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The role of dendritic cells in the pathogenesis of cigarette smoke-induced emphysema in mice

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ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) is an important lung and airway disease which affects the lives of around 200 million people worldwide. The pathological hallmark of COPD is emphysema and bronchiolitis and is based on the inflammatory response of the innate and adaptive immune system to the inhalation of toxic particles and gases. The inflamed airways of COPD patients contain several inflammatory cells including neutrophils, macrophages, T lymphocytes, and dendritic cells (DC). The potential role of DCs as mediators of inflammation in the airways of smokers and COPD patients is poorly understood. The current study investigated the role of DC subsets in an animal model of cigarette smoke-induced lung emphysema through the expansion or depletion of DC subsets. Expansion of both myeloid DC (mDC) and plasmacytoid DC (pDC) by Flt3L treatment induced a decline in macrophage numbers and increased the levels of fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF) in the bronchoalveolar lavage (BAL) fluid of smoke-exposed animals. The increase in the mean linear intercept (Lm) following Flt3L treatment was decreased by pDC depletion. In conclusion, pharmacological modulation of DC subsets may have an effect on the development of airway responses and emphysema as indicated by the decline in macrophage numbers and the increase in FGF and VEGF levels in the bronchoalveolar lavage fluid. Moreover, the depletion of pDCs decreased the Lm which might suggest a role for pDC in the pathogenesis of lung emphysema.
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1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is an umbrella term for a multicomponent pathology that results from persistent obstruction of the airways caused by severe emphysema, chronic bronchitis and bronchiolitis (Barnes, 2003, 2004). COPD is mainly caused by cigarette smoke with an increasing incidence particularly in developing countries and is predicted to be the third most frequent cause of death in the world by 2030 (Mannino and Buist, 2007; GOLD, 2009; Stockley et al., 2009; Gershon et al., 2011; WHO, 2011). Smoking causes several well established phenomena which contribute to the disease including immune alterations, proteolytic activity, oxidative stress and endothelial dysfunction (Barnes, 2000; Sandford and Silverman, 2002; Chung and Marwick, 2010; Wanner and Mendes, 2010). Several inflammatory cells from both the innate and adaptive immune system, together with their mediators, participate in the inflammatory response of COPD. (Yoshida and Tuder, 2007; Hogg and Senior, 2002; Barnes et al., 2003). The contribution of dendritic cells (DCs) as crucial professional antigen-presenting cells to this process is to date, however, not well documented (Tsoumakidou et al., 2008; Kheradmand et al., 2009). In humans and mice, several subtypes of DCs, characterized by surface markers and function, have been described (Vermaelen and Pauwels, 2005; Palucka and Banchereau, 1999). Two major DC subsets in the mouse are myeloid/conventional DC (mDC/cDC) and plasmacytoid DC (pDC) that originate from bone marrow precursors that colonize to the peripheral tissues through the blood or lymph circulation (Hart, 1997; Webb et al., 2005). It was also demonstrated that treating animals with recombinant Flt3 ligand increased the numbers of mDC and pDC in the circulation as well as in peripheral organs. There is evidence for distinct roles of these subsets in the regulation of T cell-mediated adaptive immunity in the lung (Maraskovsky et al., 1996; Masten et al., 2004; de Heer et al., 2005).

In vitro studies using bone marrow and monocyte-derived DCs exposed to varying doses of nicotine (Nouri-Shirazi and Guinet,

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2006; Aicher et al., 2003) and cigarette smoke extract (CSE) (Vassallo et al., 2005; Kroening et al., 2008; Mortaz et al., 2009a, 2009b) have yielded contrasting data with respect to their effect on DC function. *In vivo* data shows the impairment of DC function by cigarette smoke (Robbins et al., 2008).

The interactions caused by these DC may influence the activation status of cells from the adaptive immune system such as $CD4^+$T cells and $CD8^+$T cells in smokers with COPD and animal models of lung emphysema (Palucka and Banchereau, 1999; Kitamura et al., 1999; Banchereau and Steinman, 1998; Tsoumakidou et al., 2008; Robbins et al., 2008). It is now accepted that $CD8^+$T cells are essential for the development of cigarette smoke-induced emphysema (Maeno et al., 2007). Although these studies show the importance of DCs, the role of different subset of DCs in the pathogenesis of cigarette smoke-induced emphysema still remains to be elucidated. In the current study we investigated the role of DC subsets by using Flt3L treatment to induce both mDC and pDC subsets and a depleting antibody 120g8, which selectively removes pDCs, in an animal model of cigarette smoke-induced emphysema.

