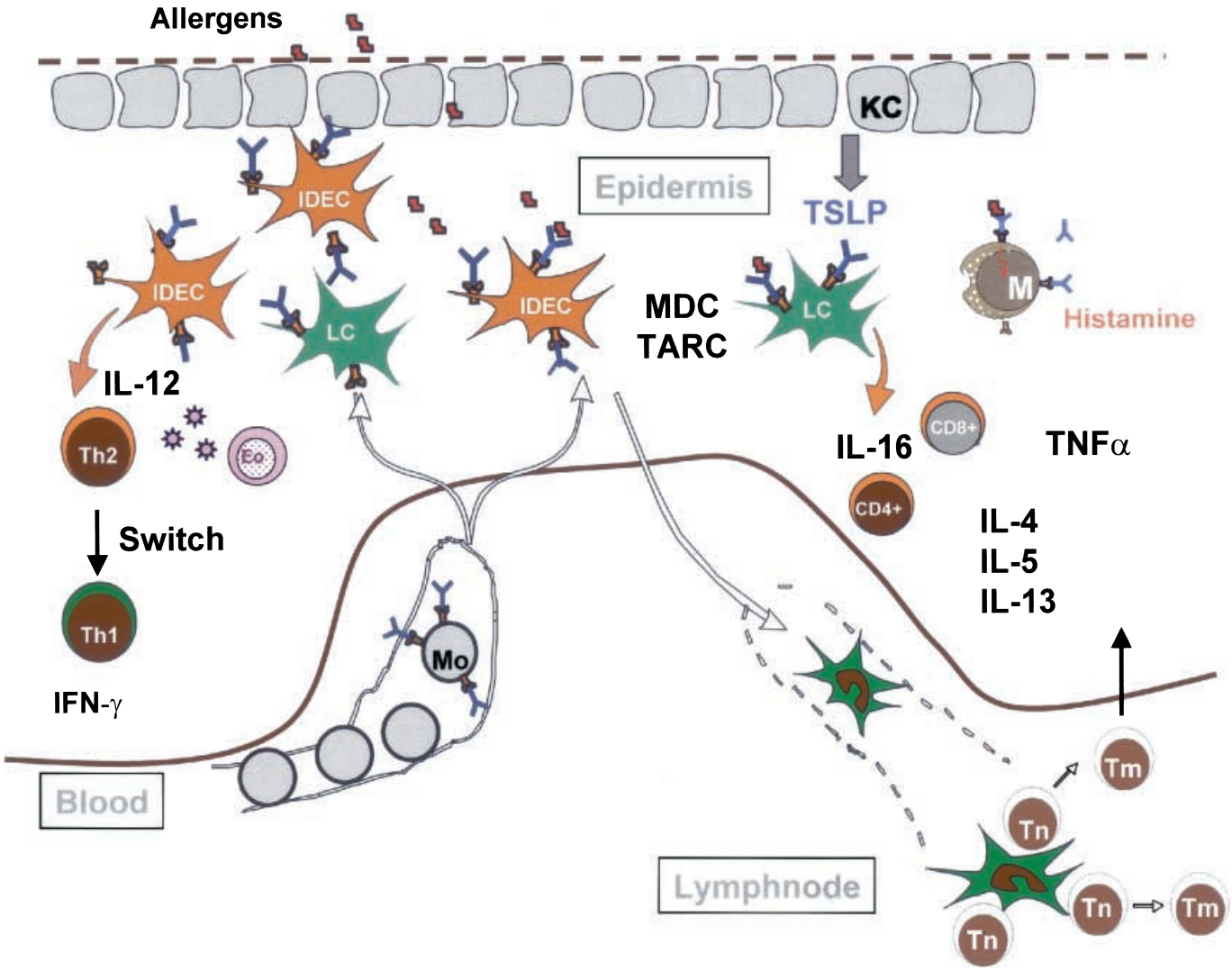

Figure 1. The role of antigen-presenting cells in the skin. Allergens invading the skin because of the reduced epidermal skin barrier are taken up by FcεRI-bearing dendritic cells, internalized and efficiently presented to T-cells. KC, keratinocytes; LC, Langerhans cells; Eo, eosinophils; Mo, monocytes; Tn, naïve T-cells; Tm, memory T-cells; TLSP, thymic stromal lymphopoetin; MDC, macrophage derived chemokine; TARC, thymus and activation regulated chemokine; IFN-γ, interferon-γ; TNF-α, tumor necrosis factor-α.

