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New evidence that aging tumor cells may be an effective cancer treatment

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Scientists at the University of Massachusetts Medical School have shown that diffuse large B-cell lymphoma (DLBCL) may be susceptible to treatment by re-activating the normal aging program in tumor cells so they can no longer divide. The study, published in *Nature Communications*, details a novel, tumor-suppressive role for the Smurf2 protein—which typically plays an "enforcer" role in cellular aging, also called senescence —in a subset of DLBCL. Identification of this novel function for Smurf2 provides a new therapeutic target for treating this cancer.

"Normally, this pathway is responsible for senescence and suppressing proliferation of B cells," said Hong Zhang, PhD, assistant professor of cell & developmental biology at UMMS and senior author of the study. "However, human DLBCL show low levels of Smurf2 expression; these low levels affect a pathway that encourages un-checked cell division and tumor growth. It's possible that restoration of Smurf2 expression may provide therapeutic benefits for patients and help encourage remission in difficult to treat cases."

Diffuse large B-cell lymphoma is the most common form of non-Hodgkin's lymphoma. An estimated 70,000 people living in the United States will be diagnosed with non-Hodgkin's lymphoma in 2013, accounting for 30 to 40 percent of all new diagnoses. Roughly 50 percent of those diagnosed will not respond to conventional treatment or will relapse within five years. Rachel Gerstein, PhD, associate professor of microbiology and physiological systems at UMMS, and co-author of

the study, notes that "the average age at the time of diagnosis with DLBCL is mid-60s. Therefore, it's particularly exciting to connect a glitch in cellular aging within DLBCL to this cancer that preferentially affects the elderly."

A 2012 *Cancer Research* study by Drs. Zhang, Gerstein and colleagues found that mice deficient in Smurf2 gene expression developed spontaneous tumors, including B-cell lymphoma. To determine if a similar Smurf2 deficiency was connected to human DLBCL, and better understand the molecular pathway being disturbed, Zhang and colleagues initiated a new study to examine Smurf2 expression in patients with DLBCL. They found that a significant subset of these tumor samples showed a marked decrease in Smurf2 expression. Furthermore, lower levels of Smurf2 correlated to poor survival prognosis. Taken together, these findings indicate a strong role for Smurf2 in human DLBCL.

Closer examination by the study authors, including first author Charusheila Ramkumar, PhD, a doctoral student in the Graduate School of Biomedical Sciences at UMMS and now a postdoctoral fellow, revealed that Smurf2 is part of a complex pathway incorporating the transcriptional regulator YY1 and the regulatory gene c-Myc (also a well known oncogene). Together, these three proteins collaborate to regulate cell proliferation and division. However, in a subset of DLBCL patients this cycle has gone awry.

Tumor cells that showed decreased levels of Smurf2 expression also had increased levels of YY1 and c-Myc expression. These increased levels of YY1 and c-Myc caused cells, including B-cells, to continue dividing. Unrestrained cell proliferation is a hallmark of many cancers and in the case of DLBCL cells with a perturbed Smurf2-YY1-c-Myc pathway, it leads to tumor formation.

Not only does the lack of Smurf2 lead to increased cell division through

this pathway but it also allows the tumor cells to continue dividing longer. Because Smurf2 (which normally plays a part in cellular aging) expression levels are already low in DLBCL cells, these tumor cells don't age normally. As a result, tumor B-cells effectively remain younger longer, allowing them to proliferate even more.

"This enhanced cell proliferation induced by YY1 and c-Myc activation, coupled with impaired senescence due to low Smurf2 levels helps drive lymphoma formation," said Zhang. "It also suggests multiple roles for Smurf2 in tumor suppression in the form of suppressed cell proliferation and senescence response."

To gauge the potential clinical relevance of this basic biological discovery, Zhang and colleagues restored Smurf2 expression in human DLBCL cells. Once restored, proliferation of these cells was inhibited, providing new hope that therapeutics designed to increase expression of Smurf2 in lymphomas, when coupled with existing treatments, will be a more effective approach to achieving remission in patients.

The next step for Zhang and colleagues is to screen for molecules that can either increase or mimic the expression of Smurf2. He will also screen other cancer types, such as liver cancer, for the Smurf2-YY1-c-Myc pathway to see if they are also susceptible to this approach.

"This is another example of a basic biological discovery having important clinical applications," said Zhang. "When we started this line of inquiry we were interested in the role of Smurf2 in cellular aging. We never expected the clinical relevance to be so immediate and striking."

Provided by University of Massachusetts Medical School

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