Scientists discover molecular 'switch' that contributes to cellular aging process

November 30 2010

A team of Harvard School of Public Health (HSPH) scientists report finding a molecular "switch" that can "turn off" some cellular processes that are protective against aging and metabolic diseases. While more research is needed, the findings may open doors for new drug treatments to halt or slow development of metabolic diseases like type 2 diabetes or heart disease. The research findings appear in the December 1, 2010 issue of *Cell Metabolism*.

Scientists want to better understand why some people – often those who are older, overweight, or obese – develop metabolic syndrome, a condition characterized by a group of risk factors, including high blood glucose, high cholesterol, insulin resistance, fatty liver, and increased abdominal fat. This condition increases the risk of heart disease, type 2 diabetes, and other diseases, including cancer.

Using genetically altered mouse models, senior author Chih-Hao Lee, assistant professor of genetics and complex diseases at HSPH, first author Shannon Reilly, an HSPH graduate student, and their colleagues focused on the role of the protein SMRT (silencing mediator of retinoid and thyroid hormone receptors) in the aging process. They found aged cells accumulate more SMRT and wanted to see if SMRT increases the damaging effects of oxidative stress on mitochondria, the cell component that converts food and oxygen into energy and powers metabolic activities. Oxidative stress is a cellular process that damages DNA, protein, and other cell functions and can lead to age-related diseases such as type 2 diabetes, Alzheimer's, Parkinson's, and

atherosclerosis.

In laboratory experiments, Reilly, Lee, and colleagues found that in older animals SMRT acts like a "switch," turning off the protective cellular activities of proteins known as peroxisome proliferator-activated receptors (PPARs). PPARs help regulate genes that promote fat burning to maintain lipid (blood fat) balance and reduce oxidative stress. The researchers were able to reduce the negative effects of oxidative stress by giving antioxidants or drugs known to turn the protective activities of PPARs back on.

The scientists knew that oxidative damage causes the body to age. What they did not know is why aged cells have more oxidative damage. "The significance of our study is that we show SMRT facilitates this process," Lee said. "In other words, the normal metabolic homeostasis is maintained, in part, by PPARs. SMRT acts as a metabolic switch to turn off PPAR activities when the cells age."

PPAR drugs have been used to increase insulin sensitivity and lower blood lipid levels. "Our study shows PPARs might also be used to boost the body's ability to handle oxidative stress," Lee said.

"With what we have learned, we believe SMRT is one of the key players that causes age-dependent decline in mitochondrial function by blocking PPAR activity, and we've found a way to boost the body's ability to better handle metabolic and oxidative stress," Lee said. "This finding is significant since increased oxidative stress, coupled with reduced metabolic function, contributes to the aging process and the development of age-related metabolic diseases."

In collaboration with epidemiologists at HSPH, the team found genetic variations in the human SMRT gene that are associated with risk of type 2 diabetes. "Through this study we were able to validate that our findings

in the animal model apply to human diseases," Lee said.

Provided by Harvard School of Public Health