



Dendritic cell subset expression in severe chronic rhinosinusitis with nasal polyps

Claudina Perez-Novo^a and Rogério Pezato^b

Purpose of review

Two main pillars are implicated in nasal polyposis development: a severe imbalance in immunomodulation and a mechanical dysfunction because of an abnormal remodeling process. Dendritic cells play a crucial role in the link between innate and adaptive immune response and orchestrating the T-cell response and are implicated in the severe inflammatory process found in nasal polypoid tissue. This review summarizes the existent knowledge about dendritic cells in nasal polyposis.

Recent findings

Dendritic cells are found increased in nasal polyposis, regardless of subset. Of interest, plasmacytoid dendritic cells are decreased in patients with a more severe Th2 profile, suggesting an important role of the cytokines milieu in their functional response or that plasmacytoid dendritic cell could act mitigating the inflamed process found in polypoid tissue.

Summary

Understanding the dendritic cell subset expression in different environments, as well as the effect of these subsets on T-cell differentiation will greatly improve the development of new therapies in nasal polyposis.

Keywords

dendritic cells, nasal polyposis, sinusitis

INTRODUCTION

Dendritic cells are among the most enigmatic cells of the immune system. Two unique properties make these cells pivotal for the development of immunity: their bridging role, connecting the innate and adaptive immune responses, and their bimodal immunomodulation property, shaping adaptive response, or induction of immune tolerance.

Dendritic cells are also among the most potent antigen-presenting cells, and thus play crucial roles in innate and adaptive immune response (pathogen recognition and regulation of T cell-mediated response type, respectively) [1].

Although these cells share phenotypic and functional features that distinguish them from other leukocytes, they can follow several pathways of differentiation and maturation, leading to high functional plasticity according to the environment. This hinders characterization and classification of dendritic cells [1,2].

HUMAN DENDRITIC CELL SUBSETS

The classification of human dendritic cells is constantly evolving. Currently, the two major dendritic

cell groups recognized are plasmacytoid dendritic cells (pDCs) and conventional/myeloid dendritic cells (cDCs/mDCs), that is, all non-pDCs.

pDCs resemble plasma cells. They represent a small portion of the dendritic cell pool and are characterized, in their steady state, by expression of the blood dendritic cell antigen 2 (BDCA2) surface marker and slight or absent expression of major histocompatibility complex class I (MHC-I), major histocompatibility complex class II (MHC-II), costimulatory molecules, CD11b, and CD11c. These cells play an important role during viral infection, producing large amounts of IFN1 through toll-like receptors 7 and 9. Although pDCs have limited

^aDepartment Biomedical Sciences, University Antwerp; Laboratory of Proteinchemistry, Proteomics Epigenetic Signaling, Wilrijk, Belgium and

^bDepartment of Otolaryngology, Head and Neck Surgery, ENT Research Laboratory, Federal University of São Paulo, São Paulo, Brazil

Correspondence to Rogério Pezato, Department of Otolaryngology, Head and Neck Surgery, ENT Research Laboratory, Federal University of São Paulo, Rua dos Otonis, 700 Piso Superior, Vila Clementino, 04025-002 São Paulo, SP, Brazil. Tel: +11 5579 6018; fax: +11 5579 6018; e-mail: pezatobau@ig.com.br

Curr Opin Allergy Clin Immunol 2017, 17:1–4

DOI:10.1097/ACI.0000000000000328

KEY POINTS

- Dendritic cells are the main antigen-presenting cells playing a crucial role in the link between innate and adaptive immune response.
- In nasal polyposis, the more severe inflammatory process found in the upper airway, dendritic cells are increased.
- Dendritic cells in nasal polyposis are able to drive T helper differentiation, whereas the Th2-derived cytokines possibly inhibit pDC presence.

antigen presentation capacity, recent studies have demonstrated that antigens targeting specific pDC receptors elicit efficient antigen presentation [3].

Because of the complexity and wide-ranging nature of the cDC category, classification of cDC subsets is based on specificity and specialization rather than on a set of markers. Broadly, cDCs express the hematopoietic markers CD45, MHC-II, and CD11c and lack T cell, natural killer cell, B cell, granulocyte, and erythrocyte lineage markers [1]. They are divided into two major subsets: cDC2s (also named mDC2s), which exhibit high expression of the blood dendritic cell antigen 3 (BDCA3 or CD141) and make up more than 10% of all cDCs; and cDC1s (also named mDC1s), which are distinguished by expression of blood dendritic cell antigen 1 marker (BDCA1 or as CD1c). Their mouse equivalents are CD8⁺ and CD8⁻, respectively. These cells make up the majority of the mDCs population.

