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Why Steroid Treatment for COPD Is Ineffective

Chronic obstructive pulmonary disease (COPD) leads to persistent inflammation of the airways and is typically managed with corticosteroids, a class of anti-inflammatory medication. However, corticosteroids do not improve survival nor alter the progression of COPD and may reduce lung symptoms as little as 20 percent. A new study led by researchers at the Johns Hopkins Bloomberg School of Public Health, found why corticosteroids do not work well for COPD patients and how additional treatment with sulforaphane -- an ingredient of broccoli and other vegetables -- can improve the effectiveness of corticosteroids. The study was published online October 17, 2011, in advance of print in the Journal of Clinical Investigation.

COPD is a major public health problem for both the developed and the developing world, and is most often caused by cigarette smoking or exposure to pollutants from combustion. Characterized by chronic bronchitis and emphysema, COPD is the third leading cause of death in the U.S. and affects 24 million Americans and 210 million people worldwide.

Histone deacetylase 2 (HDAC2) is critical component in a chain of reactions that enable corticosteroids to reduce inflammation. However, HDAC2 is substantially reduced in the lung tissue of individuals with COPD. In the study, Johns Hopkins researchers found that S-nitrosylation causes HDAC2 dysfunction and leads to corticosteroid insensitivity in the alveolar macrophages of the lungs of individuals with COPD. S-nitrosylation of HDAC2 occurs from exposure to cigarette smoke, a primary cause of COPD.

"This study provides the mechanism of exaggerated inflammation observed in COPD patients during exacerbations, which has been a barrier to developing effective therapy," said Rajesh Thimmulappa, PhD co-author of the study and an assistant scientist in the Bloomberg School's Department of Environmental Health Sciences.

Furthermore, the research team found that treatment with sulforaphane restored HDAC2 activity and corticosteroid sensitivity. Previous studies by the research team showed sulforaphane activates the Nrf2 pathway (nuclear factor erythroid 2-related factor 2) and it is being tested in clinical trial for patients with COPD.

"Restoring corticosteroid sensitivity in patients with COPD by targeting the Nrf2 pathway holds promise for effectively treating exacerbations," said Shyam Biswal, PhD, senior author of the study and professor in the Bloomberg School's Department of Environmental Health Sciences and Division of Pulmonary and Critical Care Medicine at the Johns Hopkins School of Medicine.
Authors of "Denitrosylation of HDAC2 by Targeting Nrf2 Restores Glucocorticosteriod Sensitivity in Macrophages from COPD Patient" are Deepti Malhotra, Rajesh Thimmulappa, Nicolas Mercado, Kazuhiro Ito, Ponvijay Kombairaju, Sarvesh Kumar, Jinfang Ma, David Feller-Kopman, Robert Wise, Peter Barnes and Shyam Biswal.

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Biswal, Thimmulappa, and the Johns Hopkins University hold intellectual property on the development of Nrf2-based therapeutics in COPD, and they have equity in Cureveda LLC, which was co-founded by Biswal and Thimmulappa, and where they serve as scientific consultants. These potential individual and institutional conflicts of interest have been reviewed and managed by the Johns Hopkins Bloomberg School of Public Health. Under a licensing agreement between Brassica Protection Products and the Johns Hopkins University, the University is entitled to royalty received on sales of products/technology described in this article. The University owns Brassica Protection Products stock, which is subject to certain restrictions under University policy. The terms of this arrangement are being managed by the Johns Hopkins University in accordance with

its conflict of interest policies. No other competing interest were declared.

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Journal Reference:
Deepti Malhotra, Rajesh K. Thimmulappa, Nicolas Mercado, Kazuhiro Ito, Ponvijay Kombairaju, Sarvesh Kumar, Jinfang Ma, David Feller-Kopman, Robert Wise, Peter Barnes, Shyam Biswal. Denitrosylation of HDAC2 by targeting Nrf2 restores glucocorticosteroid sensitivity in macrophages from COPD patients. Journal of Clinical Investigation, 2011; DOI: 10.1172/JCI45144

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