GÖTEBORGS UNIVERSITET

The Effects of Tobacco Smoke on the Lymphocyte Recruiting Cytokine Interleukin-16

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet offentligen kommer att försvaras på svenska språket fredagen den 18:e november 2011 kl. 13.00 i Hjärtats aula, Vita stråket 12, Sahlgrenska sjukhuset,

av

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Fakultetsopponent:

Professor Magnus Sköld, Karolinska Institutet, Stockholm

Avhandlingen baseras på följande delarbeten:

I. Anders Andersson, Ingemar Qvarfordt, Martti Laan, Margareta Sjöstrand, Carina Malmhäll, Gerdt C. Riise, Lars-Olof Cardell och Anders Lindén
Impact of tobacco smoke on interleukin-16 protein in human airways, lymphoid tissue and T lymphocytes
Clinical and Experimental Immunology, 2004 Oct;138(1):75-82.

II. Anders Andersson, Apostolos Bossios, Carina Malmhäll, Margareta Sjöstrand, Maria Eldh, Britt-Marie Eldh, Pernilla Glader, Bengt Andersson, Ingemar Qvarfordt, Gerdt C. Riise och Anders Lindén
Effects of tobacco smoke on IL-16 in $CD8^+$ cells from human airways and blood: a key role for oxygen free radicals?
American Journal of Physiology, Lung Cellular and Molecular Physiology 2011 Jan;300(1):L43-55.

III. Anders Andersson *), Apostolos Bossios*), Carina Malmhäll, Birgitta Houltz, Margareta Sjöstrand, Ingemar Qvarfordt och Anders Lindén
Decrease in Interleukin-16-expressing NK cells in the Blood of Long-Term Tobacco Smokers
*I manuskript. *) Bidrog med lika delar till arbetet.*

The Effects of Tobacco Smoke on the Lymphocyte Recruiting Cytokine Interleukin-16

Anders Andersson, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Sweden, 2011. English text with a summary in French.

ABSTRACT

There is an increased number of $CD8^+$ cells in the airways in chronic obstructive pulmonary disease (COPD) and also an increased number of $CD4^+$ cells in severe COPD. The CD4 cell chemo-attractant interleukin (IL)-16 is also increased in the airways of tobacco smokers. In this thesis, we re-evaluated whether there is a local increase in IL-16 and determined whether there are systemic IL-16 alterations. We also investigated whether tobacco smoke causes a release of IL-16 in $CD8^+$ cells and elucidated cellular mechanisms. We measured extracellular IL-16 protein (bronchoalveolar lavage fluid, BALF; plasma and serum), intracellular IL-16 protein (BAL $CD8^+$ cells) and IL-16 mRNA (BAL cells) in long-term tobacco smokers. In occasional tobacco smokers, we analysed extracellular IL-16 protein (BALF). IL-16 protein in tonsils of tobacco smokers was assessed. For the *in vitro* studies, isolated human blood $CD8^+$ cells were cultivated with and without water-soluble tobacco smoke components (CSE), an oxygen free radical (OFR) scavenger (glutathione) or a non-selective phosphodiesterase inhibitor (aminophylline) and analysed for extra- and intracellular IL-16 protein and IL-16 mRNA. Protein oxidation in CSE-treated $CD8^+$ cells was measured. In long-term tobacco smokers, we confirmed an increase in IL-16 protein in BALF. We revealed a decrease in intracellular IL-16 protein in $CD8^+$ cells as well as in IL16 mRNA in BAL cells. We found no corresponding impact on IL-16 protein in plasma or serum. In contrast, occasional smokers did not exhibit any substantial alteration in IL-16 protein in BALF. However, tobacco smokers were found to have a decrease in IL-16 in tonsils. In cell culture of $CD8^+$ cells, CSE caused a release of IL-16 protein and a decrease in both intracellular IL-16 protein and IL-16 mRNA. These alterations were prevented by glutathione but not by aminophylline. CSE-treated $CD8^+$ cells exhibited a marked increase in oxidized proteins. Tobacco smoke mainly exerts an effect on IL-16 release locally in the airways. $CD8^+$ cells constitute a source of IL-16 and tobacco smoke depletes these cells by causing an extracellular release of this protein and a decrease in its mRNA. OFRs are involved as mediators of these effects.

Keywords: tobacco, CD8, IL-16, COPD, airways, host defence, adaptive immunity, OFR, aminophylline

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