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Review Article

Dendritic Cells can be Beneficial in Respiratory Diseases

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Abstract

Dendritic cells (DCs) are classically known to have the function of recognizing antigens, migrating to lymph nodes and presenting antigens to T cells, so they can differentiate and secrete inflammatory cytokines. However, DCs may assume a different phenotype of these conventional DCs, assuming a plasmacytoid profile, being able to induce immune tolerance and secrete anti-inflammatory cytokines. DCs may also assume a regulatory profile with expression of immunosuppressive markers and act in a resolving phase of inflammation. This review discusses the role of these DCs in the control of respiratory diseases, emphasizing mainly their mechanisms of action and possible flaws in their responses.

Keywords: *Dendritic Cells; Tolerance; Immunosuppression; Regulatory Cells; Respiratory Diseases*

Abbreviations

cDCs: Conventional Dendritic Cells; COPD: Chronic Obstructive Pulmonary Disease; DAMPS: Danger-Associated Molecular Patterns; DCreg: Regulatory Dendritic Cells; DCs: Dendritic Cells; ICOS: Inducible Costimulatory; ICOS-L: Inducible Costimulatory-Ligand; IDO: Indoleamine; IFN: Interferon; IL: Interleukin; MHC: Major Histocompatibility Complex; NLRs: Nucleotide-Binding Oligomerization Domain-Like Receptors; NK: Natural Killer Cell; NOD: Nucleotide-Binding Oligomerization Domain; PAMPS: Pathogen-Associated Molecular Patterns; pDCs: Plasmacytoid Dendritic Cells; PD-L1: Programmed Death-Ligand 1; PGE2: Prostaglandin E2; PRPs: Pattern Recognition Receptors; RIG: Retinoic-Acid-Inducible Gene I; RLRs: Retinoic-Acid-Inducible Gene I: Like Receptors; TLRs: Toll-Like Receptors; TGF: Transforming Grown Factor; TNF: Tumor Necrosis Factor; Treg: T Regulatory Cell

Introduction

In 2011, Ralph Sternmamm won the Nobel Prize in Physiology or Medicine for discovering dendritic cells (DCs) and his immune activity in the 1970s [1,2]. Since then knowledge about these cells has increased. To bridge innate and adaptive immunity, exist DCs. Classically, DCs are located in epithelial barriers and are capable of recognizing harmful signals through pattern recognition receptors (PRPs). Express many PRPs, such toll-like receptors (TLRs), retinoic-acid-inducible gene I (RIG-I)-like receptors (RLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), that recognize pathogen-associated molecular patterns (PAMPS) and danger-associated molecular patterns (DAMPs) [3,4]. These activated DCs upregulate the expression of major histocompatibility complex (MHC) molecules, costimulatory molecules and proinflammatory cytokines to induce proliferation and differentiation of naïve T cells and

initiate the adaptive immune response. They capture and process the antigen, migrate to regional lymph nodes to present the antigens to naïve T cells, which can differentiate into Th1, Th2 or Th17 subtype according to the antigen presented [5,6].

However, under specific physiological and pathological conditions, during the maturation process, DCs may lose MHC expression and costimulatory molecules and express anti-inflammatory cytokines, promoting tolerogenic responses, as well as inducing regulatory T cells (Treg) [7].

Mechanism of tolerance and regulation of inflammation by DCs

DCs previously thought to be immature had low levels of MHC II and costimulatory molecules, being able to promote T cell anergy and Treg production, promoting immune homeostasis [8-12].

Currently, DCs can be classified into conventional (cDCS) or plasmacytoid (pDCs) [13].

The cDCs have classical morphology, high MHC II expression and can be localized to tissues and lymph nodes. In tissues are called migratory DCs and lymph nodes of lymphoid DCs. Migratory DCs carry the antigens to the lymph nodes, and are divided into $CD103^+$ and $CD103^-$ [13]. $CD103^+$ cDCs are involved in the presentation of antigens to $TCD8^+$ cells while CD103- are effective in antigen clearance and T cells recruitment [13]. $CD103^+$ cells are found in the lungs and intestines and induce the generation of Treg and production of interleukin (IL)-10 [9], with the involvement of transforming growth factor (TGF)-β and retinoic acid signaling [14,15].

Lymphoid DCs and cDCs are classified according to the expression of CD8α ($CD8\alpha^+$ cDCs and $CD8\alpha^-$ cDCs) which is regulated by various cytokines and transcription factors [16,17]. $CD8\alpha^-$ cDCs induce Th2 response via MHC II and $CD8\alpha^+$ cDCs mediate the presentation to cytotoxic T cells, which are essential for combating tumor cells and viral infections [18]. $CD8\alpha^+$ cDCs induces tolerance through T cell inhibition and Treg cell induction [19,20].

