

The crucial role of dendritic cells in rhinitis

Alex KleinJan

Department of Pulmonary Medicine, Erasmus MC
Rotterdam, Rotterdam, The Netherlands

Correspondence to Alex KleinJan, PhD, Department of
Pulmonary Medicine, Erasmus MC Rotterdam,
Dr Molewaterplein 50, 3015 GE Rotterdam,
The Netherlands
Tel: +31 10 7043701; fax: +31 10 7044728;
e-mail: a.kleinjan@erasmusmc.nl

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Purpose of review

Dendritic cells generally play an important role as sentinels in the immune system. They are also very important in protecting the airways from invading pathogens and harmful particles and antigens. This review discusses current knowledge about dendritic cell function and the interaction between dendritic cells and their surroundings, the epithelium, during their presence in the nasal mucosa.

Recent findings

There are some phenotypical differences between myeloid dendritic cells and plasmacytoid dendritic cells in different types of rhinitis. Since it has become possible to perform functional studies on purified dendritic cell populations obtained from the upper airway mucosa, a number of studies have appeared. Some confirm that thymic stromal lymphopoietin is present in the nasal mucosa and that it may influence dendritic cell–T-cell interaction in a pro-Th2 way. Epithelial cells share several characteristics with dendritic cells, but they cannot migrate and move antigens to draining lymph nodes.

Summary

Several functional dendritic cell studies have been published indicating that there are disease-dependent dendritic cell differences in rhinitis. In addition to these differences, factors like epithelial cells and T cells influence dendritic cells. Several new therapeutic options are available targeting direct or indirect dendritic cell functions.

Keywords

epithelium, myeloid dendritic cell, plasmacytoid dendritic cell, thymic stromal lymphopoietin

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Introduction

The nose is the part of the human body with mucosal tissue that comes into contact with inhaled air and is continuously exposed to pathogens. Protection against these threats requires a good physical barrier and defence mechanisms that guard against potentially harmful invading pathogens. When this protection proves insufficient, immune cells provide a second line of defence. Dendritic cells are important immune cells in the epithelium. Dendritic cells are in close relation to epithelial cells and they can be activated by harmful invading pathogens, and by cytokines and chemokines produced by epithelial cells. Dendritic cells serve as a link between the innate and adaptive immune systems. Mucosal dendritic cells are very important in the process of antigen uptake and antigen presentation. Moreover, they act as sentinels, preventing injury by potentially harmful invading pathogens.

Dendritic cell activation

In steady-state conditions, few of these professional antigen-presenting cells (APCs) are present. These den-

dritic cells form an intensive network of cells between the epithelial cells [1–3]. Dendritic cells can open the tight junctions that allow dendrite to sprout beyond the epithelium [3,4^{••}]. The dendritic cells can sample the lumen, as has been observed in the lower airway [5]. Moreover, the epithelium and the epithelial lining fluid contain all kind of cytokines and chemokines that can stimulate or trigger dendritic cells [6]. The dendritic cells are activated when they are triggered by their pathogen-recognizing molecules in the ‘pathogen-associated molecular pattern’ (PAMP) – Toll-like receptors (TLRs), nucleotide binding and oligomerization domain (NOD)-like receptor (NLR) pathways. Dendritic cells can also be activated through triggering of the IgE receptor (FcεRI) or IgG receptors (FcγR) and through complement factors. During activation, they change from immature dendritic cells into mature dendritic cell phenotypes.

Dendritic cell migration from peripheral tissue to draining lymph nodes

Once dendritic cells have been activated, they express CCR7 and react to chemokines, signalling CCL19

(MIP3 β) and CCL22 (MDC). Dendritic cells then start to migrate in the direction of a lymph node. This process is generally the same for all immune responses, as has been shown in skin painting studies of the migration of dendritic cells/Langerhans cells from the epidermis to the draining lymph node, and in the lower airways by introducing Fite into alveolar space that can be traced back in the mediastinal lymph node. Moreover, in the upper airways, this is indicated by (tumour-specific pulsed) dendritic cells introduced by injection into the nasal inferior turbinates and traced back to the injection side of the nose and the regional lymph nodes [7]. Tumour-specific T-cell reaction was found in the ipsilateral, but not in the contralateral, lymph nodes [7]. Although the dendritic cells used in this study were blood-monocyte-derived dendritic cells, they still had a clear localized draining and migration pattern. Similar observations have been made in models by introducing Carboxyfluorescein succinimidyl ester (CFSE)-labelled murine dendritic cells into the nasal mucosa in droplet form. This resulted in detectable CFSE-labelled dendritic cells in the nasal mucosa in the nasal-associated lymphoid tissue (NALT) and in the cervical lymph node which drains the nose. No CFSE-labelled cells have been detected in either the mediastinal lymph node or in the lung [8].

