



**Karolinska
Institutet**

**Institutet för miljömedicin
Enheten för lung- och allergiforskning**

Inflammation and Cell Migration in Chronic Obstructive Pulmonary Disease (COPD)

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska
Institutet offentligen försvaras i Atrium, Nobels väg 12

Fredagen den 10:e februari, 2012, kl 9:00

av

Kristin Blidberg

M.Sc.

Huvudhandledare:
Professor Kjell Larsson
Karolinska Institutet
Institutet för miljömedicin

Bihandledare:
Docent Lena Palmberg
Karolinska Institutet
Institutet för miljömedicin

Fakultetsopponent:
Professor Arne Egesten
Lunds Universitet
Institutionen för kliniska vetenskaper

Betygsnämnd:
Docent Caroline Olgart Höglund
Karolinska Institutet
Institutionen för medicin och
Institutionen för fysiologi och farmakologi

Professor Magnus Sköld
Karolinska Institutet
Institutionen för medicin

Professor Jonas Erjefält
Lunds Universitet
Institutionen för experimentell medicinsk
vetenskap

Stockholm 2012

ABSTRACT

Chronic obstructive pulmonary disease (COPD), the fourth most common cause of death worldwide, is characterised by chronic airflow obstruction and chronic inflammation which affects large and, especially, small airways. There is an accumulation of inflammatory cells in the airways in COPD, in particular neutrophils, macrophages and CD8⁺ T-cells. Neutrophil numbers correlate with disease severity and neutrophils have been attributed a central pathophysiological role in COPD. The overall aim of this thesis was to elucidate how neutrophil function is altered by the inflammation observed in COPD. Thus, study I, II and IV were all performed on three groups of subjects, healthy non-smoking controls, smokers without COPD and smokers with COPD.

In *paper I* neutrophil release of CXCL8, MIP-1 α and MCP-1 in response to different stimuli were studied. Also the role of TNF- α in regulating these responses was studied by inhibition of endogenous TNF- α with an anti-TNF- α antibody (infliximab). Neutrophil derived TNF- α contributed to the release of these chemokines after stimulation with LPS and organic dust as the response was inhibited by infliximab. In the COPD group infliximab did not inhibit the release of CXCL8 suggesting that the role of TNF- α is somehow altered in COPD.

In *paper II* chemotaxis towards CXCL8 was increased in smokers with and without COPD and migration towards LTB₄ was increased in smokers without COPD compared to healthy controls. In the smoker groups serum TNF- α and migration induced by CXCL8 and LTB₄ correlated. Thus chemotaxis of circulating neutrophils towards CXCL8, and partly towards LTB₄, is increased in smokers. Hence smoking may cause neutrophil activation and pro-inflammatory stimuli, such as TNF- α , may be central in this activation. The enhanced migration could to some degree explain the increase in neutrophil numbers observed in the COPD lung.

In *paper III* we studied the influence of a β_2 -agonist (formoterol) and a glucocorticoid (budesonide) on circulating neutrophils isolated from healthy subjects. Budesonide inhibited and formoterol enhanced LPS-induced release of IL-6, CXCL1 and CXCL8. Moreover, formoterol up-regulated the chemokine receptors CXCR1 and CXCR2, while budesonide up-regulated CXCR2. However, the drugs did not affect the chemotactic response. Thus budesonide and formoterol, which are often used in the treatment of COPD, affect chemokine release and receptor expression, but the functional consequences of these findings are unclear.

In *paper IV* T-cell and alveolar macrophage (AM) interaction in COPD was examined by investigating if the production of CXCR3 binding chemokines (CXCL9, -10, -11) by AMs is enhanced in COPD. The macrophage product was also assessed for its chemotactic effects on CXCR3 expressing T-cells. No difference in chemokine release by AMs was detected and while the AM supernatant induced migration in CXCR3 expressing T-cells there was no difference between the groups. We thus conclude that the increase of CXCR3 expressing T-cells, which has been observed in the COPD lung, is not caused by the CXCR3 binding chemokines released by AMs.

Taken together these studies show an alteration in different aspects of neutrophil function in smokers with COPD but also in smokers without COPD.