Additional dendritic cell subsets are also recognized. Langerhans cells, found mainly in the epidermis, express the markers langerin and E-cadherin. In terms of MHC-II and CD11c expression, langerhans cells resemble pDCs, with low levels of these markers and poor T-cell stimulation, offset by their capacity to induce regulatory T-cell differentiation. CD14⁺ cDCs, which resemble monocyte-derived macrophages, are also found in the skin [4].

The dendritic cells found in inflamed tissue have a transcriptome resembling that of macrophages, which has given rise to the suspicion that these cells are monocyte derived (moDCs). Indeed, moDCs can be derived from monocytes *in vitro* by exposure to granulocyte macrophage colony-stimulating factor and IL-4 [5].

The superior ability of cDCs to induce immunity and enforce tolerance is based on their strategic location in the marginal zone of the spleen, their ability to carry antigens to the T-cell zone in lymph nodes, and their capacity to stimulate and differentiate naïve T cells [1].

DENDRITIC CELLS IN NASAL POLYPOSIS

Although it is known that dendritic cells play a pivotal role in the pathophysiology of airway diseases, especially in the lower airways, research about these cells in the upper airways is quite limited.

The inflammatory process found in polyp tissue in patients with nasal polyposis is among the most severe to affect the upper airway mucosa. As expected, the frequency of dendritic cells (regardless of subset) is increased in nasal polyposis-affected tissue [2[■],6]; pDC, cDC1, and cDC2s counts are significantly increased in nasal polyp tissue when compared with healthy nasal mucosa from the inferior turbinate [2[■],6] and middle meatus [7[■]], regarded as the best control tissue in nasal polyposis studies [8]. In addition, one of the features of nasal polyposis is an imbalance in the cDC/pDC ratio when the relative increase in pDC and cDC counts is assessed [2[■],9]. Increased moDC counts have been found in patients with nasal polyposis, and were associated with Th2-biased systemic inflammation, but these findings were based on peripheral blood measurements and did not take nasal polyposis phenotype into account [10].

Polypoid tissue from patients with chronic rhinosinusitis (CRS) with nasal polyposis exhibits higher cDC1 and cDC2 counts when compared with nasal tissue from patients with CRS without nasal polyposis [7[■]]. The frequency of CD40⁺ (a costimulatory molecule) among CD11c⁺ cells in nasal polyposis tissue is 30–50% [11].

The role of dendritic cells in skewing T helper responses in the nasal mucosa has been widely questioned. Nasal polyposis is classically divided into two subsets: eosinophilic nasal polyposis (eNP), which is found mainly in European and American patients and features a Th2 signature, and noneosinophilic nasal polyposis (nNP), found mainly in Asian patients (almost half of nasal polyposis cases in Asia are nNP) with a mixed Th1/Th17 pattern of inflammatory response. It is well established that, in inflamed tissue, thymic stromal lymphopoietin-activated dendritic cells induce a Th2 response through the OX40 ligand (OX40L). In eNP, levels of thymic stromal lymphopoietin, OX40L, programmed cell death ligand 1 (PD-L1), and OX40L positive cDCs/pDCs are increased when compared with nNP [12[■]]. Supporting a role of dendritic cells in skewing Th2, eNP-derived dendritic cells cocultured with naïve T cells have been found to induce Th2 responses [12[■]]. A recent study [13] conducted in peripheral blood samples showed a different microRNA expression profile of dendritic cells in CRS subsets and controls, which could have implications for dendritic cell regulation and T-cell differentiation, and consequently nasal polyposis phenotype.

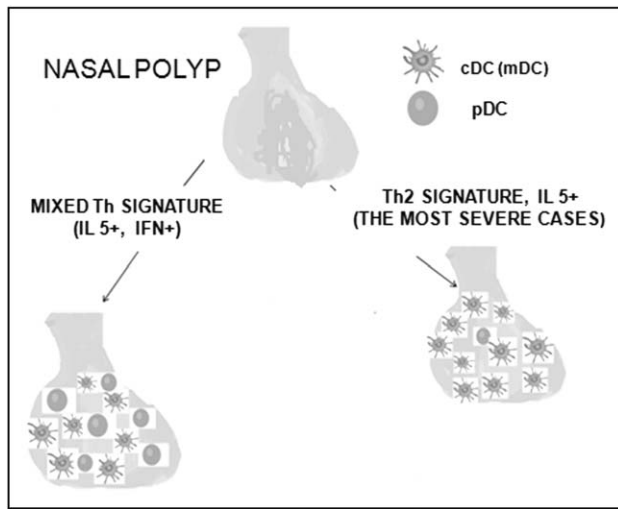


FIGURE 1. Illustration of DC subsets frequency in nasal polyposis. There is an increase in pDCs and cDCs (mDCs) in nasal polyposis. In the more severe inflammation, when orchestrated by Th2 cells, the number of pDCs decreased. cDC, conventional dendritic cells; mDC, myeloid dendritic cell; pDC, plasmacytoid dendritic cell.