Phenotypic variation in myeloid dendritic cell/plasmacytoid dendritic cell ratio in different upper airway diseases

The presence of myeloid dendritic cells (mDCs)–plasmacytoid dendritic cells (pDCs) studied in chronic rhinosinusitis (CRS) indicates that the majority of the dendritic cells are of the mDC phenotype in CRS without polyps, whereas there are more pDCs in CRS with polyps; the levels for control patients were between the levels for CRS with and without polyps [9]. In blood, the mDC/pDC ratio was highest in CRS without polyps and different from CRS with polyps and controls, which do not differ from each other. Nasal mucosa T cells in CRS with polyps showed a higher CXCR3/CCR4 ratio (representing the Th1/Th2 ratio) than CRS without polyps and controls. This suggests that T cells in CRS with polyps have a more pro-Th2 phenotype [9], although transcription factors for T-Bet Th1 or Gata3 Th2 are more specific for T-helper phenotypes. These results can be seen as an important step. However, additional research is needed because it is extremely difficult to draw functional conclusions from these data about pro-Th1 or pro-Th2. In Th2 diseases, flow cytometric analysis from blood identified a higher proportion of mDCs and, in infections, a higher proportion of pDCs. Moreover, in general, there is a lower percentage of pDCs in allergic patients than healthy controls [10]. The ratio mDC/pDC in healthy individuals is nearly one. The depletion of pDCs in asthma models indicates an increase in severity of, and susceptibility to, eosinophilic inflam-

mation [11], although we were unable to prove this in allergic rhinitis models [2].

Discovering the source of rhinitis

How are these dendritic cells activated? Which pathways are involved during activation? Which cytokine do they produce? These questions need answers because dendritic cells may carry the ‘fingerprint’ of the source, which could be very helpful in furthering research and clarifying how the harmful invading ‘bugs’ cause, and are responsible for, the disease. Moreover, it would be of interest to know how dendritic cells in CRS with or without polyps get activated. Which PAMPs are involved? Which pathways are activated? Moreover, it would be important to see whether damage-associated molecular patterns (DAMPs) are involved and to study exposure to all kinds of harmful agents such as cigarette smoke, ozone, diesel particles, fine particles and ultra fine particles. The need for additional study of the MHC peptides present in the MHC groove may show what kinds of protein are responsible for dendritic cell activation and, ultimately, T-cell activation and stimulation in different types of rhinitis. Proteomics could be very helpful in identifying the source. At the moment, little or no data are available in this field of rhinitis.

Functional aspects of nasal mucosa dendritic cells

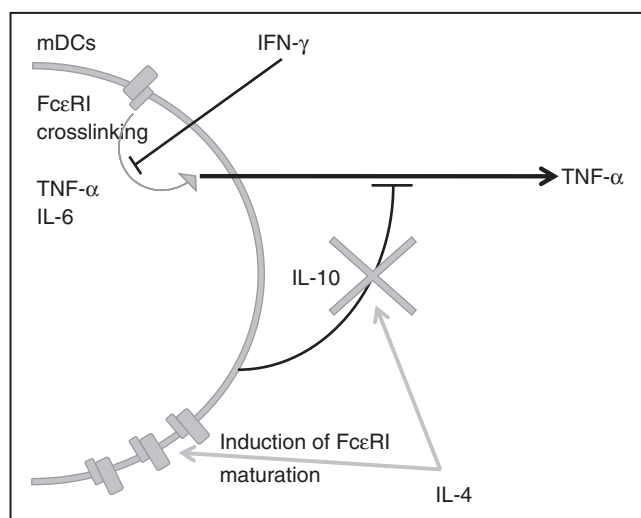
Myeloid dendritic cells isolated from nasal turbinate express higher levels of Fc ϵ RI in atopic patients than in nonatopic patients [12^{••}] (Fig. 1). The dendritic cells from atopic patients produce IL-6 and TNF α upon activation via the Fc ϵ RI [12^{••}]; dendritic cells from nonatopic patients produce IL-10 [12^{••}]. When dendritic cells were cultured with IL-4, they inhibited Fc ϵ RI-mediated IL-10 production [12^{••}]. This result suggests that the function of Fc ϵ RI can alter depending on the micro-environment and can vary from a proinflammatory phenotype in atopic patients to an immune-suppressive phenotype in nonatopic patients.

