and permeability was assessed by electrical cell–substrate impedance sensing.

Measurement and Main Results: In the isolated perfused human lung, CFH increased lung permeability over 2 hours compared with control lungs (12% vs. 2% weight gain from baseline, $P = 0.03$). Increased vascular permeability was confirmed by a 4.8-fold increase in Evans blue dye–labeled albumin in the airspace compared with control lungs. Pretreatment with APAP prevented lung weight gain ($P = 0.06$ vs. CFH). In human pulmonary microvascular endothelial cells, CFH increased monolayer permeability ($P = 0.03$ vs. control), and this was attenuated by APAP ($P = 0.045$ vs. CFH).

Conclusions: Circulating CFH increases vascular permeability in the isolated perfused human lung and paracellular permeability in lung microvascular endothelial cells. These effects may explain the association of plasma CFH levels with PGD. The hemoprotein reductant APAP attenuates the effects of CFH and merits further exploration as a potential therapy for PGD prevention.

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Gene Expression Profiling of Bronchoalveolar Lavage Cells Preceding a Clinical Diagnosis of Chronic Lung Allograft Dysfunction

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Chronic lung allograft dysfunction (CLAD) is the main limitation to long-term survival after lung transplantation. Although CLAD is usually not responsive to treatment, earlier identification may improve treatment prospects. In a nested case–control study, 1-year posttransplantation surveillance bronchoalveolar lavage (BAL) fluid samples were obtained from incipient CLAD ($n = 9$) and CLAD-free ($n = 8$) lung transplant recipients. Incipient CLAD cases were diagnosed with CLAD within 2 years, whereas control subjects were free from CLAD for at least 4 years after bronchoscopy. Transcription profiles in the BAL cell pellets were assayed with the HG-U133 Plus 2.0 microarray (Affymetrix, Santa Clara, CA). Differential gene expression analysis, based on an absolute fold change (incipient CLAD vs. no CLAD) greater than 2.0 and an unadjusted P value not exceeding 0.05, generated a candidate list containing 55 differentially expressed probe sets (51 up-regulated, 4 down-regulated). The cell pellets in incipient CLAD cases were skewed toward both innate and adaptive immune responses, suggesting that dysregulated immunity may precede a clinical diagnosis of CLAD. Both hierarchical clustering and a supervised machine learning tool were able to correctly categorize most samples into incipient CLAD and CLAD-free categories. A larger prospective investigation of a BAL cell pellet transcriptome as a biomarker for CLAD risk stratification is warranted.

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Bioactive Lipid Mediators Regulate Lung Epithelial and Mesenchymal Cell Reparative Processes *In Vitro*

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Lung wound–healing responses such as the epithelial-to-mesenchymal transition (EMT) can be reparative or pathologic processes. During lung transplantation, wound healing must occur, yet unchecked responses can result in negative outcomes including bronchiolitis obliterans. A class of specialized proresolving lipid mediators (SPMs) derived from omega-3 fatty acids has been found to contribute to the regulation of wound healing, including both positive and negative actions on EMT-related pathways.

To explore the role of SPMs in regulating lung wound healing, we examined how SPM maresin-1 (MaR1), a derivative of the omega-3 fatty acid docosahexaenoic acid (DHA), affects key cellular players of the lung EMT. When primary isolated human bronchial epithelial cells were treated with 1–100 nM MaR1, transforming growth factor (TGF)- β_1 -induced EMT processes were altered. MaR1 repressed TGF- β_1 -induced loss of E-cadherin expression and reduced matrix metalloprotease-2 activities and fibronectin production, while not impairing TGF- β_1 -mediated wound-healing capacity. Interestingly, MaR1 also regulated the actions of primary isolated human lung mesenchymal stem (stromal) cells (MSCs). MaR1 (1–100 nM) dose-dependently increased MSC metabolic activity; similar effects were seen with 1–100 nM DHA treatment. MaR1 treatment was also protective against protease activation of MSCs under inflammatory conditions. Furthermore, when conditioned medium from DHA-treated MSCs was used to culture bronchial epithelial cells, the epithelial cells exhibited modulation of protease activation.

Our results identify DHA and MaR1 as regulators of reparative processes after lung inflammation and wounding, including effects on two pivotal cellular players—bronchial epithelial cells and MSCs. Future mechanistic and therapeutic investigations are warranted to ascertain the clinical usefulness of these lipids in regulating lung repair processes relevant to lung transplantation.

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