Cigarettes leave deadly path by purging protective genes

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A University of Rochester scientist discovered that the toxins in cigarette smoke wipe out a gene that plays a vital role in protecting the body from the effects of premature aging. Without this gene we not only lose a bit of youthfulness – but the lungs are left open to destructive inflammation and diseases such as chronic obstructive pulmonary disease (COPD) and lung cancer.

By identifying the Sirtuin (SIRT1) gene's role in pulmonary disease, scientists also hope to find ways to restore it and jump-start lung healing. They've begun testing the powerful antioxidant resveratrol, which is extracted from red grape skins, to develop a treatment to target SIRT1 and reverse lung damage, or at least enhance the way standard COPD therapies work.

"This novel protein will allow us to program our body's immune-inflammatory system against lung damage and premature aging. The hallmark of this discovery is that we may be able to provide remedies to millions of smokers who would like to quit but cannot kick their addiction, and millions of former smokers who, despite quitting, remain at risk for illness as they age," said Irfan Rahman, Ph.D., associate professor of Environmental Medicine and an investigator in the University of Rochester's Lung Biology and Disease Program.

The research was published in two separate studies, in the American Journal of Respiratory Critical Care Medicine, appearing online Jan. 3, 2008, and in the *American Journal of Physiology*, appearing Dec. 27,

2007.

Approximately 23 million Americans have COPD, which is induced by inflammation and results in progressive breathlessness. By the year 2020, it is expected to be the third leading cause of death worldwide; today at least 9 percent of the elderly population is estimated to suffer from debilitating lung conditions.

Rahman has spent years studying how the 4,700 toxic chemical compounds in cigarettes assault lung tissue. He also focuses on why some people seem genetically predisposed to develop lung diseases while others are more fortunate, despite being smokers.

SIRT1 plays a pivotal role in the puzzle. It belongs to a class of genes that regulate chronic inflammation, cancer and aging. When SIRT1 is highly active, or over-expressed in mice, worms and fruit flies, their life spans are greatly increased. Recent studies also show that SIRT1 plays a positive role in stress resistance, metabolism, apoptosis and other processes involved in premature aging. However, environmental stress such as cigarette smoke or pollution can decrease production of SIRT1 in the lungs.

In collaboration with Vuokko L. Kinnula, M.D., at Helsinki University Hospital in Finland, Rahman's team studied the levels of SIRT1 in the lungs of nonsmokers and smokers with and without COPD. Thirty-seven patients from Helsinki who were undergoing either a lung resection for suspected cancer or a lung transplant, volunteered to provide tissue samples for the study. Researchers confirmed that SIRT1 was significantly lower in smokers who had COPD and in smokers who did not have disease, compared to nonsmokers.

The next step was to investigate what pathways lead to the depletion of SIRT1. Researchers found that Sirtuin also plays a role in regulating the

entire chemical signaling system that protects the lungs from smoke and pollution. They investigated how SIRT1 relates to another key protective molecule, Nrf2, a transcription factor. Just as in the case of SIRT1, an airway deficient in Nrf2 is weak and inflamed and more prone to conditions such as COPD, researchers found.

Nrf2 was also important because it directly regulates several antioxidant genes such as gluthathione (GSH), the most abundant cellular antioxidant responsible for detoxifying the airways. Therefore, the pathway from SIRT1 to Nrf2 ultimately leads to the depletion of GSH, exacerbating the organ's aging process.

"You can be 45 years old and look great on the outside, but if you are a smoker or former smoker, your lungs can easily be 60 years old because of the chemical assault," Rahman said.

Other University of Rochester research teams are investigating the Nrf2 pathway and various ways to boost fundamental genetic changes in the body that would arm it with amplified natural antioxidants. The result could be the development of a target for new drugs that would protect us from age-related diseases such as cancer and emphysema.

Although he was not involved in the study, James D. Crapo, M.D., a leading expert in the field of lung disease and a professor of Medicine at the National Jewish Medical and Research Center, University of Colorado Health Sciences Center in Denver, said Rahman's novel finding opens new doors. "This is certainly an important breakthrough in understanding the persistent lung damage and inflammation that occur in patients with COPD, and therapies can now be directed towards this protein."

Source: University of Rochester Medical Center