European Respiratory Society
Annual Congress 2013

Abstract Number: 5111

Publication Number: P3112

Abstract Group: 11.1. Lung Cancer

Keyword 1: Lung cancer / Oncology **Keyword 2:** Molecular pathology **Keyword 3:** No keyword

Title: Proapoptotic effects of PAI-1 protein on lung and prostate cancer cells

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Body: Plasminogen activator inhibitor type 1 (PAI-1) is the most potent physiological inhibitor of urokinase - a key regulator of tumor growth and metastasis. The proteolytic activity of urokinase determines its effect on cell migration and invasion, as well as proliferation and apoptosis. PAI-1 directly inhibits the enzymatic activity of urokinase and stimulates internalization of urokinase complexed with a specific receptor. Previously we shown that very long half-life PAI-1 (VLHL PAI-1) with prolonged anti-proteinase activity demonstrated considerable inhibitory activity on the proliferation of lung and prostate cancer cells. The aim of this study was to analyze the impact of increasing concentrations of PAI-1 mutant forms: VLHL PAI-1, Vn neg PAI-1 devoid of affinity towards vitronectin and wild form (wt PAI -1) on apoptotic activity of lung cancer (A549 and H1299) and prostate cancer (LNCaP and DU145) cell lines, characterized by normal or high urokinase production, respectively A549 and LNCaP vs H1299 and DU145. DNA fragments associated with histones were spectometrically quantitated in cell cytoplasm after 24 hrs incubation with increasing doses of PAI-1 proteins. VLHL PAI-1 protein (10 µg/ml and 100 µg/ml) strongly up-regulated apoptotic activity in all examined human lung and prostate cancer cell lines ($p<0,001$). In DU145 prostate cancer cell line this effect was dose-dependent. In contrast, PAI-1 protein devoid of vitronectin affinity as well as wild type PAI-1apoptosis did not affected cancer cells apotosis. Conclusion: in vitro proapoptotic effect of PAI-1 on cancer cells is due to anti-proteolitic and anti-adhesion properties.