Previously unknown mechanism identified in oncogene-induced senescence

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Cell aging, or cellular senescence, has an important role in the natural physiological response to tumor development. Activated oncogenes are able to induce senescence, and recent findings have suggested that oncogene-induced senescence (OIS) could play a key role in future cancer therapy. Researchers have now identified a previously unknown mechanism in the regulation of OIS. This study is published online in advance of the January issue of *The American Journal of Pathology*.

In many types of normal cells, OIS depends on induction of DNA damage response. Oxidative stress and hyper-replication of genomic DNA have already been proposed as major causes of DNA damage in OIS cells. A group of investigators from New York, Oregon, and Michigan reports that down-regulation of deoxyribonucleoside pools is another endogenous source of DNA damage. In normal human cells, "OIS represents an important fail-safe mechanism that suppresses proliferation of pre-malignant cells," explains lead investigator Dr Mikhail Nikiforov, PhD, Department of Cell Stress Biology, Roswell Park Cancer Institute, Buffalo, New York. "Compelling evidence suggests that one of the intrinsic processes required for the induction of OIS is the cellular response to DNA damage."

The group investigated endogenous processes that caused DNA damage in human fibroblasts undergoing OIS and demonstrated that DNA damage, at least partially, originates from under-expression of key enzymes involved in deoxyribonucleoside biosynthesis and subsequent depletion of endogenous deoxyribonucleoside triphosphate (dNTP)

pools. They found that even partial restoration of depleted intracellular dNTP pools is sufficient for substantial suppression of DNA damage and senescence.

"We believe our data identify a previously unknown role of deoxyribonucleotides in regulation of oncogene-induced senescence. Our results suggest that both nucleotide depletion and active DNA replication are required for efficient induction of DNA damage and OIS," he concludes.

More information: "Depletion of Deoxyribonucleotide Pools Is an Endogenous Source of DNA Damage in Cells Undergoing Oncogene-Induced Senescence," by Sudha Mannava, Kalyana C. Moparthy, Linda J. Wheeler,Venkatesh Natarajan, Shoshanna N. Zucker, Emily E. Fink, Michael Im, Sheryl Flanagan, William C. Burhans, Nathalie C. Zeitouni, Donna S. Shewach, Christopher K. Mathews, and Mikhail A. Nikiforov. dx.doi.org/10.1016/j.ajpath.2012.09.011. It appears in *The American Journal of Pathology*, Volume 182, Issue 1 (January 2013)

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