soluble factors such as IL-5, IL-13 and tumor-necrosis-factor (TNF)-α and initiate the production of chemokines by DC such as macrophage-derived chemokine (MDC) or thymus and activation-regulated chemokine (TARC), which attract T-cells of the Th2 type (20).

The invasion of IDEC into the epidermis together with eosinophils is assumed to boost the pro-inflammatory process and causes the switch of the initial Th2 dominated acute phase of AD into an immune response in which interferon (IFN)-γ producing Th1 T-cells predominate (21).

Indeed, precedence for a major role of IDEC in the exacerbation of AD arises from the finding that after successful topical treatment and clinical improvement of the skin lesions the number of IDEC decreases below the detectable level (22). This indicates that IDEC represent promising cellular targets for successful treatment strategies aimed at effectively breaking down the recurrent exacerbation of this chronic-inflammatory skin disorder.

It is of special notice that pDC, which are involved in anti-viral defense by the production of large amounts of IFN-α and IFN-β are present only in low amounts in the epidermis of AD patients in contrast to other inflammatory skin diseases such as Psoriasis vulgaris, Contact Dermatitis or Lupus erythematodes (23–25). The lack of this DC subset in AD might be one reason for the high predisposition of these patients for viral infections such as eczema herpeticatum, which represents a frequent complication of AD (23).

Antigen presenting cells of the nasal mucosa

Rhinitis is characterized by chronic relapsing episodes of nasal itch, sneezing, rhinorrhea and nasal congestion (26–29), going along with inflammation and irritation of the mucous membranes that line the nose (30).

In the nasal epithelium and the lamina propria of healthy donors, APC with characteristics of LC have been identified. These LC like cells bear IgE on their cellular surface and are MHC II$^+$ and Langerin positive. Secondly, CD1a$^+$ Langerin$^-$ DC and MHC II$^+$ CD1a$^+$ cells, such as LC-precursor cells or LC which already have diminished their CD1a$^+$ expression are located within the epithelia of the nasal mucosa (Table 1) (31). In the absence of invading allergens, these DC reside in their immature state.

In atopic patients, an enhanced number of cells bearing the high-affinity receptor for IgE (FcεRI) and expressing high amounts of the co-stimulatory molecules CD80 and CD86 are detectable in the mucosa after allergen challenge (Fig. 2) (32). About two percent of these FcεRI$^+$ cells were identified as CD1a$^+$ DC and carry IgE-molecules on their cell surface, while another part of the high affinity receptor binding site for IgE remains unoccupied in most of these DC. Local production of IgE and allergen specific IgE in nasal B-cells and plasma cells of patients suffering from allergic rhinitis is the most likely cause for the high level of IgE binding of DC in the nasal mucosa (33, 34). The cytokine milieu in the airway environment at the time of exposure is crucial in the process of DC activation and maturation. As important mediators of the cellular recruitment process, chemokines such as TARC and MDC are present in high amounts in the mucosal tissue of the respiratory tract and promote the recruitment of distinct cell types acting in allergic inflammation, such as DC and CD4$^+$ T-cells (35–37). The contact with allergens sets off a series of events that supply DC with the necessary equipment to migrate to the regional lymph nodes and activate allergen specific Th2 cells (38).

