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A gene expression signature of emphysema-related lung destruction and its reversal by the tripeptide GHK

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease consisting of emphysema, small airway obstruction, and/or chronic bronchitis that results in significant loss of lung function over time.

Methods: In order to gain insights into the molecular pathways underlying progression of emphysema and explore computational strategies for identifying COPD therapeutics, we profiled gene expression in lung tissue samples obtained from regions within the same lung with varying amounts of emphysematous destruction from smokers with COPD (8 regions × 8 lungs = 64 samples). Regional emphysema severity was quantified in each tissue sample using the mean linear intercept (Lm) between alveolar walls from micro-CT scans.

Results: We identified 127 genes whose expression levels were significantly associated with regional emphysema severity while controlling for gene expression differences between individuals. Genes increasing in expression with increasing emphysematous destruction included those involved in inflammation, such as the B-cell receptor signaling pathway, while genes decreasing in expression were enriched in tissue repair processes, including the transforming growth factor beta (TGFβ) pathway, actin organization, and integrin signaling. We found concordant differential expression of these emphysema severity-associated genes in four cross-sectional studies of COPD. Using the Connectivity Map, we identified GHK as a compound that can reverse the gene-expression signature associated with emphysematous destruction and induce expression patterns consistent with TGFβ pathway activation. Treatment of human fibroblasts with GHK recapitulated TGFβ-induced gene-expression patterns, led to the organization of the actin cytoskeleton, and elevated the expression of integrin β1. Furthermore, addition of GHK or TGFβ restored collagen I contraction and remodeling by fibroblasts derived from COPD lungs compared to fibroblasts from former smokers without COPD.

Conclusions: These results demonstrate that gene-expression changes associated with regional emphysema severity within an individual's lung can provide insights into emphysema pathogenesis and identify novel therapeutic opportunities for this deadly disease. They also suggest the need for additional studies to examine the mechanisms by which TGFβ and GHK each reverse the gene-expression signature of emphysematous destruction and the effects of this reversal on disease progression.

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