Myeloid dendritic cells isolated from surgically removed nasal mucosa and sorted by Magnetic-activated cell sorting (MACS) express muscarinic receptor 3. When cells are activated with metacholine binding M3, induction of the OX40l expression in dendritic cells is observed. Staphylococcal enterotoxin B (SEB) increases the expression of M3 in dendritic cells in a dose-dependent way [13[•]].

Dendritic cells in Waldeyer’s ring

Plasmacytoid dendritic cells obtained from the tonsils represent approximately 65% of the total tonsil dendritic cell population. They have a partially immature phenotype, expressing HLA-DR and CD40 but low levels of

Figure 1 FcεRI cross-linking induce the production of pro-inflammatory cytokine like TNF-α



The TNF-α production stops due to the production of IL-10. This IL-10 effect could be inhibited by IL-4; moreover IL-4 induces the expression of FcεRI molecules and the maturation of dendritic cells.

other costimulating markers like OX40l, CD80, CD83, PDL1 and B7RP1 (ICOSL). Plasmacytoid dendritic cells isolated from tonsils have the capacity to generate functional CD4+FOXP3+ Tregs [14]. Dendritic cells isolated from tonsils (mDC and pDCs) respond similarly: IL-12p70 release, upon stimulation with IFN-γ, anti-CD40 and LPS, which are strong and potent dendritic cell activators. Poli IC inhibited activation by IFN-γ, anti-CD40 and LPS from tonsil dendritic cells [15].

Functional differences between blood dendritic cells obtained from allergic patients and healthy controls

Myeloid (CD1c+) dendritic cell frequencies are higher in patients with grass pollen allergic rhinitis than in healthy controls. The levels of peripheral blood CD1c+ dendritic cells are unaltered after 7 days of nasal allergen challenge in allergic rhinitis patients, suggesting that, if there is extravasation into the shock organ shortly after allergen challenge, as reported in asthmatics after inhaled allergen challenge, replenishment to the original levels has already occurred or – in a less likely scenario – that there is no extravasation during challenge or after the challenge period [16]. The CD1c+ dendritic cells expressed the highest level of FcεRI mRNA and expressed the surface protein FcεRI, which was found in elevated levels upon allergen challenge [16]. It is known from blood mDCs that, upon FcεRI stimulation, they produce TNF-α, which peaks at 4 h, followed by a decline in the production of TNF-α and an increase in IL-10 which reaches a maximum 30 h after FcεRI stimu-

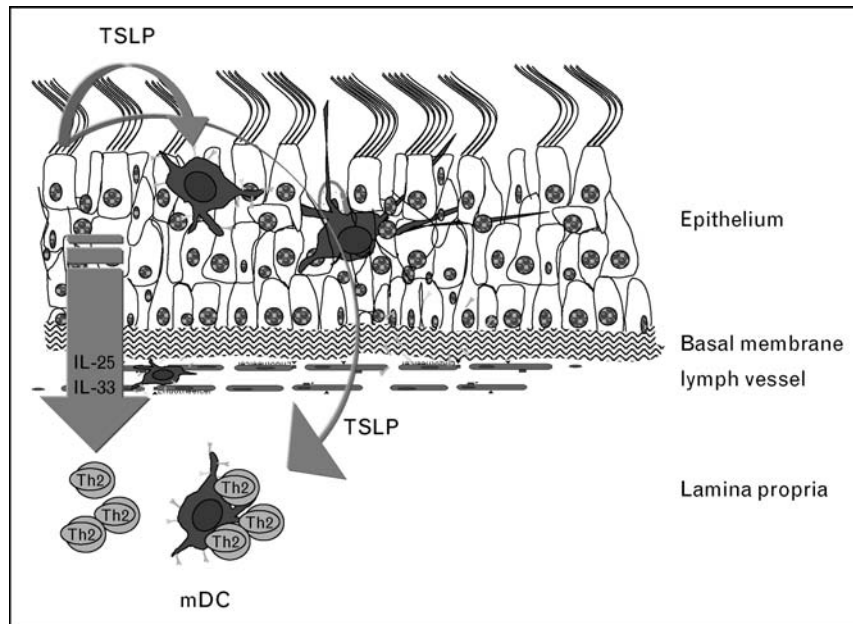
lation [17]. At that point, TNF-α production has come to a complete stop because IL-10 inhibits the de-novo synthesis of TNF-α by blood mDCs upon FcεRI stimulation. Moreover, IL-10 has no effect on costimulatory molecule expression or FcεRI expression, whereas IFNs counteract the FcεRI-dependent proinflammatory cytokine response [17]. This induction can alter the immune suppression action of IL-10, which offsets the production of proinflammatory cytokines like TNF-α.