Furthermore allergen provocation induces an increase of eosinophils and IL-8, IL-13 and regulated upon activation, normal T-cell expressed and secreted (RANTES) mRNA-positive cells (39). Most interestingly, a

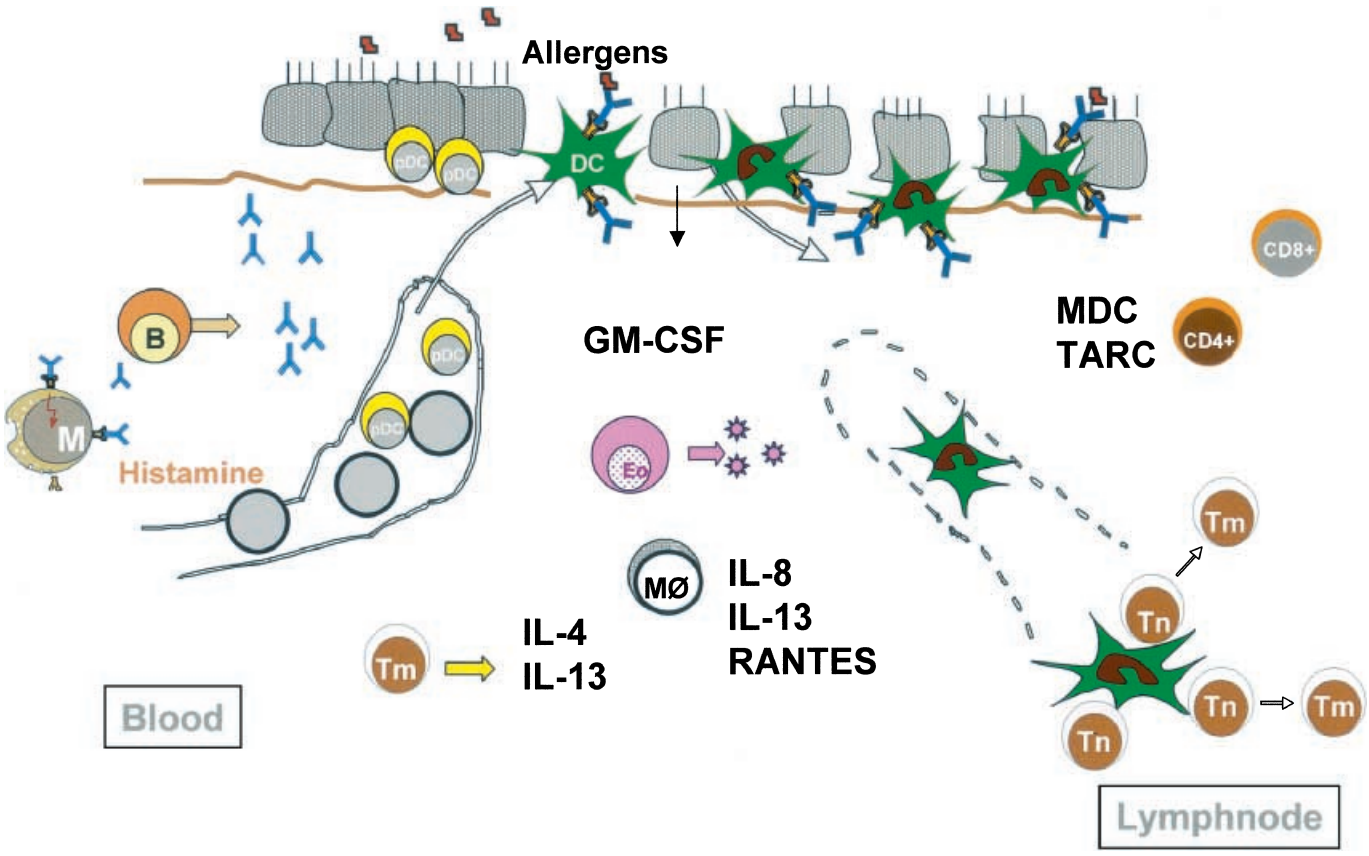

Figure 2. Subtypes of dendritic cells (DC) invade the nasal mucosa after allergen challenge. After allergen challenge, APC migrate to the lymph nodes and plasmacytoid DC are recruitet to the nasal mucosa. PDC, plasmacytoid dendritic cells; MØ, macrophages; B, B-cells; M, mast cells; Tn, naïve T-cells; Tm, memory T-cell; Eo, eosinophils; GM-CSF, granulocyte-macrophage stimulating factor; MDC, macrophage derived chemokine; TARC, thymus and activation regulated chemokine; RANTES, regulated upon activation normal T-cell expressed and secreted.

