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The Role of Dendritic Cells in the Pathogenesis of COPD: Liaison Officers in the Front Line

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ABSTRACT

Dendritic cells are professional antigen presenting cells linking innate and adaptive immune responses. Different dendritic cell subsets were identified in human lung, each with their own functional characteristics. As innate and adaptive immune responses are activated in Chronic Obstructive Pulmonary Disease (COPD), dendritic cells could play a role in the pathogenesis of this disease. Indeed, cigarette smoke appears to modulate dendritic cell function in vitro and alters dendritic cell numbers and function in cigarette smoke exposed mice. The number of pulmonary dendritic cells differs between COPD patients, smokers and non-smokers. Moreover, the number of Langerhans-type dendritic cells increases with the severity of the disease. In this review we will discuss the scientific evidence regarding the role of dendritic cells in COPD and we will put forward the concept of modulation of dendritic cell differentiation and function as a crucial step in the pathogenesis of COPD.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is an inflammatory disease of the airways and lung parenchyma due to the inhalation of noxious particles and gases, and is associated with an abnormal systemic inflammatory response. To-

bacco smoke and pollutants originating from biomass combustion are the most important environmental risk factors. COPD is characterized by an airflow limitation that is not fully reversible, and that is usually progressive, even after smoking cessation (1). The airflow limitation is caused by an inflammation of the small airways (i.e., bronchiolitis) combined with a destruction of the alveolar septa (i.e., emphysema), the latter resulting in enlargement of the alveolar air spaces and an impaired gas exchange. The exact pathogenetic mechanisms of the ongoing pulmonary inflammation and damage in COPD, even after the initial inciting agent has disappeared (i.e. smoking cessation), are poorly understood. Latent viral respiratory infections, chronic bacterial colonization of the lower airways, repetitive infectious exacerbations, auto-immune responses against changed epitopes in the lung and certain genetic predispositions are proposed as important driving mechanisms of the perpetuating inflammation in patients with COPD (2).

The lungs of COPD patients are infiltrated with cells of the innate immune system such as neutrophils and macrophages (3, 4), but there is also evidence for an activated adaptive immune response with accumulation of CD8+ T cells, B cells and the presence of lymphoid follicles (5–7).

Dendritic cells (DCs) are professional antigen presenting cells, originating from the hematopoietic system. In general, DCs are divided in two main populations: myeloid DCs (mDCs)

Keywords: COPD, dendritic cells, airway inflammation, antigen presentation, cigarette smoke, dendritic cell maturation

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and plasmacytoid DCs (pDCs). mDCs are thought to originate from myeloid precursors, whereas pDCs originate from lymphoid progenitors, although there is evidence that bone marrow pDCs could also differentiate into mDCs (8).

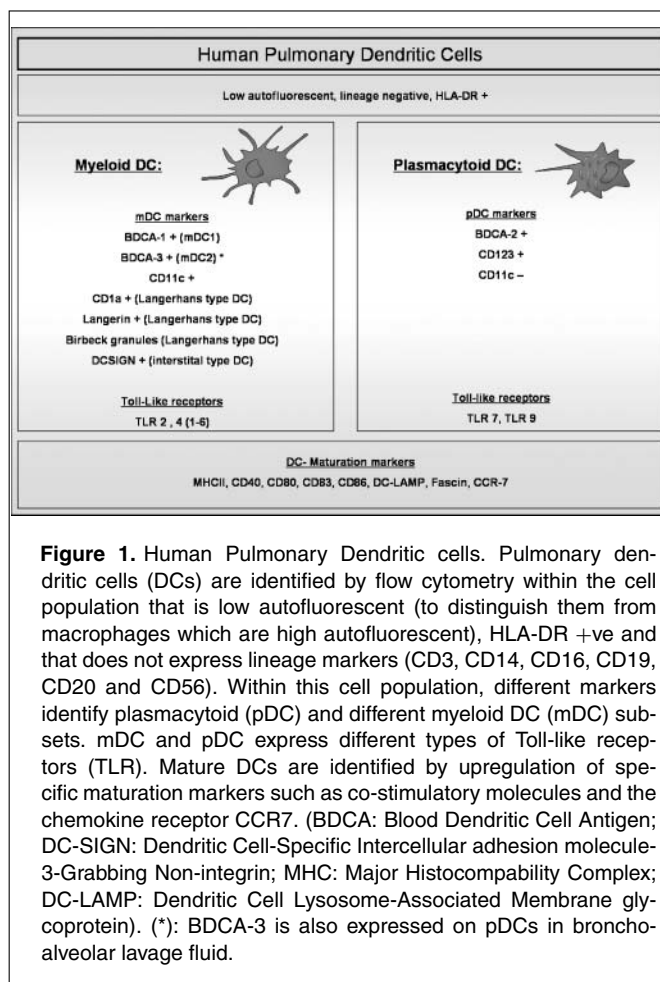
DCs are present in the skin and mucosal surfaces, where they continuously sample antigens. Simultaneously, they sense the environment for microbial compounds and danger signals, using pathogen recognition receptors (Toll-like receptors (TLR), Nod-Like receptors and C-type lectins) and damage associated pattern recognition receptors. DCs integrate the information from the antigens and danger signals and subsequently migrate towards the draining lymph nodes, whilst processing the antigen and upregulating the expression of co-stimulatory molecules (i.e., maturation) (9).

