37. Fadok VA, Bratton DL, Konowal A, et al. Macrophages that have ingested apoptotic cells during apoptotic cell phagocytosis by macrophages. Modulation of Rho-GTPases, including RhoA, but had no effect on expression of macrophage efferocytosis receptors. To determine whether lovastatin enhanced efferocytosis in vivo, mice were challenged intratracheally with apoptotic thymocytes, in the presence and absence of lovastatin or the Rho kinase inhibitor (Y-27632), and clearance of these apoptotic thymocytes was assessed. Both lovastatin and Y-27632 enhanced efferocytosis in vivo. These findings suggest that statins enhance efferocytosis in vitro and in vivo, and may ultimately play a role in the development of chronic inflammatory lung diseases (e.g., chronic obstructive pulmonary disease and cystic fibrosis). Cleared lungs were used in the next experiment to assess the efficacy of lovastatin in vivo. Mice were challenged intratracheally with apoptotic thymocytes, and clearance of these apoptotic thymocytes was assessed. Both lovastatin and Y-27632 enhanced efferocytosis in vivo. These findings suggest that statins enhance efferocytosis in vitro and in vivo, and may ultimately play a role in the development of chronic inflammatory lung diseases (e.g., chronic obstructive pulmonary disease and cystic fibrosis).
an important therapeutic role in diseases where effecrocycosis is impaired and inflammation is dysregulated.

**Conflict of Interest Statement:** K.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. W.J.J. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.B.F. is the recipient of a Pfizer Atorvastatin Research Award totaling $100,000. Y.Q.X. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. K.A.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. V.M.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.A.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. P.M.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. R.W.V. is the recipient of the Pfizer Atorvastatin Research Award totaling $100,000. Y.Q.X. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

**Background:** Prostaglandin I$_2$ synthase (PGI$_2$S) expression within lung tumors. Lung-specific overexpression of PGI$_2$S has protective effects in both chemical- and tobacco smoke–induced murine models of lung tumorigenesis. Lastly, PGI$_2$S expression within lung tumors may correlate with survival. Here, we hypothesize that an imbalance in COX-2, PGE$_2$, and PGI$_2$S may be important to the pathogenesis of other smoking-related lung diseases such as chronic obstructive pulmonary disease and that tobacco smoke may alter PGI$_2$S expression. **Design:** We evaluated PGI$_2$S expression in both normal and emphysematous human lung tissue samples by: (1) immunohistochemistry, (2) quantitative PCR, (3) Western analysis, and (4) both 6-keto PGF$_1$α (the stable metabolite of prostacyclin) and PGE$_2$ levels by ELISA. In addition, we treated primary human pulmonary microvascular endothelial cells (HPMVEC) with varying concentrations of cigarette smoke extract (CSE). Treated cells were assessed for PGI$_2$S, COX-2, VEGF, and cPLA$_2$; gene expression, and 6Keto-PGF$_1$α and PGE$_2$ levels. **Measurements and Results:** In this study, we observed that human lung emphysema tissue exhibited lower PGI$_2$S expression in the endothelium than normal lung tissue. Furthermore, in HPMVEC, CSE suppresses PGI$_2$S gene expression while potently inducing COX-2, cPLA$_2$, and VEGF expression. Pretreatment with potent antioxidants did not alter this imbalance with the exception of N-acetylcysteine (NAC), which reversed the induction of COX-2 by CSE. **Conclusions:** The main finding of this investigation is the demonstration of decreased PGI$_2$S protein and mRNA in the lungs from patients with emphysema. CSE reduces the expression of the PGI$_2$S gene and increases the expression of VEGF, COX-2, and cPLA$_2$ in HPMVEC. Decreased PGI$_2$S expression is likely multifactorial, including oxidant stress, loss of alveolar capillary endothelial cells, nitric oxide–related suppression, and altered transcriptional control. **In vitro** work by our laboratory has demonstrated that PGI$_2$S gene expression in lung carcinoma cell lines is partially controlled through methylation silencing. Our demonstration that PGI$_2$S is diminished in both human emphysema tissue and **in vitro** by CSE, as well as similar observations in carcinomas of the lung, suggest that this imbalance may be an early tobacco smoke–induced event and relevant to the pathogenesis of both diseases.