When blood plasmacytoid dendritic cells isolated with BDCA2 were stimulated with CpG (an agonist of TLR9), the levels of IFN-α were six times higher in nonallergic than in allergic patients [18]. When allergic rhinitis patients with an allergy to House Dust Mite (HDM) underwent subcutaneous immunotherapy (SCIT) immunotherapy, dendritic cells function altered, restoring dendritic cell TLR9-mediated IFN-α production in a five-fold increase, approaching the levels in nonallergic individuals [19].

The influence of the micro-environment on dendritic cells: a role for thymic stromal lymphopoietin

Thymic stromal lymphopoietin (TSLP) triggers dendritic cells to promote Th2 responses. In recent decades, data have accumulated that appear to suggest that TSLP is a very important cytokine, being produced by epithelial cells, usually in the airways that stimulate dendritic cells, in such a way so that they promote T cells to produce Th2 cytokines [20]. TSLPs were discovered first in relation to atopy and proved to be important in atopic dermatitis [21]. Dendritic cells express the receptor complex for TSLP, which consists of a heterodimer of TSLPR and IL-7ra. TSLP in the absence of IL-12 induces the expression of OX40l in dendritic cells. The interaction between OX40 on T cells and OX40l on dendritic cells is critical for dendritic cell ability to drive Th2 differentiation [22•]. Moreover, TSLP-activated dendritic cells support the maintenance and polarization of CCR2-positive Th2 effector memory cells [22•]. Anti-TSLP treatments are novel treatment opportunities [20].

In vivo in nasal mucosa, dendritic cells are located in the epithelium and lamina propria. The intraepithelial location allows the dendritic cells to sample the lumen and there is possible influence from both the luminal and epithelial sides. Ongoing suggestions about an important role for TSLP and the presence of TSLP in the nasal mucosa have been proven (Fig. 2). Several studies have mentioned the presence of TSLP in allergic rhinitis [4•,23,24•,25]. TSLP mRNA expression is significantly increased in the nasal mucosa of allergic rhinitis patients compared with controls [4•,23,24•,25]. This is confirmed by other techniques like Western

Figure 2 Elevated numbers of dendritic cells are present in the inflamed nasal mucosa epithelium of allergic rhinitis patients

Epithelial cells produce all kinds of proinflammatory cytokines and chemokines like TSLP, IL-25 and IL-33. TSLP binds to the TSLP receptor and IL-7-receptor on dendritic cells to maintain the Th2 response. IL-25 and IL-33 are important chemokines for the recruitment of Th2 cells. TSLP, Thymic stromal lymphopoietin.