In the lymph nodes, mature DCs present the antigen on Major Histocompatibility (MHC) class II molecules to naïve CD4+ T lymphocytes. In addition, they can present and cross-present antigens to CD8+ T cells using MHC class I molecules. This immunological synapse allows for the selection of lymphocytes with the antigen-matched T cell receptor. Depending on the degree of expression of the co-stimulatory molecules and the cytokines produced by the DC, the lymphocytes can undergo clonal expansion. Moreover, the co-stimulatory process can steer the expanding T cells towards a T-helper (Th) 1, Th 2, Th 17 or regulatory T cell response. Thus, DCs are important orchestrators of immunity, linking innate and adaptive immune responses (10).

Human pulmonary dendritic cell subsets

The exact definition of the different DC subtypes in the human lung is incomplete. Two groups identified myeloid DCs and plasmacytoid DCs in mononuclear single cell suspensions from digested human lung tissue by flowcytometry (Figure 1) (11, 12). Both groups defined DCs within the low autofluorescent, lineage negative (–ve), HLA-DR positive (+ve) cell population. Demedts et al used Blood Dendritic Cell Antigen (BDCA) 1, 3, and 2 to identify mDC type 1, mDC type 2 and pDCs respectively. In contrast, Masten et al. defined mDCs as CD11c +ve cells that were CD1a +ve or BDCA1 +ve, and pDCs as CD11c –ve, CD123 +ve cells. mDCs and pDCs were also identified in human broncho-alveolar lavage (BAL) fluid. In BAL, BDCA-3 was also present on pDCs, suggesting that this marker does not delineate a separate mDC2 subset in all compartments of the lung (13). mDCs and mature DCs were identified in induced sputum (14, 15). In addition, *Langerhans-type DCs* (defined as langerin +ve or Birbeck granule +ve DCs) (11, 16, 17) and DC-SIGN (CD209) +ve *interstitial-type DCs* (18) were identified in the human lung by electron microscopy or immunohistochemistry.

Evidence from in vitro studies suggests that monocytes are important precursors of DCs. (19, 20) When studying human pulmonary mDCs, one should keep in mind that antigen presenting cells partially consist of a spectrum of specialized differentiated monocytes ranging from DCs to macrophages (21). The exact interrelationship of the different markers of monocytes



and DCs and how they reflect different subsets of pulmonary DC (precursors) largely remains to be elucidated.

It is tempting to speculate that, within these different DC subsets, carrying different surface markers, functional specialization does occur. Indeed, human pulmonary mDC type 1 and 2 were shown to release proinflammatory cytokines (TNF- α , IL-1 β , IL-6 and IL-8) in response to Toll-like receptors (TLR)-2 and TLR-4 ligands, whereas pulmonary pDCs released high amounts of interferon- α in response to the TLR-9 ligand CpG oligonucleotides (22). Moreover, mDCs derived from human lung digests or from BAL fluid were shown to be strong inducers of T cell proliferation in a mixed leukocyte reaction, while pDCs hardly induced any T cell proliferation (22, 23). Functional specialization of DC subsets has also been described in other organs such as the skin with for instance altered susceptibility to TLR ligands in Langerhans-type DC versus interstitial-type DC (24).