Migratory DCs in the thymus (thymic DCs) can still be classified into 2 subtypes: $CD8^{low}$Sirpalpha+ and $CD8^{high}Sirpalpha^{low}$, both involved in central tolerance. cDCs $CD8^{low}$Sirpalpha induces Treg [21].

The pDCs are able to produce type I interferon (IFN) after activation of TLR7 and TLR9 in response to viral RNA and CpG-rich sequences [22,23]. After activation of the pDCs, naive T cells produce IFN-γ and IL-10 and promote Th1 differentiation. IDO is responsible for causing pDCs to induce Tregs and suppress T cell activation and induce their anergy [24-26]. The pDCs express CD123 [27] and are skilled in capturing allergens with high affinity for Immunoglobulin (Ig)E and have the ability to present to $TCD8^+$ cells [28].

Regulatory DCs (DCreg) have the ability to present antigens to antigen-specific T cells, decreasing the expression of costimulatory molecules (CD40, CD80 and CD86), proinflammatory cytokines, such as IL-12 and increasing the expression of immunosuppressive molecules, such as programmed death-ligand 1 (PD-L1), indoleamine (IDO) and CD95L and anti-inflammatory cytokines such as TGF-β and IL-10 [29]. They are mechanisms in which DCreg cells promote immune tolerance and induce the generation of Treg, inhibition of T cell response and induction of T cell apoptosis [30].

$CD11b^{high}Ia^{low}$ DCreg acts directly by secreting soluble factors to inhibit T cell proliferation, whereas $CD11c^{low}$CD45RB+ DCreg induces the production of IL-10 by Treg [31,32]. CD1c+ DCreg expresses less tumor necrosis factor (TNF), IL-6 e IL-12, and more IL-10 e IDO in response to *E. coli* [33,34].

INKT cells are a distinct population of T cells that express an invariant aβ T cell receptor and a number of cell surface molecules in common with natural killer cells (NK). INKT cells induce the generation of IL-1β producing tolerogenic DCs, contributing to the generation of Treg [35,36].

However, one study pointed out that DCs can induce the generation of Treg in the presence of TGF-β and IL-6 and promote maintenance and accumulation of the Treg population via MHC II expression and CD80 and CD86 costimulatory molecule [37].

Dendritic cells against respiratory diseases

DCs are located in the basolateral layer of airway epithelium projecting into the lumen, where they recognize and capture the antigens [38].

The first reported a beneficial effect of DCs on respiratory diseases was seen in asthma in 2001. DCs are found in the bronchial lymph nodes twenty-four hours after exposure to ovalbumin and expressed IL-10 [39].

In asthma, CDCs promote Th2 sensitization to the inhaled agent after reaching the mediastinal lymph node [40-42], while pDCs mediate tolerance to inhaled antigen (ovalbumin) through induction of Treg [25,43,44]. The pDCs can also suppress eosinophilic inflammation of the airways by down-regulating the function of the cDCs [44].

When pDCs are removed from the lung there is increased inflammation after challenge with allergen in sensitized. Some chemokines appear to be involved in the recruitment of pDCs to the lungs, such as CCL2 (MCP-1), CCL3 (MIP-1), CCL5 (RANTES), CCL12 (MCP-5), CxCL10 (IFN-γ and CxCL12 (stromal cell-derived factor 1) are up-regulated in allergic lungs [45] and the pDCs express receptors for most of these cytokines CCR1, CCR2, CCR5, CCR7, CXCR3 and CXCR4 [46-48], could also have involvement of Chem R23, a receptor involved in the migration of DCs and expressed in pDCs [49].

CCL18 chemokine is upregulated in patients with diseases such as asthma [50] and chronic rhinosinusitis [51]. CCL18 inhibits the Th2 allergic response *in vivo* and *in vitro* [52]. This chemokine is expressed in DCs and is a tolerance inducer, but the mechanisms that activate or inhibit its expression have not been elucidated [52]. In alveolar macrophages, the Th2 response increases the expression of CCL18 in macrophages, whereas interferon gamma inhibits its production [52].

In some diseases such as asthma, chronic obstructive pulmonary disease (COPD) and cystic fibrosis, IL-10 levels in the lungs are reduced compared to healthy subjects, suggesting that the reduction of IL-10 may be a crucial point for the maintenance of chronicity of pulmonary diseases [53,54].