2. Materials and methods

2.1. Animals and groups of study

Specific-pathogen-free male C57Bl/ 6 mice, 6–8 weeks of age, were obtained from Charles River Laboratories and housed under controlled conditions in standard laboratory cages in the animal facility. They were provided free access to water and food. All *in vivo* experimental protocols were approved by the animal care committee of Utrecht University and performed under governmental and international guidelines on animal experimentation. Mice were divided in two main groups of smoke-exposed and control (air-exposed) with each group further divided into subgroups (Table 1A).

2.2. Smoke exposure

Mice were exposed nose-only to the diluted mainstream and side stream smoke generated by the burning of commercially available Lucky Strike cigarettes without filter (British-American Tobacco, Groningen, The Netherlands), using the TE-10z smoking machine (Teague Enterprises, Davis, CA), programmed to smoke cigarettes according to the Federal Trade Commission protocol (35 ml puff volume drawn for 2 s, once per min). Before starting smoke exposure, mice were accustomed to the nose-only exposure chambers (In-Tox Products Inc., Albuquerque, NM) by gradually prolonging their stay in the tubes over the course of 2 weeks. Smoke exposures were conducted twice every weekday for 3 months after an adaptation period of 2 weeks, starting with 1×1 cigarette which was gradually increased from 1 to 4 cigarettes per run with an increment of 1 per week. Control mice underwent the same procedures, but were allowed to breathe room air throughout the whole exposure period. The average total suspended particulate (TSP) concentration of the smoke inside the exposure chamber was 85 mg/m^3 as determined by the gravimetric analysis of Emfb filter samples (Pall Corporation, East Hills, NY, USA). The carbon monoxide (CO) content of the smoke inside the exposure chamber was measured by sampling with a Monoxor II CO analyzer (Bacharach Inc, New Kensington, PA, USA) at 15 s intervals during 2 runs and was around 1200 ppm. The mice were sacrificed 16–24 h after the last air or smoke exposure (Van et al., 2006) (Table 1B).

Table 1
Diagram of animal groups (A) and exposure protocol (B).

A		
	Smoke exposed	Control (air-exposed)
PBS	*	*
120g8	*	*
Flt3L	*	*
Flt3L+120g8	*	*

B Smoke exposure protocol for 3 months
1×1 cigarette (from day 7)
2×2 cigarette (from day 14)
2×3 cigarette (from day 21)
2×4 cigarette (from day 28 till end of experiment periods)

2.3. Depletion of the pDC population

pDCs were depleted by the i.p. injection of 150 μg 120g8 antibody (Gift from Dr. Louis Boon, Bioceros Institute BV, Utrecht, The Netherlands) in 100 μl of PBS, twice a week for the entire duration of the experiment. Control mice received matched injection of either PBS or 150 μg of the relevant isotype control antibody (Rat IgG, Sigma). This would be consistent with the previously reported ability of 120g8 treatment to specifically deplete pDCs (Asselin-Paturel et al., 2003; Blasius et al., 2006; Smit et al., 2008).

2.4. Expansion of the mDC population

Mice were injected i.p with recombinant human Flt3L (eBioscience, NL) ± 120g8 antibody at a concentration of 10 μg/mouse in PBS (Masten et al., 2004), once daily, twice a week for the entire duration of the experiment.

As Flt3L increases both the mDC and pDC subsets (Vassallo et al., 2010), in the combination group (Flt3L+120g8) in which the pDC subset underwent depletion by the 120g8 antibody (150 μg/mouse), allowing only the mDC population expanded in response to the treatment.

Control mice received matched injections of either PBS or serum albumin (0.01% in PBS) and all groups were sacrificed 24 h after the last treatment.

2.5. Growth patterns

Individual animal body weight was recorded weekly for the 12 weeks of the experimental procedure. Growth in % was calculated as (body weight day $X -$ body weight day-1)/body weight (day-1) $\times$ 100.

2.6. Lung function

In the invasive system, airway responsiveness was assessed as a change in airway function to aerosolized methacholine (acetyl-β-methyl-choline chloride, Sigma) 24 h after the last exposure to smoke. Methacholine was administered for 10 s (60 breaths/min; tidal volume, 500 μl) in increasing concentrations. Anesthetized (pentobarbital sodium, 70–90 mg/kg i.p.), tracheotomised (18-gauge cannula) mice were mechanically ventilated (160 breaths/min; tidal volume, 150 μl; positive end-expiratory pressure, 2–4 cm H_2O; ventilator model 683; Harvard Apparatus, Natick, MA, USA). Lung resistance (R_L) and dynamic compliance (C_{dyn}) were continuously computed (LabVIEW; National Instruments Austin TX) by fitting flow, volume, and pressure to an equation of motion. Maximum values of R_L and minimum levels of C_{dyn} were determined and expressed as the percent change from baseline after PBS aerosol (EMKA Technologies, Paris, France).

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