blot, immunohistochemistry, ELISA and mRNA [4^{••},23,24[•],25]. Correlations between levels of IL-4 mRNA and TSLP mRNA suggest a close relationship between these two cytokines [25]. Moreover, IL-4 is, at least *in vitro*, an important dendritic cell differentiation cytokine, supporting dendritic cell-dependent Th2 differentiation. Furthermore, murine studies showed that IL-13 induces TSLP expression in a stat6-dependent way. Stat6 is a signal transduction protein downstream from the IL-4/IL-13 receptor. Mice treated with IL-13 intranasally show eosinophilia and goblet cell hyperplasia and the expression of TSLP in the nasal mucosa. This suggests that TSLP may act not only downstream from IL-13 but also upstream from IL-13, supporting and maintaining allergic inflammation [24[•]]. Epithelial cells are the predominant cellular source of TSLP, as detected by immunohistochemistry [4^{••}]. Moreover, it has been suggested that mast cells regulate epithelial TSLP expression [24[•]]. Nasal fibroblast can produce TSLP in response to both TNF- α and IL-4/IL-13 stimulation [26]. The observation that dendritic cells are in close proximity to TSLP-positive epithelial cells suggest major physiological consequences for dendritic cell functions [4^{••}]. Interestingly, it has been observed that chitin, a biopolymer found in fungal cell walls and the exoskeleton of insects, lowers the expression of TSLP only in sinonasal epithelial cells derived from patients with recalcitrant CRS with nasal polyps [23]. Dendritic cells are continuously influ-

enced by other chemokines and cytokines produced by the epithelium, such as CCL20 (MIP3 α) and GM-CSF. The latter is an important growth factor for dendritic cells. Moreover, the epithelium can produce the pro-Th2 cytokines CCL11 and CCL17. The epithelium not only has a direct impact on dendritic cells; it also affects the production of IL-33 and IL-25 (Fig. 2). IL-33 and IL-25 are cytokines that drive the production of Th2-associated cytokines and function as a chemo-attractant for Th2 cells. IL-33 expression is higher in epithelial cells cultured from the sinus nasal mucosa of patients with treatment-recalcitrant chronic rhino sinusitis with polyps than in treatment-responsive patients [27].

Epithelial cells fulfil some dendritic cell functions

Epithelial cells play several supportive roles in the defence mechanism. Dendritic cells are located primarily in the epithelium [2,3]. They anchor in the epithelium with tight junctions [3,4^{••}]. In addition to producing inflammatory cytokines related to dendritic cells and T cells, epithelium can act as an APC [28,29]. However, the difference with dendritic cells is that epithelial cells cannot migrate to a draining lymph node, even though they may play an important role in the secondary immune response and in maintaining immune responses. Moreover, epithelial cells clearly share characteristics with APCs, such as the presence of all kinds of costimulatory molecules like

CD80, CD86, PD-L1, PD-L2 ICOS-L [29,30]. Several of these molecules can be induced by TLR ligands and other ligands like ITIM and NOD that trigger the epithelium. The epithelium in general contains T cells that express certain integrins and other molecules for the structural support of the epithelium [30].

Dendritic cells and T cells in the nasal mucosa

It is known that dendritic cells can cluster with T cells, resulting in a focal dense infiltrate in the nasal mucosa [2]. In-vitro studies of dendritic cell/T-cell interaction indicate that memory CD4⁺ T cells can change the transcriptional profile of dendritic cells. Blood memory CD4 T cells can educate dendritic cells and induce the up-regulation and down-regulation of several genes, which can be independent of the allergic status of the patient [31]. Moreover, CD30 (TNF receptor) and MMP25 were up-regulated in blood-monocyte-derived dendritic cells when subjected to memory T-cell co-culture. ICOSL up-regulation occurred exclusively in educated dendritic cells from allergic patients [31]. Furthermore, nasal mucosal tissue T cells clearly produced IFN- γ in CRS patients [32]. These observations support the close relationship between T cells and dendritic cells and *vice versa* because memory T cells are instructed by dendritic cells earlier in their proliferation to become activated and antigen-specific. This observation illustrates once again that once dendritic cells have been instructed wrongly, it is very difficult indeed to re-instruct the cascade of dendritic cell/T-cell interaction in a nonpathological way.

Targeting dendritic cells and dendritic cell functions

Specific immunotherapy (SIT) suppresses Th2 responses via the modulating T-cell immunoglobulin mucin domain molecule (TIM)1 with its ligand, TIM4, on dendritic cells [33]. Dendritic cells express TIM4, which is a ligand of TIM1, on CD4 T cells and induces their development into Th2 cells. Fluorescence-activated cell sorting (FACS) analysis has shown that there are more TIM1⁺IL-4⁺ T cells in the blood of allergic rhinitis patients compared with healthy controls [33]. The levels of these T cells declined gradually to control level after 5 days of culture, the result of the natural decay of TIM1 expression during culture [33]. Moreover, dendritic cells play a critical supportive role in maintaining the levels of IL-4, but not of IFN- γ , via TIM4, which is expressed at higher levels in blood dendritic cells in allergic rhinitis. Analysis has shown that there is more expression of TIM4 in allergic rhinitis dendritic cells compared with healthy control dendritic cells [33]. Confirming the importance for TIM4 of dendritic cells, TIM4 can be silenced with SiRNA and TIM1 expression declines accordingly. In allergic rhinitis patients treated with SIT, TIM4 expression is suppressed in dendritic cells

