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Title: Loss of plasma phospholipid transfer protein (PLTP) activity enhances inflammatory responses to cigarette smoke in the lung

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Body: PLTP is a protein that classically functions to shuttle phospholipids amongst lipoprotein particles in the circulation. Though it has been best studied in the plasma, its primary site of expression and activity is within the lung epithelium. This study aimed to determine if cigarette smoke exposure induced inflammatory responses by altering PLTP activity in the lung. PLTP activity was measured in the lung lavage fluid of advanced emphysema subjects (Gold 3 or greater) and age-matched normal controls. Enzymatic activity was significantly reduced in the lung lavage of emphysema subjects. To determine the etiology of this decrease, recombinant PLTP protein was incubated for 24 hours with lung lavage from normals, smokers and emphysema subjects. In contrast to normal lung lavage, lavage fluid from smokers and emphysema subjects degraded PLTP protein via a serine protease sensitive mechanism. To determine the impact of the loss of PLTP activity on lung inflammation, mice in the A/J background were treated via the nares with control siRNA or PLTP siRNA followed by cigarette smoke or LPS exposure. Silencing PLTP expression significantly increased the inflammatory response to both cigarette smoke and LPS exposure in mice. Indeed, siPLTP treated mice had higher ERK activation, γ-inteferon expression and lung lavage cellularity in response to these inflammatory stimuli. Thus, PLTP is an important modulator of lung inflammation and the loss of PLTP activity measured in this disease likely contributes to the damaging inflammatory changes that occur in COPD.