dramatic increase of another DC subtype, the $CD11c^-$ $CD123^+$ $CD45RA^+$ pDC, which are present in low numbers in the normal nasal mucosa of atopic individuals can be observed during the allergen season and after experimentally induced allergen provocation (19). These invading pDC express the adhesion molecule L-selectin and are recruited from organized lymphoid tissue into the site of inflammation through adressin expressing endothelial venules (24). Plasmacytoid DC are able to induce naïve T-cells to produce Th2 cytokines and are involved in the outcome and maintenance of the inflammatory response in allergic airway diseases of the nasal mucosa (40). Another possible function of these pDC arises from the recent finding of a constitutive expression of indoleamine 2,3-dioxygenase (IDO) in pDC. Cells which express the tryptophan-catabolizing enzyme IDO are capable of inhibiting T-cell proliferation *in vitro* and have been shown to reduce T-cell immune responses efficiently *in vivo* (39). Therefore it is feasible that the recruitment of this regulatory subset of pDC as a consequence of allergen challenge in rhinitis is part of an attempt by the immune system to cause an antigen-specific depletion of specific T-cell subsets and thereby selectively block the immunological response of these T-cell subsets. By contrast, no evidence has been seen so far that indicates that pDC play a role in lower respiratory tract immunology (40).

A number of mechanisms described above could account for the effects of therapeutic treatment strategies such as the use of topical corticosteroids in suppressing the seasonal increases in the number of nasal mucosal $CD1^+$ LC by the inhibition of the release of cytokines such as Granulocyte-Macrophage-Colony-Stimulating-Factor (GM-CSF) from the epithelial cells of the respiratory tract and IL-4, which favour the activation and differentiation of DC *in vivo* and *in vitro* (39, 41–45).

Furthermore local corticosteroids have been shown to act through the inhibition of the production of chemokines such as TARC and MDC in the nasal mucosa, which enables them to inhibit the allergen uptake of nasal DC to allergen specific T-cells (36).

Antigen presenting cells of the lower respiratory tract

Chronic inflammatory processes within the respiratory tract of asthmatic patients have shifted attention to the underlying mechanisms of the induction and maintenance of the allergic immune response within these tissues. Distinct subpopulations of DC have been identified at all levels of the respiratory tree including the epithelium and the submucosa of the airways the interstitium of the lung parenchyma and the tissues surrounding the blood vessels within the pleura and the alveolar surface (Table 1). In contrast to DC in the skin, which show a turnover rate of about three weeks in animal models, the turnover rate of DC of the respiratory tree and mucosa of the intestinal tract is much faster and lies between three to ten days (46, 47). In response to a challenge with allergens airway DC are immediately recruited from myeloid DC of the blood through the release of chemotactic factors such as macrophage inflammatory protein (MIP)-3α and epithelial β-defensins or MDC, TARC, IL-8 and RANTES (Fig. 3) (2, 48–51). The DC expressing the chemokine receptor CCR5 and CCR6 are continuously recruited in a circular flow from immature DC of the bone marrow to the lung. In parallel, the number of $CD1a^+$ $HLA\text{-}DR^+$ myeloid DC in the lamina propria of the lung increases within a few hours after allergen challenge. Furthermore, DC of asthmatics display an enhanced amount of FcεRI on their surface in comparison to non-asthmatics (52, 53). This process implies a pivotal role of DC in allergen induced immune responses since DC are able to induce a strong pulmonary inflammatory reaction mediated through the activation of T-cells and eosinophils which infiltrate the airways and are responsible for the increased production of the Th2 cytokines IL-4 and IL-5 (54, 55) found in the bronchial lavage fluid. They are also responsible for an increased local IgE production within the mucosa by plasma cells. The view that DC play a major role in accelerating the allergic immune response in the airways is further supported by the observation that intratracheally introduced DC primed with *Ovalbumin* (OVA) antigen were able to induce an asthma-like disease. After allergen up-take DC down-regulate the chemokine receptor CCR6 and up-regulate the chemokine receptor CCR7 which allows them to migrate to the draining lymphoid organs in which high amounts of the chemoattractant MIP-3β occur. During their migration DC undergo a full maturation and increase their stimulatory capacity toward T-cells. Later on, the processed antigens are presented in the peptide groove of MHC II molecules and the activation of naïve T-cells, which is a unique feature of DC in the immune system, into effector cells occur. Furthermore, the freshly polarized effector cells leave the lymph nodes via the lymph vessels and migrate to the peripheral inflammatory tissue such as the airways, where they participate in the allergic inflammatory process. As main mediators, chemotactic factors such as TARC (56) and MDC (2, 57) in addition to IL-16 released by DC and epithelial cells are responsible for the recruitment of activated $CCR4^+$ and $CCR8^+$ Th2 cells as well as DC precursor cells.