[33]. In addition, in CRS, Staphylococcal enterotoxin B (SEBs) induce and enhance TIM4 expression in dendritic cells that drive naïve T cells in a Th2 direction [34]. Immune complexes can modulate TIM4 in such a way that, through via Fc γ RI, they enhance or reduce the expression of TIM4 in dendritic cells. The observation that the major allergen of house dust mite, the *Dermatophagoides pteronyssinus* (Der)/IgG/Fc γ RI complex, was detected in dendritic cells from patients with allergic rhinitis before SIT, whereas high levels of Der/IgG/Fc γ RII complex were detected in dendritic cells after SIT suggests that the dendritic cells were reprogrammed via the immune complexes present [33].

Other experimental methods in models indicate that CD40 silenced dendritic cells with minimal expression of CD40 and that pretreatment with SiRNA-silenced CD40 [35^{••}]. OVA dendritic cells were less potent as inducers and initiators of the immune response, as has been shown by the restimulation of spleen-cell proliferation, and they do not produce IL-4 and IL-5 [35^{••}]. Furthermore, OVA-specific serum IgE and IgG are not found in animals immunized with SiCD40 OVA dendritic cells. The local nasal response measured with nasal symptoms and tissue eosinophilia, serum OVA-specific IgE and IgG1 and spleen lymphocyte proliferation and cytokine production dropped after treatment with SiCD40 OVA dendritic cells compared with control dendritic cells or with PBS treatment, suggesting an active mechanism that suppresses the Th2 response [35^{••}]. OVA-specific active suppression results from the induction of Tregs and supports an active role for Tregs. In addition, the induction of Tregs is very important in the reduction of airway inflammation [35^{••}].

In addition to these experimental therapeutic opportunities, there are several others that target dendritic cells directly or indirectly. The PI3K delta inhibitors open up a unique opportunity for the selective blocking of type I IFN production by pDCs, while preserving NF- κ B-dependent responses that are induced in response to threats that could have important proinflammatory or regulatory effects through the modulation of T-cell responses [36]. CCR2 antagonist blocking CCR2 may modulate the key mechanisms of fibroblast differentiation into myofibroblasts. The expression of MCP-1 is elevated in various diseases characterized by chronic inflammation and large numbers of infiltrating monocytes [37]. CRTH2 antagonist treatments may target dendritic cells indirectly to prevent the influx of Th2 cells which will then be prevented from stimulating dendritic cells [38].

Conclusion

Dendritic cells play an important role in rhinitis. Dendritic cells together with epithelial cells play an important role in

the immunological defence mechanism from innate to adaptive immune response of the upper airways. There is still a lot to discover in CRS with or without polyps. With new techniques, it is possible to dig deeper into the immune problems of the diseased tissue and it would be worthwhile to identify more of the functional possibilities of dendritic cells in the diseased upper airway.

Acknowledgement

I thank Pete Thomas for correcting the English.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 64).