Functional differences in dendritic cells exposed to cigarette smoke

Several in vitro studies have evaluated the effect of nicotine and cigarette smoke extract (CSE) on the maturation process and T cell stimulatory capacity of mDCs. Human monocyte-derived DCs, which have a predominant interstitial phenotype,

showed increased maturation and increased IL-10 and IL-12 production upon exposure to a high dose nicotine (25), whereas a low dose of nicotine resulted in a decreased immature DC dependent T- cell proliferation and a decreased IL-12 production after Lipopolysaccharide (LPS) stimulation (26). These nicotine-exposed DCs were indeed less capable to induce differentiation of naïve T cells into T-helper 1 cells (27). Adding CSE to monocyte-derived DCs resulted in an attenuation of the maturation process with reduced expression of costimulatory molecules and a reduced expression of CCR7, a chemokine receptor involved in DC trafficking towards lymphoid tissues. Moreover, the DC-induced T cell proliferation was significantly reduced when DCs were cultured in the presence of CSE. Maturing CSE exposed DC produced less IL-12 and IL-23 and skewed the T cell response towards a Th 2 profile (28, 29). In addition, the production of the neutrophil attracting chemokine IL-8 was upregulated in these cigarette smoke exposed maturing monocyte derived DC (30). In summary, these in vitro data suggest that cigarette smoke directly inhibits the process of monocyte-derived DC maturation and skews the adaptive immune response away from Th1 towards a Th2 response.

In a mouse model of COPD, upregulation of pulmonary DC maturation markers was accompanied by the characteristic airway inflammation and emphysema (31). In contrast, Robbins et al found, using another protocol of smoke exposure, decreased expression of the maturation marker CD80 on pulmonary DC in the absence of pulmonary inflammation (32). Moreover, using the latter protocol, there was an impaired DC maturation in murine thoracic lymph nodes of smoke exposed mice compared to air exposed controls (33). Interestingly, *ex vivo* data from human mDC in BAL showed an increased expression of maturation markers by mDC combined with a decrease of CCR7 expression in smokers compared to non-smokers (34), whereas smoking reduced the number of mature DCs in bronchial biopsies of asthma patients (35). The issue of altered DC maturation by smoking and in COPD is controversial due to these conflicting data and due to the fact that there is currently no single

established marker that clearly defines the mature status of human pulmonary DCs.

Apart from the integration of danger signals and antigens, DCs are also capable of producing substantial amounts of proteinases, contributing to the proteinase-antiproteinase imbalance in COPD. Mouse DC showed indeed an increase of Matrix metalloproteinase-12 production upon cigarette smoke exposure, and could thereby contribute to the pathogenesis of emphysema (36).

Dendritic cells in smokers and COPD patients

There have been only a few studies addressing the number and distribution of DCs in the lungs of smokers and patients with COPD (Table 1). Most of these descriptive studies have a cross-sectional design, implicating that the sequence of events can not be established and that any evidence for causality is weak. At first sight, some data in the literature do appear discrepant or even contradictory, but this may be due to differences in the area of interest (bronchial biopsies sampling large airways *versus* surgical resection specimens sampling small airways and parenchyma *versus* BAL sampling the alveolar lumen), differences in the examination techniques (electron microscopy, flowcytometry or immunohistochemistry) or differences in the immunohistochemical markers used to identify and enumerate the DCs. It is also critical to discriminate between the effects of smoking *per se* on DC numbers, phenotypic markers or functions *versus* the disease-specific effects of COPD on DCs, irrespective of the current smoking status.