More insight into these processes comes from the finding that the release of GM-CSF of epithelial cells in the lung, which express in high amounts the proteinase-activated receptor (PAR)-2, induces a continuous activation of lung DC (30). This is supported by the finding that a substantial number of the most relevant aeroallergens such as house dust mite *Dermatophagoides pteronyssinus* (*Der p*) are proteases, which are capable of cleaving PAR on airway epithelial cells, and can thereby cause the production of DC-activating cytokines such as GM-CSF

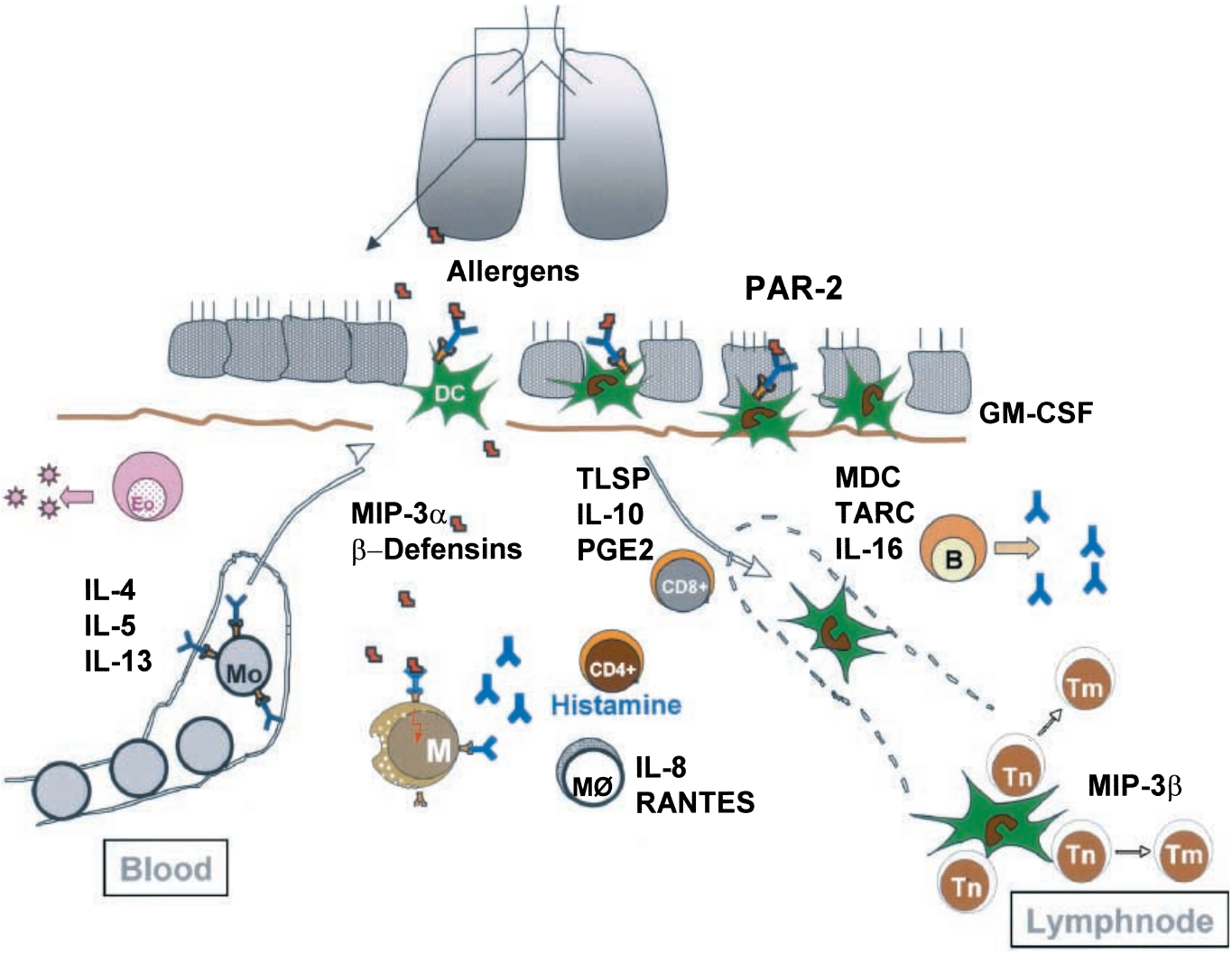

Figure 3. Recruitment and activation of antigen-presenting cells (APC) in the lower respiratory tract. APC recruited from the peripheral blood take-up allergens and migrate to the peripheral lymphoid organs. Eo, eosinophils; B, B-cells; Tn, naïve T-cells; Tm, memory T-cells; M, mast cells; MØ, macrophage; TLSP, thymic stromal lymphopoetin; PGE2, prostaglandin E2; MIP-3α, macrophage inflammatory protein-3α; MDC, macrophage derived chemokine; TARC, thymus and activation regulated chemokine; RANTES, regulated upon activation normal T-cell expressed and secreted.

(30). It is reasonable to hypothesize that the predominance of an immune response of the Th2 type within the airways is further sustained by the release of soluble mediators, a diminishing IL-12 production of DC such as TSLP and an increased IL-10 and prostaglandin E2 (PGE_2) production by airway epithelial cells. As a paradigm shift in the field of allergy, it has been shown that CD11c DC of the mucosal tissue are capable to induce effective tolerance to inhaled allergens, which reach the lung. This has been found to be mainly regulated by the DC-driven production of IL-10 and the co-stimulation of T-cells via Inducible-costimulator-Ligand (ICOS-L), which leads to the induction of regulatory T-cells (TR_1) with a high production of the anti-inflammatory, tolerogenic mediator IL-10 and – at the end – the effective suppression of the allergic immune response (58, 59).

Based on these observations one might speculate that the respiratory exposure to allergens normally induces the development of T-regulatory cell mediated T-cell tolerance. It could very well be that a defective production of IL-10 by DC in the respiratory tract of allergic asthmatics might contribute to the development of asthma. The benefit of putative futural studies using IL-10 and ICOS-L expressing DC as therapeutic target cells to break down allergen specific T-cell responses, which might evolve from these findings, will require further experimental studies. As an important therapeutical mode of action the high expression of TARC in the airway epithelium of asthmatics can be downregulated by glucocorticoid treatment (56, 57).

This indicates that effective therapeutic strategies interfere with the initial steps of the ongoing allergic cascade such as the recruitment of inflammatory DC to the airways (60). Together these findings show that DC of the respiratory tract represent the heart of both the acceleration of allergic-inflammatory immune responses and the inhibition of these processes.