- 1 Jahnsen FL, Farkas L, Lund-Johansen F, Brandtzaeg P. Involvement of plasmacytoid dendritic cells in human diseases. *Hum Immunol* 2002; 63:1201–1205.
- 2 KleinJan A, Willart M, van Rijt LS, *et al.* An essential role for dendritic cells in human and experimental allergic rhinitis. *J Allergy Clin Immunol* 2006; 118:1117–1125.
- 3 Takano K, Kojima T, Go M, *et al.* HLA-DR- and CD11c-positive dendritic cells penetrate beyond well developed epithelial tight junctions in human nasal mucosa of allergic rhinitis. *J Histochem Cytochem* 2005; 53:611–619.
- 4 Kamekura R, Kojima T, Koizumi J, *et al.* Thymic stromal lymphopoietin enhances tight-junction barrier function of human nasal epithelial cells. *Cell Tissue Res* 2009; 338:283–293.
- This study showed the production of TSLP in nasal biopsy specimens from normal versus allergic rhinitis patients.
- 5 Hammad H, Chieppa M, Perros F, *et al.* House dust mite allergen induces asthma via Toll-like receptor 4 triggering of airway structural cells. *Nat Med* 2009; 15:410–416.
- 6 Chawes BL, Edwards MJ, Shamji B, *et al.* A novel method for assessing unchallenged levels of mediators in nasal epithelial lining fluid. *J Allergy Clin Immunol* 2010; 125:1387.e3–1389.e3.
- 7 Horiguchi S, Matsuo K, Okamoto Y, *et al.* Migration of tumor antigen-pulsed dendritic cells after mucosal administration in the human upper respiratory tract. *J Clin Immunol* 2007; 27:598–604.
- 8 KleinJan A, Lambrecht BN. Dendritic cells in rhinitis. *Handb Exp Pharmacol* 2009; 188:115–136.
- 9 Kirsche H, Niederfuhr A, Deuschle T, *et al.* Ratio of myeloid and plasmacytoid dendritic cells and Th2 skew in CRS with nasal polyps. *Allergy* 2010; 65:24–31.
- 10 Hartmann E, Graefe H, Hopert A, *et al.* Analysis of plasmacytoid and myeloid dendritic cells in nasal epithelium. *Clin Vaccine Immunol* 2006; 13:1278–1286.
- 11 de Heer HJ, Hammad H, Soullie T, *et al.* Essential role of lung plasmacytoid dendritic cells in preventing asthmatic reactions to harmless inhaled antigen. *J Exp Med* 2004; 200:89–98.
- 12 Faith A, Singh N, Chevretton E, *et al.* Counter regulation of the high affinity IgE receptor, FcεpsilonRI, on human airway dendritic cells by IL-4 and IL-10. *Allergy* 2009; 64:1602–1607.
- This is an interesting study demonstrating that isolated nasal mucosa dendritic cells produce several cytokine upon FcεpsilonRI stimulation.
- 13 Liu T, Xie C, Chen X, *et al.* Role of muscarinic receptor activation in regulating immune cell activity in nasal mucosa. *Allergy* 2010; 65:969–977.
- This is an interesting study demonstrating dendritic cell cytokine production and the role of Muscarinic receptor 3 and Staphylococcal enterotoxin B.
- 14 Palomares O, Rückert B, Küçüksezer UC, *et al.*, editors. Induction and maintenance of FOXP3⁺ Treg cells in human Tonsils as first line organs of immune tolerance. WIRM IV Davos Switzerland; 2010 March; Davos, Switzerland. Davos Switzerland 2010.
- 15 Polak ME, Borthwick NJ, Gabriel FG, *et al.* Activation of tonsil dendritic cells with immuno-adjuvants. *BMC Immunol* 2008; 9:10.
- 16 Lundberg K, Greiff L, Borrebaeck CA, Lindstedt M. FcεpsilonRI levels and frequencies of peripheral blood dendritic cell populations in allergic rhinitis. *Hum Immunol* 2010; 71:931–933.
- 17 Le T, Tversky J, Chichester KL, *et al.* Interferons modulate FcεpsilonRI-dependent production of autoregulatory IL-10 by circulating human monocytoic dendritic cells. *J Allergy Clin Immunol* 2009; 123:217–223.
- 18 Tversky JR, Le TV, Bieneman AP, *et al.* Human blood dendritic cells from allergic subjects have impaired capacity to produce interferon-alpha via Toll-like receptor 9. *Clin Exp Allergy* 2008; 38:781–788.
- 19 Tversky JR, Bieneman AP, Chichester KL, *et al.* Subcutaneous allergen immunotherapy restores human dendritic cell innate immune function. *Clin Exp Allergy* 2010; 40:94–102.
