Scientists identify major source of cells' defense against oxidative stress

April 6 2012

Both radiation and many forms of chemotherapy try to kill tumors by causing oxidative stress in cancer cells. New research from USC on a protein that protects cancer and other cells from these stresses could one day help doctors to break down cancer cells' defenses, making them more susceptible to treatment.

In the March 23 issue of the Journal of Biological Chemistry, scientists led by USC Professor Kelvin J. A. Davies demonstrated that a protein known as Nrf2 governs a cell's ability to cope with oxidative stress by increasing the expression of key genes for removing damaged proteins.

Typically, oxidative stress is to be avoided. People eat foods high in antioxidants (such as fruits and vegetables) to try to block oxidation in their cells, in hopes of lowering their risk of illnesses such as cancer, heart disease, stroke and Alzheimer disease – which are all linked to oxidative stress.

But in the case of cancer cells, if the Nrf2 response could some day be selectively turned off, treatments like chemotherapy and radiation could be more effective, Davies said.

"One of the problems you have is that cancer cells start becoming resistant to those treatments: they adapt," said Davies, who holds joint appointments in the USC Davis School of Gerontology the USC Dornsife College of Letters, Arts and Sciences. "The next time they may be more resistant because they've seen it before."

Nrf2 is a transcription factor protein, meaning that it binds to specific sequences of DNA, turning on the process of copying the blueprints encoded in those DNA sequences into functional enzymes. In particular, the new work from the Davies lab shows that production of proteasome and a proteasome regulator (Pa28) is controlled by Nrf2 during oxidative stress. Proteosome, in turn, is a large protein enzyme that breaks down oxidized proteins that would otherwise accumulate and cause cells to die.

When oxidative stress increases (simulated in the lab by adding hydrogen peroxide – the major product of both radiation therapy and chemotherapy), Davies and his team found that the Nrf2 in a cell starts ramping up proteasome production.

The researchers then tested their findings by blocking Nrf2 with various chemical and genetic inhibitors, which in turn decreased the cell's ability to make more proteasome and cope with the hydrogen peroxide.

In normal young cells, Nrf2 allows continuous regulation of proteasome production in response to changing oxidative environments. This ability may decline in aging and age-related diseases, making older individuals less able to cope with stress.

"We would like to be able to reverse this decline in normal cells, while making cancer cells less stress-resistant and more easily killed by radiation therapy and chemotherapy," Davies said.

Provided by University of Southern California