THE ENVIRONMENT AND DENDRITIC CELLS IN NASAL POLYPOSIS

Vitamin D₃

Pediatric patients with nasal polyposis have low plasma levels of vitamin D₃ (both lower than those of controls and below the minimum recommended level of 30 ng/ml). The level of vitamin D₃ has been shown to correlate inversely with CD209 positive nasal polyposis-derived cells (receptor expressed on the surface of dendritic cells and macrophages), although the results were based on a retrospective study [14] and used immunostaining for dendritic cell detection. It is reasonable to believe that vitamin D₃ is implicated in dendritic cell modulation, as it exerts a tolerogenic role on these cells [15].

Biofilms

A biofilm is a group of adherent bacteria anchored to a surface and enclosed in a matrix of exopolysaccharide. This complex makes the bacteria resistant to fluctuations in moisture, pH, and temperature, as well as to antibiotic therapy.

Although the topic remains controversial, the prevalence of biofilms in nasal polyposis appears to be higher than in patients with CRS without nasal polyposis and in healthy controls [16].

Biofilm-positive nasal polyps display an increased number of dendritic cells positive for CD209 when compared with biofilm-negative nasal

polyps [17], strengthening the hypothesis of biofilm as a maintainer of chronic inflammation.

Inflammatory milieu

As noted above, pDC counts are increased in nasal polyposis, but these cells show a peculiar behavior according to the severity of the inflammatory process and clinical characteristics of the patient. In more severe phenotypes, such as nasal polyposis with comorbid asthma or aspirin sensitivity, pDC frequency is decreased in comparison with less severe groups such as nasal polyposis without asthma, and aspirin-tolerant nasal polyposis. Furthermore, the severe phenotypes exhibit high levels of IgE driven by Th2 cells, as classically demonstrated in eNP [2^o]. In this line, pDCs have been shown to correlate positively with interferon, a Th1 cytokine (Fig. 1).

It has been demonstrated that massive recruitment of pDCs after allergen challenge mitigates eosinophilic airway inflammation, whereas suppression of pDCs restores airway eosinophilia [18].

Expression of the enzyme indoleamine 2,3-dioxygenase (IDO) is low under homeostatic conditions, but increases during chronic inflammatory diseases in an attempt to mitigate inflammation. IDO is expressed mainly by dendritic cells. In nasal polyposis tissue, levels of this enzyme are increased in comparison with healthy nasal mucosa, especially in severe cases (nasal polyposis with asthma or aspirin sensitivity), as expected. In nasal polyposis, pDC counts correlate inversely with IDO levels [2^o]. These findings support an impaired immunosuppressive role of pDCs in nasal polyposis when orchestrated by Th2.

CONCLUSION AND FUTURE PERSPECTIVES

First, additional studies are needed to confirm our impressions of the role of dendritic cells in nasal polyposis. Assessments of pDC behavior in less Th2-influenced milieus would be of particular interest; studies involving Asian populations could bring new insights in this respect.

As dendritic cells exhibit great plasticity from their immature to their mature phenotype, dual immunomodulatory action (ranging from anti to proinflammatory), and ability to induce T helper differentiation in different directions according to the inflammatory environment, it is essential that research be conducted to elucidate the cytokines implicated in dendritic cell behavior and explore dendritic cell-targeting therapeutic strategies.

In this context, stimulation of dendritic cells with stable tolerogenic functions could be a new strategy

in balancing the immune response in nasal polyposis. In other tissues, dendritic cells pulsed with specific antigens could stimulate tolerogenic dendritic cells expressing low levels of costimulatory molecules, such as CD40, CD70, CD80, CD83, CD86, OX40L, glucocorticoid-induced tumor necrosis factor receptor-related protein ligand, lymphotoxin beta receptor, and high levels of suppressive molecules such as IL-10 and PD-L1, inducing T-cell anergy, T-cell apoptosis, or expansion of regulatory T cells [19,20]. Tolerogenic antigens might even be helpful in topical treatment of the nasal mucosa in patients with CRS.

In summary, the role of dendritic cells in nasal polyposis is still unclear. Additional data are needed to elucidate the true involvement of these cells and their implications for therapy.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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

1. Merad M, Sathe P, Helft J, *et al.* The dendritic cell lineage: ontogeny and function of dendritic cells and their subsets in the steady state and the inflamed setting. *Annu Rev Immunol* 2013; 31:563–604.
2. Pezato R, Pérez-Novo CA, Holtappels G, *et al.* The expression of dendritic cell subsets in severe chronic rhinosinusitis with nasal polyps is altered. *Immunobiology* 2014; 219:729–736.

