Title

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Sustained Marcks Phosphorylation Contributes To Tobacco Smoke-Enhanced Lung Cancer Malignancy Through EGFR-Erk Signaling

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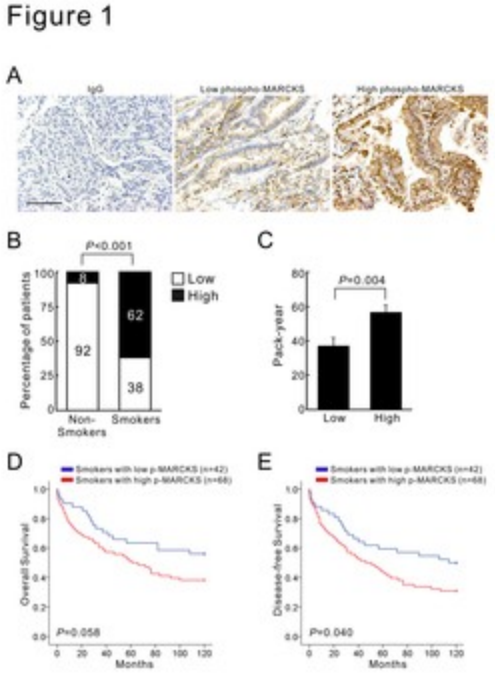
Rationale: Exposure to tobacco smoke is a major risk factor for lung cancer development and progression. Although many carcinogenesis-associated pathways have been discovered, how tobacco smoke activates these pathways in promoting cancer malignancy remains poorly understood. Previously, we identified up-regulation of phosphorylated myristoylated alanine-rich C kinase substrate (phospho-MARCKS) as a novel predictor of lung cancer malignancy. In this study, we aimed to determine if persistent elevation of phospho-MARCKS (ser159 and ser163) results from exposure to tobacco smoke and serves as a key player in smoke-related lung cancer.
Methods: The clinical relevance of phospho-MARCKS in smoke-related lung cancer was first confirmed. Next, we examined the effect of smoke exposure on phospho-MARCKS levels in airway epithelium and lung cancer. We also used genetic approaches to verify the functionality and molecular mechanism of smoke-induced phospho-MARCKS. Finally, lung cancer cells with smoke exposure were pharmacologically inhibited for MARCKS activity and then subjected to functional bio-assays.
Results: Strong phospho-MARCKS staining was observed in lung cancer specimens from smokers and was positively correlated, as compared to non-smokers (n=122, P<0.001). Particularly, high phospho-MARCKS levels were significantly associated with higher smoking pack-year (n=110, P<0.01) and poor survival (n=110, P=0.04) in lung cancer patients with smoking history. We found that MARCKS becomes activated in airway epithelium and lung cancer in response to tobacco smoke, both in vitro and in vivo. Functionally, tobacco smoke-triggered elevation of phospho-MARCKS was demonstrated to act in parallel with activation of the EGFR-ERK pathway and to promote malignant progression of lung cancer cells including cancer cell growth, invasion and migration. Of note, through treatment with an inhibitor of phospho-MARCKS, the MPS peptide, we showed that suppression of smoke-induced MARCKS activity was able to down-regulate EGFR-ERK signaling and reverse malignant changes of lung cancer cells.
Conclusions: Our data suggest that MARCKS phosphorylation functions in smoke-mediated lung cancer progression and also provide a potential biomarker for predicting prognosis and malignant behavior in smoke-related lung cancer.

figure 1.jpg



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