Leukotriene A4 Hydrolase and Tri-aminopeptidase Activity as Potential Quantifiable Biomarkers in the Study of Patients With COPD

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A newly described inflammatory pathway begins with the breakdown of collagen resulting in proline-glycine-proline (PGP). This acts as a chemoattractant for neutrophils and as a substrate for the tri-aminopeptidase (TAP) site of leukotriene A4 hydrolase (LTA4H). LTA4H produces a proinflammatory molecule leukotriene B4 (LTB4) and has an anti-inflammatory role by degrading PGP. Cigarette smoke causes TAP inhibition in animal models and in vitro. Thus, LTA4H fails to degrade PGP causing increased levels of neutrophils. The goal of the current study was to determine whether the LTA4H effects shown in mice occur in healthy smokers and COPD patients. A population of 13 COPD current smokers (COPD-c), 10 COPD former smokers (COPD-f), 26 healthy smokers (HS), and 22 nonsmokers (NS) was studied based on demographics, lung function, quality of life, and sputum analysis. ELISA kits were used to analyze sputum LTA4H and MPO levels. Tandem mass spectroscopy (MS) was used to analyze LTB4, PGP, Ac-PGP, and TAP activity. In HS, LTA4H levels were increased vs NS (418 vs 161 pg/mL; P = .04) and continued to increase in COPD-f (1,678 pg/mL) and COPD-c (2,139 pg/mL). MPO levels were increased in HS (202 ng/mL), COPD-f (177 ng/mL), and COPD-c (240 ng/mL) vs NS (63 ng/mL). PGP levels are higher in HS and COPD-c compared with NS (213 pg/mL, 234 pg/mL, and 99 pg/mL, respectively) and continued to increase in COPD-c (486 pg/mL). Standardized TAP activity (TAP/LTA4H) shows decreased levels in HS compared with NS (3.9 vs 14.9 ng/mL/min/pg enzyme) and declines in COPD-f (1.6 ng/mL/min/pg enzyme) and COPD-c (0.7 ng/mL/min/pg enzyme). Elevated sputum LTA4H levels with impaired TAP activity are caused by cigarette smoke and become intrinsic to COPD even after smoking cessation. While ELISA analysis of LTA4H or MPO can be readily implemented in most laboratory settings, MS analysis would require high test volume to be financially prudent.

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