Antigen presenting cells of the gastrointestinal mucosa

Within the immune system of the gastrointestinal tract complex mechanisms have evolved in order to provide a rapid response against invasive organisms on the one hand and tolerance against harmless antigens such as food proteins on the other hand. The mucosa of the gastrointestinal tract resembles a unique immunological unit with a high frequency of allergen contact. As the induction of allergic contact sensitivity reactions is rarely seen within these tissue, it is apparent that tolerance inducing immunological mechanisms are of primary importance within the gastrointestinal tract (61, 62). Important features of the mucosal tissue which are implicated in providing this unique immunological privilege include a complex epithelial barrier system (63, 64). Furthermore the capability to produce IgA antibodies and the property to develop Th2 helper cell responses to a lesser extent (Fig. 4) (65). Importantly, IgA is resistant to cleavage by secretory proteases and is the main factor that blocks the penetration of allergens within the mucosal tissue (65). In contrast to parenterally administered allergens, orally applicated allergens underlie the activity of salivary enzymes, proteases and the low pH, which as the first line mechanisms of defense inactivate most of the relevant epitopes of the allergens before they reach the APC of the mucosal tissue (66).

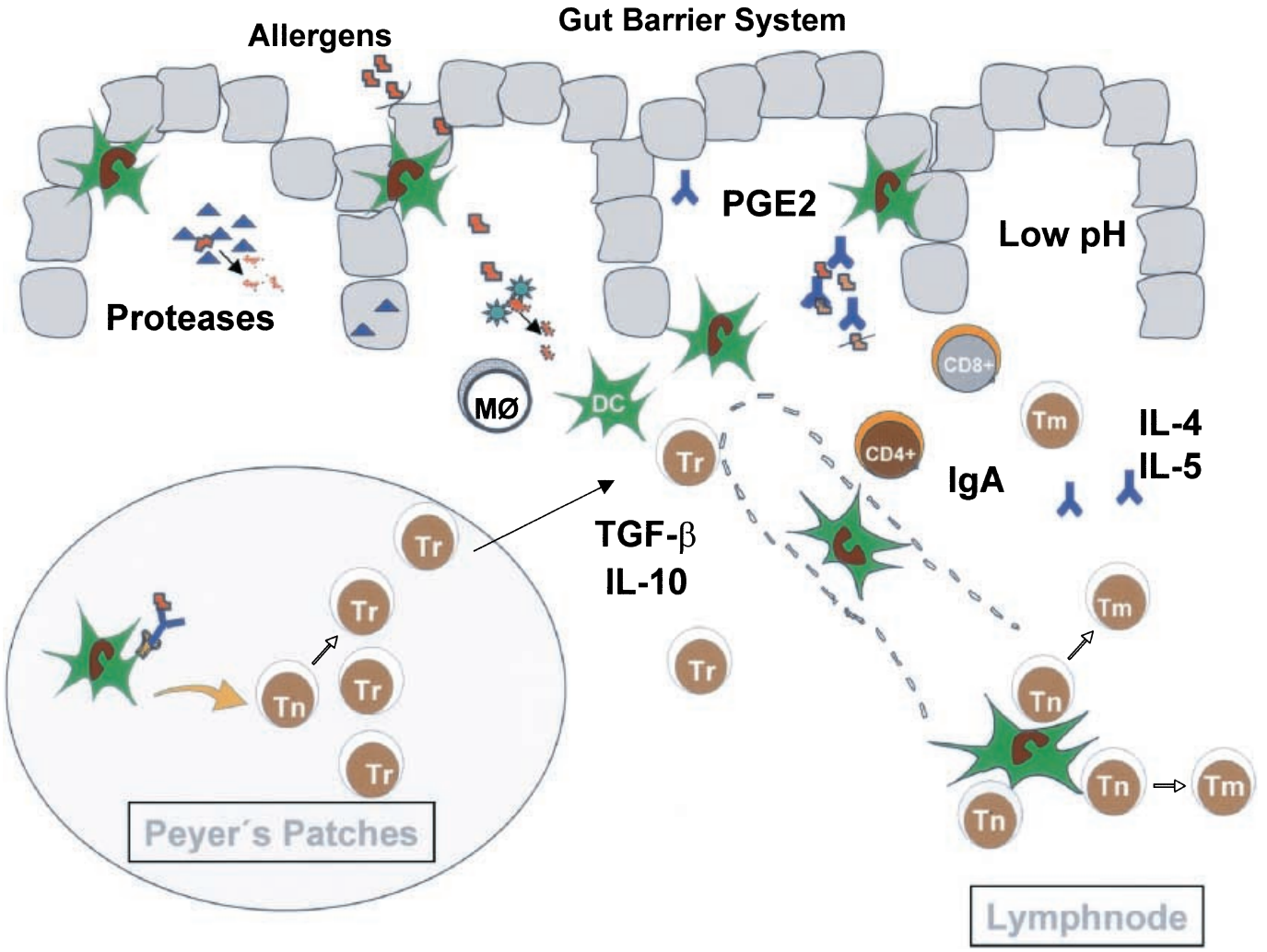

Figure 4. Induction of regulatory T-cells by DC of the gastrointestinal mucosa DC of the gastrointestinal mucosa produce TGF-β, which leads to the induction of tolerogenic regulatory T-cells. MØ, macrophages; DC, dendritic cells; Tn, naïve T-cells; Tm, memory T-cells; Tr, regulatory T-cells; PGE2, prostaglandin E2; TGF-β, transforming-growth-factor-β.

Regarding the mucosal surfaces of the gastrointestinal tract the primary APC type at the interface to the environment are DC which are regarded as the key factors in controlling T-cell responses in the gut wall (Table 1) (67–70).

This opens-up an exciting field of DC-controlled strategies which underlie the development of protective tolerance against allergens in the mucosal tissue (71). Functional clues as to their silencing role in this processes have come from experiments in which DC isolated from the mesenteric lymph nodes of mice administrated with OVA expressed increased amounts of TGF-β and enhanced the production of TGF-β by CD4 T-cells (62, 72). In doing so, they are capable of breaking down the inflammatory immune response by the induction of TH_3 cells (73), which as their main feature have a high capacity to produce the tolerogenic cytokine TGF-β in order to calm down T-cell responses substantially.