When there is exposure to the allergen, the number of pDCs increases in the lung and decreases in the periphery [55]. A primary defect in pDCs may be responsible for asthma, this effect appears to be on response rather than on recruitment or activation, since pDCs appear in greater numbers in subjects with allergic rhinitis, allergic and non-allergic asthma [56,57]. Defects in the responses of pDCs may be associated with genetic abnormalities such as nucleotide polymorphisms of TLR7 [58,59].

Another important observation is that expression of the IgE receptor, FcεRIα in pDCs is greater in asthmatics [60] and prevents the release of type I and type III IFN from these cells [60-63]. The use of omalizumab (anti-IgE) in turn is capable of decreasing FcεRI expression in human pDCs in severe asthma [64]. In addition, this drug was able to cause down-regulation of TLR9 through the production of TNF-α by pDCs [65].

The pDCs have an antiviral function with rapid production of type I IFN [22], but in asthmatics, there may be a failure in the production of type I IFN in the airways in response to infection and may be due to failure to maintain pDCs homeostasis in the face of infection [66].

Although pDCs inhibit the development of allergic airway inflammation and have an antiviral effect, respiratory syncytial virus infection interferes with the function of pDCs, inhibiting the tolerance function. Once infected with respiratory syncytial virus, pDCs do not induce Treg and IL-10 in the lungs of mice and lose the ability to resolve allergic airway inflammation [67].

In animals challenged with *Bordetella pertussis*, CD11c+CD8α+ DCs were found in cervical lymph nodes and lungs 1 to 7 days post-infection [68]. These pDCs expressed MHC I and II, costimulatory molecules (CD40, CD80 and CD86), CD103 and secreted IFN-γ, IL-4, and IL-10 [68]. Depletion of the pDCs throughout the infection before and after challenge with *B. pertussis* delayed clearance of the bacteria, suggesting that pDCs play an essential protective role in infection [68]. The same happened with the blocking CD103. It may be that CD103 is involved in homing between tissue and lymph node since it is also present in DCs with inflammatory activity in viral infection model and airway hypersensitivity [68-70].

In severe infection with *Chlamydia pneumoniae* there is recruitment of many pDCs in the lung, with increased Treg cells and increased IL-10 [71,72]. The depletion of the pDCs leads the mice to death after infection with *C. pneumoniae*, suggesting that it plays a key role in the control of infection [71]. Depletion of the pDCs does not change the number of Tregs of the lung and draining lymph nodes, indicating that other mechanisms are involved in the maintenance of Treg and that these cells are not sufficient to maintain infection control [71].

DCs require stimuli such as TGF-β and M-CSF (macrophage colony-stimulating factor) to be differentiated into DCreg in the pulmonary stroma. In stroma, DCregs act by secreting PGE2 and IDO, which together stimulate IL-10 production and inhibit T-cell proliferation [73].

$CD1c^+$ DCs from lung tissue explants from COPD patients exhibit immunosuppressive functions and favor the differentiation of IL-10 secreting $CD4^+$ cells that suppress other inflammatory responses in a manner dependent on IL-27, IL-10, inducible costimulatory (ICOS)/ inducible costimulatory-ligand (ICOS-L) [74]. CD40 may be associated with increased immunosuppressive function of CD1c+ DCs in COPD patients [75]. These DCregs favor the differentiation of IL-10 secreting T cells which suppress naive T cells and effector T cells [74]. TCD4+ cells are induced with immunosuppressive function, expressing PD-1, PDL-1, ICOS, being dependent on the production of IL-10 and TGF-β [74].

Conclusion

DCs, although traditionally divided into classical plasmacytoid, can also be classified as regulatory. Although there are few studies on their mechanisms of action, there is no one to explore the difference between them, and it is necessary to take into account that the DCreg is characterized by the release of classical immunosuppressive mediators, which are not seen reported in the studies involving the pDCs. There are still not many reports in the literature about pDCs in respiratory diseases, is the first report of 2011 let alone DCreg. Most studies correlate their mechanisms of action with those of Treg, but other regulatory cells may be involved. It is noticeable that pDCs participate in an initial moment of the inflammatory response, whereas DCreg is present at a later time, in a resolution phase. The pDCs appear to play an essential role in maintaining the anti-inflammatory response, especially against allergens. Potential flaws in pDCs may be the answer to maintaining the chronicity of allergic diseases, such as asthma.

Conflict of Interest

The author declares no financial or commercial conflict of interest.

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