UNIVERSITÀ DEGLI STUDI DI SALERNO

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Is the inflammasome at the crosstalk between COPD and lung cancer?

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ABSTRACT

Background. Chronic obstructive pulmonary disease (COPD) is considered as a risk factor for lung cancer establishment. Epidemiological evidence indicate that patients with COPD have a 6.35-fold higher risk to develop lung cancer compared to the normal population.

Aim. Based on the notion that chronic inflammation is common to both COPD and lung cancer and that in our laboratory we found that the inflammasome is involved in lung carcinogenesis, we focused our attention on this multimeric complex, which role in both pathologies still counts many controversies in literature.

Therefore, the main goal of this PhD project was to evaluate whether the inflammasome was at the crosstalk between COPD and lung cancer. In particular, we focused our attention on air pollution and smoking as inflammasome inducers.

1st year results. The exposure of peripheral blood mononuclear cells (PBMCs) isolated from smokers to ultrafine particles (UFPs), which mimic small size air pollutants, led to an inflammatory process that was responsible for IL-1-like cytokines release and was associated to the activation of the canonical, caspase-1-dependent, NLRP3 inflammasome. This effect was not observed in non-smoker subjects, who instead released higher levels immunesuppressive IL-10 (Chapter 1). Instead, UFPs induced the release of IL-18 and IL-33 from exacerbated COPD-derived circulating cells in a NLRP3-/caspase-1- and caspase-8-independent manner (Chapter 2).

2nd year results. The exposure to UFPs *in vivo* led to a state of latent lung inflammation and bronchial dysfunction in mice; this effect was caspase-1-independent and associated to an immunesuppressive lung microenvironment, characterized by high levels of IL-10 (Chapter 3). Moreover, to understand the role of the inflammasome in COPD, we stimulated PBMCs with

NLRP3 or AIM2 inflammasome activators. The sole AIM2 inflammasome was functional in that its activation led to IL-1α-dependent TGF-β release via the canonical, caspase-1-dependent, and non-canonical, caspase-4-dependent, pathway from exacerbated COPD-derived PBMCs (Chapter 4).

3rd year results. To pursue the investigation on the inflammasome in the lung, we used a mouse model of smoking mice in the attempt to mimic COPD to be compared to a mouse model of carcinogen-induced lung cancer. The exposure to cigarette smoking increased the alveolar space, induced bronchial tone impairment and an immunesuppressive microenvironment, which were not reverted by caspase-1 inhibition. Interestingly, we found that the expression of IL-1α and AIM2 was increased both in smoke- and carcinogen-treated mice (Chapter 5).

Conclusions. Both smoking and air pollution can prompt towards lung immunesuppression and pulmonary inflammation in an IL-1-like manner, most likely via the AIM2 inflammasome activation. Therefore, although other studies are needed, we found that the common pathways between COPD and lung cancer stand in the activation of AIM2 and the ensuing IL-1α, as demonstrated by preclinical models and human lung cancer samples.

These results improve the knowledge on the inflammasome biology in COPD and lung cancer and suggest a potential pro-carcinogenic role of IL-1α and AIM2 in COPD.