Medical Xpress

Newly discovered weakness in cancer cells make them more susceptible to chemotherapy

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A new weakness has been discovered in cancer cells that may make them more susceptible to chemotherapy and other treatments. In a research report appearing in the September 2013 issue of *The FASEB Journal*, scientists identify the HDAC5 protein as being essential for the maintenance of structures, called telomeres, within cancer cells that promote cancer cells longevity. Cancer cells with longer telomeres tend to be more resistant to therapies, while cancer cells with shorter telomeres tend to be more susceptible. By targeting the mechanism used by cancer cells to maintain telomeres, HDAC5, existing therapies could become far more effective at eradicating cancer than they are today.

"Our study can contribute to the development of new combined anti-cancer therapies," said Denis Mottet, Ph.D., a researcher involved in the work from the University of Liege Sart-Tilman, Groupe Interdisciplinaire de Génoprotéomique Appliquée (GIGA)-Cancer, Metastasis Research Laboratory, in Liege, Belgium. "By maintaining a reduced telomere length via HDAC5 inhibition, cancer cells are more sensitive to chemotherapeutic drugs."

To make this discovery, Mottet and colleagues analyzed several cancer cell lines with different backgrounds regarding their telomere biology (different telomere lengths and different molecular mechanisms to maintain telomere length) and found that HDAC5 co-localized with telomeres only in cancer cells with very long telomere lengths. Researchers then depleted this HDAC5 protein in cancer cells with varied telomere lengths and observed a phenotype (shortening of

telomeres) exclusively in cancer cells that originally had longer telomeres. Cells with shorter telomeres did not seem to be affected by the absence of the HDAC5 protein. They also found that some cancer cells with very long telomeres were resistant to death induced by common chemotherapy drugs, but the reduction of HDAC5 protein levels in these cells and the subsequent telomere shortening sensitized the cells to these agents, leading to massive cell death. Telomere shortening also is directly linked to cell aging, the development of premature aging syndromes, and advanced aging diseases, this research could eventually have widespread clinical impact.

"The 'cure for cancer' may not come from a single discovery, but will surely arrive step-by-step. This study defines one of those steps." said Gerald Weissmann, M.D., Editor-in-Chief of *The FASEB Journal*. "What these scientists have done is to accelerate the aging of cancer cells , so as to weaken them enough to be killed by anti-cancer drugs. This type of discovery was unfathomable when Nixon first declared war on the disease in 1971."

More information: Clara Lopes Novo, Catherine Polese, Nicolas Matheus, Anabelle Decottignies, Arturo Londono-Vallejo, Vincent Castronovo, and Denis Mottet. A new role for histone deacetylase 5 in the maintenance of long telomeres. *FASEB J*, September 2013, DOI: 10.1096/fj.12-224204

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