**Conflict of Interest Statement:** None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

**Prostaglandin Synthase in Smoking-related Lung Disease**

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**Background:** Prostaglandin (COX) pathway with both potent vasodilatory and antimitotic properties. Previous studies have demonstrated an increase in cyclooxygenase 2 (COX-2), prostaglandin E$_2$, cytosolic phospholipase A2 (cPLA$_2$), and vascular endothelial growth factor (VEGF), but decreased prostacyclin synthase (PGI$_2$S) expression within lung tumors. Lung-specific overexpression of PGI$_2$S has protective effects in both chemical- and tobacco smoke–induced murine models of lung tumorigenesis. Lastly, PGI$_2$S expression within lung tumors may correlate with survival. Here, we hypothesize that an imbalance in COX-2, PGE$_2$, and PGI$_2$S may be important to the pathogenesis of other smoking-related lung diseases such as chronic obstructive pulmonary disease and that tobacco smoke may alter PGI$_2$S expression. **Design:** We evaluated PGI$_2$S expression in both normal and emphysematous human lung tissue samples by: (1) immunohistochemistry, (2) quantitative PCR, (3) Western analysis, and (4) both 6-keto PGF$_1$α (the stable metabolite of prostacyclin) and PGE$_2$ levels by ELISA. In addition, we treated primary human pulmonary microvascular endothelial cells (HPMVEC) with varying concentrations of cigarette smoke extract (CSE). Treated cells were assessed for PGI$_2$S, COX-2, VEGF, and cPLA$_2$; gene expression, and 6Keto-PGF$_1$α and PGE$_2$ levels. **Measurements and Results:** In this study, we observed that human lung emphysema tissue exhibited lower PGI$_2$S expression in the endothelium than normal lung tissue. Furthermore, in HPMVEC, CSE suppresses PGI$_2$S gene expression while potently inducing COX-2, cPLA$_2$, and VEGF expression. Pretreatment with potent antioxidants did not alter this imbalance with the exception of N-acetylcysteine (NAC), which reversed the induction of COX-2 by CSE. **Conclusions:** The main finding of this investigation is the demonstration of decreased PGI$_2$S protein and mRNA in the lungs from patients with emphysema. CSE reduces the expression of the PGI$_2$S gene and increases the expression of VEGF, COX-2, and cPLA$_2$ in HPMVEC. Decreased PGI$_2$S expression is likely multifactorial, including oxidant stress, loss of alveolar capillary endothelial cells, nitric oxide–related suppression, and altered transcriptional control. **In vitro** work by our laboratory has demonstrated that PGI$_2$S gene expression in lung carcinoma cell lines is partially controlled through methylation silencing. Our demonstration that PGI$_2$S is diminished in both human emphysema tissue and **in vitro** by CSE, as well as similar observations in carcinomas of the lung, suggest that this imbalance may be an early tobacco smoke–induced event and relevant to the pathogenesis of both diseases.

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**IFN-γ–dependent DNA Injury and/or Apoptosis Are Critical in Cigarette Smoke–induced Murine Emphysema**

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There is mounting evidence that Tc1 immune responses contribute to the pathogenesis of pulmonary emphysema. This includes studies demonstrating increased number of IFN-γ–producing inflammatory cells and increased expression of IFN-γ target genes in lungs from patients with chronic obstructive pulmonary disease. Although cigarette smoking is a key risk factor for pulmonary emphysema, the roles of IFN-γ and apoptosis in these responses are poorly understood. We hypothesized that IFN-γ–dependent apoptosis plays an important role in the pathogenesis of cigarette smoke (CS)–induced murine emphysema. To test this hypothesis, we exposed male C57BL/6 wild-type and IFN-γ null (−/−) mice to the CS from 2R4 research cigarettes, 20 puffs/session, two sessions/d, 5 d/wk for 6 mo. Emphysema was then assessed with the NIH Image Analysis program, which provided morphometric measurements of alveolar chord length. DNA injury and apoptosis–like cell death were evaluated with TUNEL assays. After 6 mo, the mean chord length was increased by 36.8% in CS-exposed mice compared with nonsmoking control