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Over the edge: New therapeutic strategy takes advantage of stressed cancer cells

A biochemical alteration that has long been viewed as an adverse aspect of tumor biology may turn out to be a deadly double-edged sword for the cancer cells themselves. Scientists have successfully exploited the oxidative stress common in cancer cells to preferentially kill malignant cells. This approach has the therapeutic advantage of selectively targeting cancer cells while exhibiting minimal toxicity in normal cells. The research is published in the September 2006 issue of the journal Cancer Cell, published by Cell Press.

Most cancer cells exhibit overproduction of reactive oxygen species (ROS), which is thought to provide favorable conditions for cancer cell growth, genetic instability, and survival. Dr. Peng Huang from the Department of Molecular Pathology at the University of Texas M.D. Anderson Cancer Center and colleagues hypothesized that increased ROS generation may also make cancer cells highly vulnerable to exogenous ROS-modulating agents that would not be toxic to normal cells with low ROS output.

The researchers examined the ability of a naturally occurring compound called â-phenylethyl isothiocyanate (PEITC), which is known to modulate cellular antioxidant pathways, to push cancer cells to even higher ROS levels that result in cell death. Oncogenically transformed cells exhibited high basal ROS levels and were more sensitive to PEITC than nontransformed cells. PEITC interfered with a specific antioxidant system that the cancer cells relied on to maintain a ROS balance that was compatible with survival. Treatment with PEITC led to further ROS accumulation that caused massive death of cancer cells but no cytotoxicity in normal cells. Importantly, PEITC also significantly prolonged survival in an animal model of human cancer.

"Our study suggests that the intrinsic oxidative stress in cancer cells associated with oncogenic transformation provides a basis for developing therapeutic strategies to preferentially kill cancer cells through ROS-mediated mechanisms, and compounds such as PEITC can be used to achieve such activity in vitro and in vivo. Further preclinical and clinical testing is warranted to determine whether highly malignant cells that are often resistant to conventional anticancer drugs may be sensitive to compounds like PEITC because of their high intrinsic ROS stress," says Dr. Huang.

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The researchers include Dunyaporn Trachootham of the Department of Molecular Pathology, The University of Texas M.D. Anderson Cancer Center in Houston, Texas, The University of Texas Graduate School of Biomedical Sciences at Houston in Houston, Texas, and the Faculty of Dentistry, Thammasat University, Rangsit Campus in Pathum-thani, Thailand; Yan Zhou of the Department of Molecular Pathology, The University of Texas M.D. Anderson Cancer Center in Houston, Texas; Hui Zhang of the Department of Molecular Pathology, The University of Texas M.D. Anderson Cancer Center in Houston, Texas and The University of Texas Graduate School of Biomedical Sciences at Houston, Houston, Texas; Yusuke Demizu of the Department of Molecular Pathology, The University of Texas M.D. Anderson Cancer Center in Houston, Texas; Zhao Chen of the Department of Molecular Pathology, The University of Texas M.D. Anderson Cancer Center in Houston, Texas and The University of Texas Graduate School of Biomedical Sciences at Houston, Houston, Texas; Helene Pelicano of the Department of Molecular Pathology, The University of Texas M.D. Anderson Cancer Center in Houston, Texas; Paul J. Chiao of The University of Texas Graduate School of Biomedical Sciences at Houston, Houston, Texas and the Department of Surgical Oncology, The University of Texas M.D. Anderson Cancer Center in Houston, Texas; Geetha Achanta of the Department of Molecular Pathology, The

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Trachootham et al.: "Selective killing of oncogenically transformed cells through a ROS-mediated mechanism by â-phenylethyl isothiocyanate." Publishing in Cancer Cell 10, 241–252, September 2006. DOI 10.1016/j.ccr.2006.08.009 www.cancercell.org

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