In the large airways (trachea, bronchi), sampled by bronchoscopy with endobronchial biopsies, the number of CD1a+ve DCs was evaluated in healthy smoking controls and current smoking COPD patients, showing no significant differences between groups (37). Others evaluated the number of DCs in large airways using electron microscopy, based upon morphologic criteria derived from cultured BDCA-1+ve DC, and showed a significant decrease in the number of DCs in the large airways

Table 1. Studies of Pulmonary Dendritic cells in Smokers and COPD patients

	Location	DC marker	Reference
Studies comparing smokers with non-smokers (without airway obstruction)	Small airways	CD1a=	16
		BDCA-1=	
	Alveoli	Langerin=	39
		CD1a ↑	16
	BAL	BDCA1 =	
		Langerin ↑	34
Studies comparing COPD patients with smokers without airway obstruction	Large airways	CD1a ↑	
		Birbeck granule ↑	17
		CD1a ↑	
Studies comparing current smoking COPD patients with ex-smoking COPD patients	Large airways	CD1a=	37
	Small airways	Langerin ↑	39
	Large airways	EM ↓	38

DC: dendritic cell
BDCA-1: blood dendritic cell antigen 1
EM: defined by electron microscopy

of smoking COPD patients versus ex-smoking COPD patients and never smoking controls (38).

In the small airways (bronchioli), which is the main location responsible for airway obstruction in COPD, the number of DC was evaluated using immunohistochemical staining for CD1a and BDCA-1, showing no difference between smokers and non-smokers (16). In patients with COPD, however, a significant increase in the number of CD207 (langerin) positive cells was found compared to never smokers and healthy smokers (without airway obstruction), suggesting an accumulation of Langerhans-type DC in COPD. Moreover, the number of langerin +ve DC further increased with the severity of the disease (39).

Studies sampling BAL fluid evaluated the number of DC between never-smokers and smokers without COPD, showing a significant increase in the expression of langerin and CD1a on myeloid DCs as well as an increase in Birbeck granule positive Langerhans-type DC in smokers versus non-smokers (17, 34). Finally, in the alveolar parenchyma, the number of CD1a +ve DCs was increased in smokers *versus* never smokers, whereas the number of BDCA-1 +ve DCs was not different (16).

In summary, evidence points towards an accumulation of mDCs with Langerhans-type cell markers (langerin, CD1a and Birbeck granules) in the small airways and alveoli of smokers and COPD patients. These langerin +ve Langerhans-type DCs are mainly regarded as immature DCs (40). This is in agreement with data from experimental models of COPD, in which mice are chronically exposed to cigarette smoke and develop manifest pulmonary inflammation and emphysema. A clear accumulation of mDCs was seen in the BAL fluid and in single cell suspensions from digested lungs of these mice (31). A recent immunohistochemical study confirmed the accumulation of DCs in cigarette smoke exposed mice (41). A different protocol of smoke exposure resulted in a decrease of the number of DCs in the lung in the absence of pulmonary inflammation (32). Evidence from the mouse model of COPD and from human lung tissue suggests that an activated macrophage inflammatory protein 3 α (MIP3 α)/CC-chemokine ligand (CCL20) – CC-chemokine receptor 6 (CCR6)- axis in COPD is responsible for the accumulation of mDCs in the lung (39, 42).

Modulation of DC differentiation and function in COPD pathogenesis

Dendritic cell precursors (blood DCs and monocytes) enter the lung from the blood stream under the influence of chemokines, defensins and heat shock proteins produced by the lung tissue (see Figure 2). Cigarette smoke could (directly or indirectly by inducing growth factor and cytokine production in the surrounding lung tissue) modulate the differentiation of DC precursors, leading to an altered composition of the DC population in the lungs of smokers and COPD patients. Current evidence shows an accumulation of Langerhans-type DCs in smokers and COPD patients, suggesting a stimulation of the differentiation process of DC precursors towards this DC

subset. Interestingly, Transforming Growth Factor beta (TGF β) and Tumor Necrosis Factor alpha (TNF α), which are known to drive Langerhans differentiation *in vitro* are increased in the airways of COPD patients (43, 44). Whether other Langerhans promoting differentiation factors—such as Notch ligand Delta-1, Interleukin-15, Activin-A and RANK-ligand - are involved in pulmonary Langerhans-type DC differentiation remains to be elucidated. It is currently unknown if other DC subsets such as interstitial-type DCs and pDCs accumulate in COPD.

