Research team uncovers new mechanisms of oxidative stress regulation

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(Medical Xpress)—Regulation of oxidative stress is critical to cell survival. New preclinical research from Roswell Park Cancer Institute (RPCI) has revealed two key mechanisms by which oxidative stress is regulated in normal and cancerous cells.

Oxidative stress occurs when a cell is not able to adequately remove reactive oxygen species (ROS), or reactive molecules that result from the metabolism of oxygen. To alleviate these toxically high levels of ROS, cells activate NF-E2-related transcription factor 2 (Nrf2), which normally resides in the cytoplasm. Under conditions of oxidative stress, however, Nrf2 relocates to the nucleus, where it induces transcription of antioxidant genes.

For many years, ROS detoxification was considered the major function of Nrf2. Reciprocally, activation of Nrf2 was considered the major and universal mechanism for ROS detoxification.

Writing in the journal *Molecular Cell*, a team led by Mikhail Nikiforov, PhD, a Professor of Oncology and member of the Department of Cell Stress Biology at RPCI, has demonstrated that under certain conditions, Nrf2 behaves in ways that are directly opposite to its normal activities. These scientists have shown that if intracellular ROS exceed a critical threshold, Nrf2 induces expression of the transcription factor Klf9 (Kruppel-like factor 9), which in turn further increases ROS levels by suppressing cellular antioxidant genes, ultimately leading to cell death. The team verified this previously unrecognized feed-forward mechanism

of ROS regulation in vivo using an animal model of idiopathic pulmonary fibrosis, a terminal disease of the lungs.

Reactive oxygen species play a dual role in tumorigenesis. While low ROS levels promote tumor cell proliferation and increase genetic instability, high amounts of ROS are detrimental to cell proliferation or survival, inhibiting both healthy and diseased cells. The team's findings identify Klf9 as a molecular "switch" between the anti- and pro-oxidative functions of Nrf2.

"Tumor cells exhibit increased generation of reactive oxygen species as a consequence of high metabolic activity. Consequently, tumors often develop adaptive mechanisms to suppress high levels of ROS, so we looked for ways to exploit their weakness in the face of ROS increase," notes Dr. Nikiforov. "Our findings suggest that Klf9 depletion could be beneficial for malignancies where high amounts of ROS hinder tumor progression, including colorectal and gynecologic cancers. Our data may also support a role for Klf9 as a general tumor suppressor and provide further insights into the mechanism by which tumors acquire resistance to higher levels of ROS."

Activation of Klf9 may prove to be an effective complement to therapies that induce oxidative stress as a mechanism of cell killing, including cisplatinum, arsenic trioxide and the experimental agent elesclomol. Dr. Nikiforov and his team have begun subsequent studies to elucidate the role of Klf9 and its targets in tumor progression and drug resistance of several difficult-to-treat cancers, including melanoma and multiple myeloma.

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The paper, "Nrf2 amplifies oxidative stress via induction of Klf9," was published online ahead of print today and can be accessed at cell.com/molecular-cell.

More information: Shoshanna N. Zucker, et al. "Nrf2 Amplifies Oxidative Stress via Induction of Klf9" *Molecular Cell*, 06 March, 2014 Elsevier, 10.1016/j.molcel.2014.01.033

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