Ghk-Cu Elicits In Vitro, Dose-Dependent Transcriptional Alterations In Pathways Relevant To Extracellular Matrix Composition

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Rationale: The lack of disease-modifying interventions in COPD represents a critically unmet medical need, the resolution of which could reduce mortality and improve quality of life for millions of Americans. A meta-analysis of gene expression signatures associated with emphysema and COPD identified the tripeptide GHK (glycyl-L-histidyl-L-lysine) as a candidate drug likely to reverse disease-associated gene expression. Consistent with this hypothesis, GHK-Cu reverses collagen-remodeling deficits present in lung fibroblasts from COPD patients. Motivated by these findings, we sought to more fully characterize the transcriptional effects of GHK in human lung fibroblasts to gain insights into GHK’s mechanisms of action.

Methods: Human fetal lung fibroblasts (HFL1) were treated for 6, 12, 24, or 48 hours with either phosphate buffered saline, GHK-Cu (0.1nM, 1nM or 10 nM), or copper acetate at a concentration equivalent to that found in the 10nM dose of GHK-Cu. RNA was isolated from the samples and hybridized to Hu 1.0ST microarrays for gene expression profiling. Within each time point, a Spearman correlation was employed to identify genes whose expression is dose-dependent to GHK-Cu. Genes were also ranked according to this correlation and analyzed for functional enrichment via Gene Set Enrichment Analysis (GSEA).

Results: We identified a signature of 329 genes with dose-responsive expression to GHK-Cu at 48 hours (q<0.05). Notably, the 238 genes whose expression is decreased with increasing GHK-Cu dose are involved with collagen fibril assembly (q<0.001) while the upregulated genes are involved with adherens junctions and cell division (q<0.001). Additionally, we find that genes with the most dose-responsive increases in transcription after 6 hours GHK-Cu treatment are disproportionately associated with the metabolism of glycosaminoglycans.

Conclusions: GHK-Cu elicits alterations in pathways relevant to the extracellular matrix (EM) within lung fibroblasts at early and late time points. Given the dysregulation of EM in emphysema, future work is warranted to clarify the mechanisms by which GHK-Cu induces these gene expression alterations and restores collagen remodeling in order to better understand its potential as a COPD therapeutic.

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