At the epithelial surface, DCs are capable of sensing danger signals and take up antigens to process them. However, little is known about the influence of cigarette smoke on the expression and function of innate receptors of DCs, including TLR and lectin-like receptors. Once the DC has sampled the antigen, it will process the antigen, upregulate the expression of CC-chemokine receptor 7 (CCR7) and migrate towards the secondary lymphoid organs (i.e. mediastinal lymph nodes). As discussed above, *in vitro* data suggest that cigarette smoke reduces the ability of DCs to mature, giving a possible mechanism for higher susceptibility for microbial infection in smokers (45) and the occurrence of low grade infection or colonization in smoking COPD patients (46). This microbial stimulus can contribute towards a perpetuating damaging inflammation which will in turn release more danger signals, eventually increasing the number of mature DCs in COPD. In addition, the reduced expression of CCR7 combined with increased expression of maturation markers on BAL DCs of smokers (34) suggest that activated DCs could be retained in the airway mucosa and present their antigens locally, inducing lymphocyte proliferation and lymphoid neogenesis in the lung and contributing to the ongoing inflammation (47). However, the whole issue on DC maturation in COPD is controversial with conflicting data as discussed above and is an important focus for future research (48, 49).

Furthermore, the altered composition of the DC population, with functionally modified DC subsets, could skew the resulting adaptive immune response away from tolerance and towards ongoing Th1 and cytotoxic CD8+ T cell responses, which are the hallmarks of the chronic adaptive inflammation in COPD (49). In accordance, the accumulating Langerhans-type DC subset is known to be a potent activator of these T cell responses (50, 51). Moreover, mouse DCs exposed to cigarette smoke extract potentiate CD8+ T cell proliferation *in vitro* (52).

A recent publication suggests a role for Langerhans-type DCs in driving the Th17 response (53), which could hypothetically be involved in COPD pathogenesis.

Finally, there are several reports on auto-immune features of COPD with a role for anti-elastin and anti-endothelial antibodies and a blunted regulatory T cell response in COPD patients (54–56). The functionally modified pulmonary DC population could play a crucial role in this process, as pulmonary DCs that are activated *in situ* by cigarette smoke induced tissue damage and inflammation could break tolerance by presenting and cross-presenting self-antigens, similar to the described role of *in situ* activated DCs in other auto-immune diseases (57).