- 20 Edwards MJ. Therapy directed against thymic stromal lymphopoietin. *Drug News Perspect* 2008; 21:312–316.
- 21 Wang YH, Ito T, Homey B, *et al.* Maintenance and polarization of human TH2 central memory T cells by thymic stromal lymphopoietin-activated dendritic cells. *Immunity* 2006; 24:827–838.
- 22 Ziegler SF, Artis D. Sensing the outside world: TSLP regulates barrier immunity. *Nat Immunol* 2010; 11:289–293.
- This is a very good updated and overview dealing with the role of TSLP in allergic inflammation.
- 23 Lalaker A, Nkrumah L, Lee WK, *et al.* Chitin stimulates expression of acidic mammalian chitinase and eotaxin-3 by human sinonasal epithelial cells in vitro. *Am J Rhinol Allergy* 2009; 23:8–14.
- 24 Miyata M, Nakamura Y, Shimokawa N, *et al.* Thymic stromal lymphopoietin is a critical mediator of IL-13-driven allergic inflammation. *Eur J Immunol* 2009; 39:3078–3083.
- This study showed the relation between TSLP and IL-13.
- 25 Mou Z, Xia J, Tan Y, *et al.* Overexpression of thymic stromal lymphopoietin in allergic rhinitis. *Acta Otolaryngol* 2009; 129:297–301.
- 26 Nonaka M, Fukumoto A, Ogihara N, *et al.* Synergistic induction of thymic stromal lymphopoietin by tumor necrosis factor alpha and Th2 cytokine in nasal polyp fibroblasts. *Am J Rhinol Allergy* 2010; 24:e14–e18.
- 27 Reh DD, Wang Y, Ramanathan M Jr, Lane AP. Treatment-recalcitrant chronic rhinosinusitis with polyps is associated with altered epithelial cell expression of interleukin-33. *Am J Rhinol Allergy* 2010; 24:105–109.
- 28 Salik E, Tyorkin M, Mohan S, *et al.* Antigen trafficking and accessory cell function in respiratory epithelial cells. *Am J Respir Cell Mol Biol* 1999; 21:365–379.
- 29 Takizawa R, Pawankar R, Yamagishi S, *et al.* Increased expression of HLA-DR and CD86 in nasal epithelial cells in allergic rhinitis: antigen presentation to T cells and up-regulation by diesel exhaust particles. *Clin Exp Allergy* 2007; 37:420–433.
- 30 Schleimer RP, Kato A, Peters A, *et al.* Epithelium, inflammation, and immunity in the upper airways of humans: studies in chronic rhinosinusitis. *Proc Am Thorac Soc* 2009; 6:288–294.
- 31 Larsson K, Lindstedt M, Lundberg K, *et al.* CD4⁺ T cells have a key instructive role in educating dendritic cells in allergy. *Int Arch Allergy Immunol* 2009; 149:1–15.
- 32 Basinski TM, Holzmann D, Eiwegger T, *et al.* Dual nature of T cell-epithelium interaction in chronic rhinosinusitis. *J Allergy Clin Immunol* 2009; 124:74–80; e1–e8.
- 33 Zhao CQ, Li TL, He SH, *et al.* Specific immunotherapy suppresses Th2 responses via modulating TIM1/TIM4 interaction on dendritic cells. *Allergy* 2010; 65:986–995.
- 34 Liu T, He SH, Zheng PY, *et al.* Staphylococcal enterotoxin B increases TIM4 expression in human dendritic cells that drives naive CD4 T cells to differentiate into Th2 cells. *Mol Immunol* 2007; 44:3580–3587.
- 35 Suzuki M, Zheng X, Zhang X, *et al.* A novel allergen-specific therapy for allergy using CD40-silenced dendritic cells. *J Allergy Clin Immunol* 2010; 125:737–743; 43.e1–43.e6.
- This study is a interesting study showing that silencing CD40 in OVA-pulsed dendritic cells protects OVA-specific allergic sensitization in mice, and that antigen-specific Treg cells are increased.
- 36 Guiducci C, Ghirelli C, Marloie-Provost MA, *et al.* PI3K is critical for the nuclear translocation of IRF-7 and type I IFN production by human plasmacytoid dendritic cells in response to TLR activation. *J Exp Med* 2008; 205:315–322.
- 37 Xia M, Sui Z. Recent developments in CCR2 antagonists. *Expert Opin Ther Pat* 2009; 19:295–303.
- 38 Boehme SA, Chen EP, Franz-Bacon K, *et al.* Antagonism of CRTH2 ameliorates chronic epicutaneous sensitization-induced inflammation by multiple mechanisms. *Int Immunol* 2009; 21:1–17.