Activating the lung's antioxidant defense by targeting Nrf2 inhibits the development of emphysema

December 22 2008

Using a molecule similar to one found in an experimental cancer drug, researchers at the Johns Hopkins Bloomberg School of Public Health demonstrated that activation of a key component of the lung's antioxidant defense system, Nrf2, can prevent emphysema in mice.

The researchers believe that activation of Nrf2 could be a novel target for therapies to prevent chronic obstructive pulmonary disease (COPD), which comprises emphysema and chronic bronchitis. COPD is a major public health problem and it is the fourth leading cause of death in the U.S. The study is published in the online *Early Edition of PNAS: Proceeding of the National Academy of Sciences*.

"There are no effective therapies for COPD and there is an urgent need to develop novel intervention strategies. Targeting the Nrf2 pathway presents a novel strategy which needs to be tested for their efficacy in intervening COPD in patients," said Shyam Biswal, PhD, senior author of the study and an associate professor in the Bloomberg School of Public Health's Department of Environmental Health Sciences and the Division of Pulmonary and Critical Care Medicine at the Johns Hopkins School of Medicine.

Nrf2 (nuclear factor erythroid-derived 2-related factor 2) works as a "master gene" that turns on numerous antioxidant and pollutant-detoxifying genes to protect the lungs from environmental pollutants,

such as cigarette smoke. Biswal previously identified that disruption of Nrf2 expression in mice caused early onset and severe emphysema. More recently, his team demonstrated for the first time a close correlation between the Nrf2 decline and the progression of COPD in humans.

For the current study, Biswal, along with postdoctoral fellows, Thomas Sussan, PhD, Tirumalai Rangasamy, PhD, and David J. Blake, PhD, observed mice exposed to cigarette smoke to determine if activation of Nrf2 could prevent emphysema. Exposed mice—fed a diet containing CDDO-Im, which is known to activate Nrf2—were significantly less likely to have oxidative stress and lung cell damage associated with emphysema. The researchers also noted substantially improved function in the portion of the heart responsible circulating oxygenated blood through the body—a function that is typically diminished with emphysema. CDDO-Im is closely related to CDDO-Me, an experimental cancer drug approved for phase II clinical trials.

"Nrf2 is an important regulator of the body's antioxidant defense system, and activation of Nrf2 is a promising therapeutic strategy for attenuating COPD progression in patients," said Thomas Sussan, PhD, lead author of the study.

According to the researchers, COPD affects more than 16 million Americans and it is the only disease among the top 10 causes of death with a rising mortality rate in the United States. It is predicted to be the third largest cause of death by 2020 and has already reached worldwide epidemic proportions.

Paper: "Targeting Nrf2 with the triterpenoid CDDO-imidazolide attenuates cigarette smoke-induced emphysema and cardiac dysfunction in mice", PNAS, www.pnas.org .

Source: Johns Hopkins University