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Title: The GPx1-PTP1B-PP2A axis: A key determinant of airway inflammation and alveolar destruction

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Body: Protein phosphatase 2A (PP2A) is a primary serine-threonine phosphatase that modulates inflammatory responses in asthma and COPD. Despite its importance, the mechanisms that regulate lung PP2A activity remain to be determined. The redox-sensitive enzyme protein tyrosine phosphatase 1B (PTP1B) activates PP2A by dephosphorylating the catalytic subunit of the protein at tyrosine 307. This study aimed to identify how the interaction between the intracellular antioxidant glutathione peroxidase-1 (GPx-1) and PTP1B impacted on lung PP2A activity and airway inflammation. Studies using gene silencing techniques in mouse lung or human small airway epithelial (SAE) cells determined that knocking down PTP1B expression blocked GPx-1’s activation of PP2A and negated the anti-inflammatory effects of GPx-1 protein in the lung. Similarly, the expression of human GPx-1 in transgenic mice significantly increased PP2A and PTP1B activities and prevented chronic cigarette smoke-induced airway inflammation and alveolar destruction. GPx-1 knockout mice, however, exhibited an exaggerated emphysema phenotype, correlating with a non-responsive PP2A pathway. Importantly, GPx-1-PTP1B-PP2A signaling becomes inactivated in advanced lung diseases. Indeed, PTP1B protein was oxidized in the lungs of advanced emphysema subjects and, unlike normal lung epithelial cells, cigarette smoke did not increase PTP1B activity within epithelial cells isolated from COPD subjects. These findings establish that the GPx-1-PTP1B-PP2A axis plays a critical role in countering the inflammatory and proteolytic responses that result in lung tissue destruction in response to cigarette smoke exposure.