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How gene profiling in emphysema is helping to find a cure

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Chronic obstructive pulmonary disease (COPD) is the third leading cause of death in the United States and is thought to affect almost three million people in the UK. New research published in BioMed Central's open access journal *Genome Medicine* has identified genes whose activity is altered with increasing lung damage and, using a database of drug effects on gene activity (the Connectivity Map), finds that the compound Gly-His-Lys (GHK) affects the activity of these genes. When tested on human cells from lungs damaged by emphysema, GHK was able to restore normal gene activity and repair cell function.

The strongest cause of COPD is smoking, and at least 25% of smokers will develop this disease. Tobacco smoke and other irritants cause oxidative stress and chronic inflammation, which over time results in emphysema, the destruction of lung alveolar cells. Without these cells, the lungs are not able to efficiently exchange oxygen for carbon dioxide, leaving the patient continuously short of breath and with low levels of oxygen in their blood.

In a ground breaking, multi-centre, study funded by the National Institute of Health (NIH), researchers used cells taken from lungs donated by patients undergoing double lung transplant, whose own lungs were irrevocably damaged by COPD. Profiling of these samples showed that 127 genes had changes in activity that was associated with worsening disease severity within the lung. As would be expected from the nature of the disease, several genes associated with inflammation, such as the genes involved in signalling to B-cells (the immune system

cells which make antibodies), showed increased activity.

In contrast genes involved in maintaining cellular structure and normal cellular function, along with the growth factors TGFβ and VEGF, were down-regulated and showed decreased activity. This included genes which control the ability of the cells to stick together (cell adhesion), produce the protein matrix which normally surrounds the cells, and which promote the normal association between lung cells and blood vessels.

Dr Avrum Spira and Dr Marc Lenburg, who co-led this study from the Boston University School of Medicine, explained, "When we searched the Connectivity Map database, which is essentially a compendium of experiments that measure the effect of therapeutic compounds on every gene in the genome, we found that how genes were affected by the compound GHK, a drug known since the 1970s, was the complete opposite of what we had seen in the cells damaged by emphysema."

Dr Joshua Campbell explained, "What got us especially excited was that previous studies had shown that GHK could accelerate wound repair when applied to the skin. This made us think that GHK could have potential drug's as a therapy for COPD."

Prof James Hogg, from the University of British Columbia continued, "When we tested GHK on cells from the damaged lungs of smokers with COPD, we saw an improvement in the structure of their actin cytoskeleton and in cell adhesion, especially to collagen. GHK also restored the ability of cells to reorganise themselves to repair wounds and construct the contractile filaments essential for alveolar function."

GHK is a natural peptide found in human plasma, but the amount present decreases with age. While more testing needs to be done on its effects in COPD, these early results are very promising. Therapeutic

studies with GHK in animal models of COPD are now underway with the ultimate goal of moving this compound into clinical trials. As more gene activity signatures are discovered, this method of matching drug to disease may provide a rapid method for discovering potential uses for existing drugs and compounds.

More information: A gene expression signature of emphysema-related lung destruction and its reversal by the tripeptide GHK Joshua D Campbell, John E McDonough, Julie E Zeskind, Tillie L Hackett, Dmitri V Pechkovsky, Corry-Anke Brandsma, Masaru Suzuki, John V Gosselink, Gang Liu, Yuriy O Alekseyev, Ji Xiao, Xiaohui Zhang, Shizu Hayashi, Joel D Cooper, Wim Timens, Dirkje S Postma, Darryl A Knight, Marc E Lenburg, James C Hogg and Avrum Spira Genome Medicine (Section: Molecular genetics, genomics & epigenetics of disease) (in press)

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