Ex-SASP-erating cancer

By Michael J. Haas, Senior Writer

German researchers have identified a hypermetabolic phenotype in senescent tumor cells that exerts tumorigenic effects on other cells in the tumor microenvironment.[1] Although the team showed that small molecule inhibitors of the phenotype reduced tumor growth and improved survival in a mouse model of lymphoma, future studies will need to determine whether the phenotype occurs in primary tumors.

Although tumor cells rendered senescent by chemotherapy are no longer malignant, they can still pose a problem for patients with cancer. Multiple preclinical studies have shown that chemotherapy-treated cancer cells can acquire the senescence-associated secretory phenotype (SASP) to produce inflammatory cytokines, growth factors and proteases. These factors can have tumorigenic effects on other cells in the tumor microenvironment and thereby contribute to disease progression.[2–4]

Moreover, the biology of senescent tumor cells is poorly understood because of challenges in detecting and separating them from cells actually killed by chemotherapy.

To overcome the challenges in selecting or enriching for such cells to study them, the German team first developed mouse models of lymphoma in which all tumor cells would become senescent—but not die—in response to chemotherapy. They accomplished this by modifying an established transgenic mouse lymphoma cell line to express the antiapoptotic protein B cell lymphoma 2 (BCL-2; BCL2) and then injected the cell line into two groups of mice.

One group of mice was deficient in *suppressor of variegation 3-9 homolog 1* (*Suv39h1*), a histone methyltransferase that plays a role in senescence. These senescence-deficient models and their tumors served as controls.

The other group of mice had normal *Suv39h1* expression. In these models, chemotherapy caused the tumor cells to become senescent instead of dying, thus leaving the cells viable and available for study.

Tumor cells from the chemotherapy-treated, senescence-capable models exhibited hypermetabolic activity that involved increased levels of glucose, glycolysis, proteotoxic stress and autophagy compared with pretreatment baselines and tumor cells from the senescence-deficient controls regardless of treatment status.

In the senescence-capable models pretreated with chemotherapy, small molecule inhibitors of glucose transporters, glycolysis or autophagy decreased tumor growth and increased survival compared with no treatment.

Lastly, the team showed that chemotherapy-induced senescence led to the same hypermetabolic phenotype in primary acute myeloid leukemia (AML) cells and in human lymphoma, leukemia, sarcoma, melanoma, colon cancer, lung cancer and other cancer cell lines. In all of these cell types, the inhibitors of glucose transporters, glycolysis or autophagy decreased tumor cell viability compared with no treatment.

"Our studies with the inhibitors demonstrate the dependence of senescent tumor cells on the hypermetabolic phenotype," team leader Clemens Schmitt told *SciBX*. "If you cut the energy supply or inhibit autophagy, the cells lose an essential mechanism—the energy-demanding process of autophagy—for coping with senescence-associated proteotoxic stress, and they subsequently die."

Schmitt is a clinician specializing in hematology and oncology and director of the Molecular Cancer Research Center at **Charité–University Hospital Berlin**. He is also head of the Cancer Genetics and Cellular Stress Responses group at the **Max Delbrueck Center for Molecular Medicine**.

The team included researchers from the **German Cancer Research Center**, **Jena University Hospital**, **Johannes Gutenberg University Mainz**, the **Max Planck Institute of Molecular Plant Physiology**, **Technical University Munich** and the **University Hospital of Wuerzburg**.

Data were reported in *Nature*.

> **"A next step is to demonstrate that this metabolic imbalance occurs in human tumors following chemotherapy treatment."**
> ***—Francis Rodier, University of Montreal***

"This study is very interesting because it provides novel ways to selectively eliminate senescent cells in tissues," said Francis Rodier, an assistant professor of radiology, radio-oncology and nuclear medicine at the **University of Montreal**.

Previously this was possible only in a few mouse models in which senescent cells—normal or cancerous—were modified to express a protein that could be therapeutically targeted,[5,6] he said.

Rodier also is a researcher at the **Montreal Cancer Institute**.

Masashi Narita, group leader at the **Cancer Research UK Cambridge Institute** at the **University of Cambridge**, agreed that the study provided a new approach for eliminating senescent tumor cells. He said that SASP can trigger an immune system response that eliminates senescent normal cells but that it is not clear how effectively that mechanism clears senescent cancer cells.

"Perturbation of the hypermetabolic state in the senescent tumor cells—which are the source of SASP—kills those cells" and could increase the overall efficiency with which they are eliminated, thereby reducing the potential effects of SASP on disease progression, said Narita.

He added that autophagy was the most attractive process to target therapeutically in the hypermetabolic phenotype. "Chloroquine can inhibit autophagy and has long been used to treat malaria in humans," which gives it a safety track record, he noted.

Schmitt agreed. "Our results in mice illustrate a therapeutic strategy that could be used in the clinic to treat patients with lymphomas, leukemias and solid tumors—a sequential approach in which conventional chemotherapy is followed by a metabolic reprogramming agent, such as an autophagy inhibitor" to target the chemotherapy-induced hypermetabolic phenotype of the senescent cells, he said.

Old cells, new questions

A key question going forward is whether the senescence-related hypermetabolic phenotype actually occurs in human tumors.

Narita said that the team identified and targeted the phenotype in human cells and cell lines but not in xenograft tumor models. Thus, "*in vivo* confirmation of the findings in different tumor types would be necessary," he said.

He also noted that many human cancers are deficient in p53 and retinoblastoma protein—tumor suppressor proteins that normal cells need to become senescent. "It is not clear how or whether cells deficient in these proteins can become senescent," he said. "Thus, I wonder if the team's approach applies to tumor cells that lack them."

Rodier said, "A next step is to demonstrate that this metabolic imbalance occurs in human tumors following chemotherapy treatment."

Schmitt said that his team has not yet conducted studies to evaluate which therapeutic strategy for eliminating senescent tumor cells—inhibition of glucose uptake, glycolysis or autophagy—has the greatest potential for translation to the clinic. However, he said that his team might begin those studies in the near future.

The findings reported in the paper are unpatented, and the team is open to corporate partnerships to develop them, Schmitt said.

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   Contact: Clemens A. Schmitt, Charité–University Hospital Berlin, Berlin, Germany
   e-mail: clemens.schmitt@charite.de
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COMPANIES AND INSTITUTIONS MENTIONED

Cancer Research UK Cambridge Institute, Cambridge, U.K.
Charité–University Hospital Berlin, Berlin, Germany
German Cancer Research Center, Heidelberg, Germany
Jena University Hospital, Jena, Germany
Johannes Gutenberg University Mainz, Mainz, Germany
Max Delbrueck Center for Molecular Medicine, Berlin, Germany
Max Planck Institute of Molecular Plant Physiology, Potsdam, Germany
Montreal Cancer Institute, Montreal, Quebec, Canada
Technical University Munich, Munich, Germany
University of Cambridge, Cambridge, U.K.
University Hospital of Wuerzburg, Wuerzburg, Germany
University of Montreal, Montreal, Quebec, Canada