The article demonstrates the influence of cytokines milieu on pDC frequency in nasal polyposis, suggesting that a Th2-driven disease limits pDC action.

3. Moffat JM, Segura E, Khoury G, *et al.* Targeting antigen to bone marrow stromal cell-2 expressed by conventional and plasmacytoid dendritic cells elicits efficient antigen presentation. *Eur J Immunol* 2013; 43:595–605.
 4. McGovern N, Schlitzer A, Gunawan M, *et al.* Human dermal CD14⁺ cells are a transient population of monocyte-derived macrophages. *Immunity* 2014; 41:465–477.
 5. Segura E, Touzot M, Bohineust A, *et al.* Human inflammatory dendritic cells induce Th17 cell differentiation. *Immunity* 2013; 38:336–348.
 6. Lin XS, Luo XY, Wang HG, *et al.* Expression and distribution of dendritic cells in nasal polyps. *Exp Ther Med* 2013; 5:1476–1480.
 7. Poposki JA, Peterson S, Welch K, *et al.* Elevated presence of myeloid dendritic cells in nasal polyps of patients with chronic rhinosinusitis. *Clin Exp Allergy* 2015; 45:384–393.
- The recent article supports the findings that DCs, especially mDCs, are increased in nasal polyposis suggesting the pivotal role of these cells in modulating a proinflammatory environment.
8. Pezato R, Voegels RL, Stamm AC, Gregório LC. Why we should avoid using inferior turbinate tissue as control to Nasal Polyposis studies. *Acta Otolaryngol* 2016; 136:973–975.
 9. Kirsche H, Niederführ 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. O'Connell BP, Schlosser RJ, Wentzel JL, *et al.* Systemic monocyte-derived dendritic cells and associated Th2 skewing in chronic rhinosinusitis. *Otolaryngol Head Neck Surg* 2014; 150:312–320.
 11. Pezato R, de Almeida DC, Bezerra TF, *et al.* Immunoregulatory effects of bone marrow-derived mesenchymal stem cells in the nasal polyp microenvironment. *Mediators Inflamm* 2014; 2014:583409.
 12. Shi LL, Song J, Xiong P, *et al.* Disease-specific T-helper cell polarizing function of lesional dendritic cells in different types of chronic rhinosinusitis with nasal polyps. *Am J Respir Crit Care Med* 2014; 190:628–638.
- Very interesting study demonstrating the ability of nasal polyp-derived dendritic cells to stimulate Th2 differentiation.
13. Ma ZX, Tan X, Shen Y, *et al.* MicroRNA expression profile of mature dendritic cell in chronic rhinosinusitis. *Inflamm Res* 2015; 64:885–893.
 14. Mulligan JK, White DR, Wang EW, *et al.* Vitamin D3 deficiency increases sinus mucosa dendritic cells in pediatric chronic rhinosinusitis with nasal polyps. *Otolaryngol Head Neck Surg* 2012; 147:773–781.
 15. Bscheider M, Butcher EC. Vitamin D immunoregulation through dendritic cells. *Immunology* 2016; 148:227–236.
 16. Arild Danielsen K, Eskeland Ø, Fridrich-Aas K, *et al.* Bacterial biofilms in chronic rhinosinusitis; distribution and prevalence. *Acta Otolaryngol* 2016; 136:109–112.
 17. Karosi T, Csomor P, Hegyi Z, Sziklai I. The presence of CD209 expressing dendritic cells correlates with biofilm positivity in chronic rhinosinusitis with nasal polyposis. *Eur Arch Otorhinolaryngol* 2013; 270:2455–2463.
 18. Kool M, van Nimwegen M, Willart MA, *et al.* An anti-inflammatory role for plasmacytoid dendritic cells in allergic airway inflammation. *J Immunol* 2009; 183:1074–1082.
 19. Segovia-Gamboa N, Rodríguez-Arellano ME, Rangel-Cruz R, *et al.* Tolerogenic dendritic cells induce antigen-specific hyporesponsiveness in insulin- and glutamic acid decarboxylase 65-autoreactive T lymphocytes from type 1 diabetic patients. *Clin Immunol* 2014; 154:72–83.
 20. Klarquist J, Zhou Z, Shen N, Janssen EM. Dendritic cells in systemic lupus erythematosus: from pathogenic players to therapeutic tools. *Mediators Inflamm* 2016; 2016:5045248.