Antigen presenting cells of the oral mucosa

Recently, we were able to show that LC of the oral mucosa phenotypically and functionally differ from classical LC of the human skin and that their functional repertoire seems to be dictated in great part by their particular oral microenvironment, in which tolerance inducing cytokines such as IL-10 and TGF-β in combination with a special tolerogenic milieu prevails (62, 72). Most interestingly, oral LC exhibit a dramatically increased expression of FcεRI on their cellular surface, which is only partially occupied with IgE molecules (74) (Table 1). In view of rising evidence for a major role of FcεRI on APC, which besides its pro-inflammatory properties is even capable of initiating anti-inflammatory signals, such as the release of IL-10 and the induction of IDO (75–77), it is tempting to speculate that engagement of FcεRI by allergens on LC of the oral mucosa contributes to the tolerogenic properties of this cell type. Furthermore the developments of the past years have uncovered the existence of a sophisticated machinery that allows mucosal DC to induce tolerance induction within their tissue of residence.

Conclusion

Dendritic cells represent the key to the secret of the immunprivilege observed at particular anatomical sites. This is because of their unique property to induce antigen-specific responsiveness and unresponsiveness depending on a distinct microenvironment in allergic diseases. This also underlines their relevance not only in several clinical situations such as allergic diseases, inflammatory diseases and autoimmune diseases but also for the maintenance of health and self protection of the immune system. Undoubtedly, learning more about the fascinating characteristics of these cells is an essential step in improving the understanding of the natural regulation and dysregulation of immune responses and the induction of tolerance to self- and nonself antigens. As such DC can be regarded as the imunological key for the development of novel therapeutic strategies to adjust the balance between health and disease.

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