

## Modulation of Nerve Growth Factor receptors in human monocytes and their influence in pulmonary inflammatory diseases

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Neurotrophins (NTs) are a family of growth/survival factors with well-established functions in the nervous system. In the last decade, novel biological actions, from oncogenicity to inflammation, have been attributed to these factors. In particular, Nerve Growth Factor (NGF) acts through two different classes of receptors: the high affinity transducing TrKA receptor, associated to proliferation/survival, and the low affinity p75 receptor that, depending on its cross talk with TrKA, induces either apoptosis or survival. Recently, NGF and its receptors have been detected in healthy pulmonary tissues and seem to be involved in pulmonary inflammatory diseases. Since the expression of these NGF receptors in circulating monocytes is controversial, our initial aim was to investigate the role of these receptors both in pulmonary tissues and in peripheral blood monocytes of patients with Chronic Obstructive Pulmonary Disease (COPD). We therefore analyzed 38 healthy control subjects divided in two groups based on their smoking status. Serendipitously, the data obtained in these two control groups may have a value of their own, with potential implications in preventive medicine.

We show here that in healthy subjects, smoking induces an early increase in p75 expression in monocytes, while TrKA seems unaffected. Furthermore, our control subjects could be divided in three subsets according to the constitutive TrKA expression in monocytes: TrKA-negatives, -intermediates (up to 50%) or -high (> 50%), independently on their smoking status. Since TrKA activation promotes inflammation, we hypothesize that subjects with high-TrKA monocytes could be more prone to pulmonary inflammatory diseases, such as COPD. In fact, all 28 COPD patients in our series belonged to the high-TrKA subset, while all long term heavy smokers with no evidence of pneumologic diseases belonged to TrKA-negative subset.

In conclusion, our data support the hypothesis that, since TrKA expression promotes survival, elevated levels of TrKA-positive monocytes may render subjects more prone to long term inflammatory diseases (e.g., COPD). Moreover, in patients constitutively expressing high levels of TrKA in monocytes, the smoking-dependent increase in p75 may in turn further extend monocytes survival, contributing to a chronic inflammation. Furthermore, the early increase in p75 expression in monocytes following smoking may support the hypothesis that p75 determination might represent a novel marker for passive smoking.

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