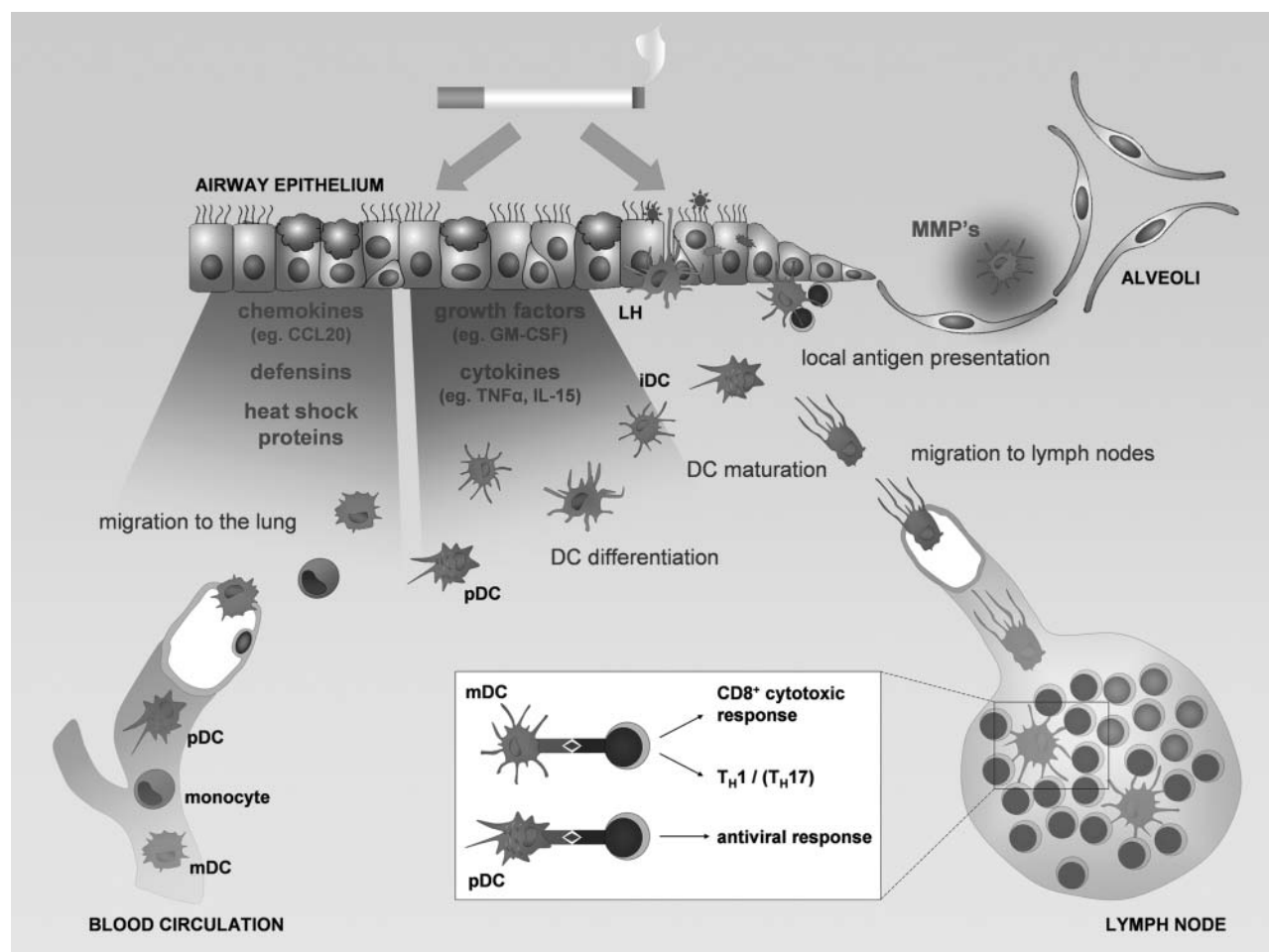


Figure 2. The role of dendritic cells in the pathogenesis of COPD. Chemokines, defensins and heath shock proteins produced by the lung tissue in response to the damaging effect of cigarette smoke attract circulating dendritic cells precursors (blood myeloid dendritic cells (mDC), plasmacytoid dendritic cells (pDC) and monocytes). The differentiation of the DC precursors into different subsets will be modulated by the growth factors and cytokines released by the damaged lung tissue, resulting in an altered DC population in the lung with increased numbers of Langerhans type DCs (LH). Together with the interstitial type DCs (iDC) and the pDCs, they sample antigens and sense for danger signals in the mucosal area. Maturing DCs migrate towards the lymph nodes where they present antigens to lymphocytes and orchestrate the outcome of the adaptive immune response. DCs can also present their antigens locally in the airway mucosa. The process of maturation can be directly attenuated by cigarette smoke. The altered DC population can skew the adaptive immune response towards a T helper 1, CD8+ cytotoxic T cell or T helper 17 profile. In addition DCs can contribute to the protease-antiprotease imbalance by producing metalloproteinases (MMP's), involved in the development of emphysema.

Perspectives

Further phenotypic evaluation of human pulmonary DCs needs to be carried out in order to identify different subsets of DC, which can be separate stages of differentiation from common blood DC precursors. Evaluating the effects of cigarette smoke on the differentiation of DCs and on the maturation of Langerhans-type DC compared to interstitial-type DC and plasmacytoid DC is mandatory to understand the role of the DC in smoking-related diseases. Moreover, the role of the plasmacytoid DC in COPD remains to be elucidated, both during stable disease and at exacerbations. Since plasmacytoid DC have important antiviral and tolerogenic properties, they could play a role in the pathogenesis of COPD.

Declaration of interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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