Lipid metabolism is potential 'Achilles' heel' for cancer stem cells

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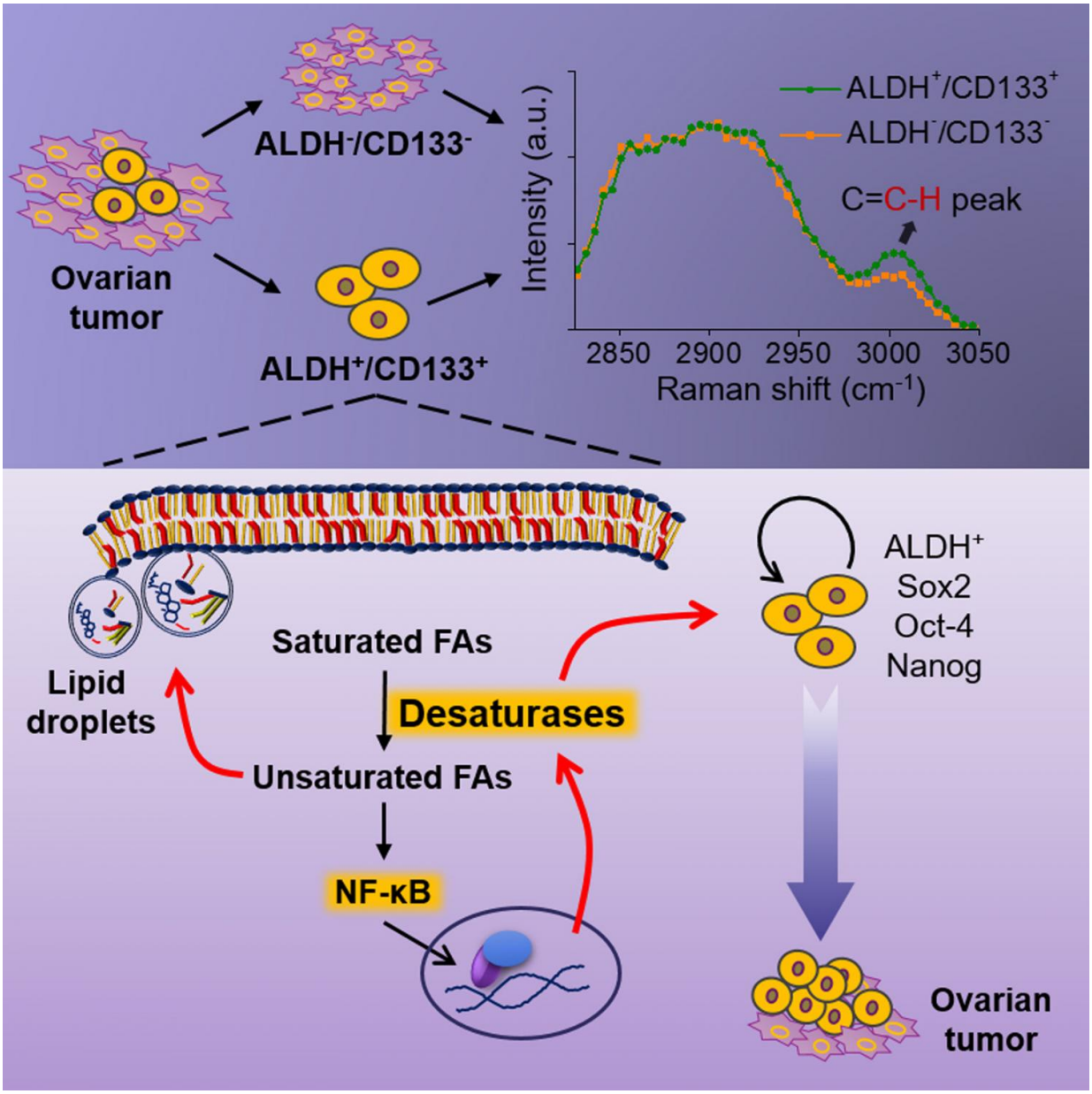

This graphic illustrates an approach to potentially treat ovarian cancer by interfering with the metabolic mechanism of “cancer stem cells,” which initiate tumor formation. Credit: Purdue University photo/Ji-Xin Cheng

Researchers have discovered a metabolic signature critical for the functioning of "cancer stem cells" that initiate tumor formation. The team also showed how to interfere with this metabolic mechanism in ovarian cancer, inhibiting tumor growth.

"The cancer stem cells are resistant to conventional therapies and are responsible for tumor relapse after chemotherapy and development of distant metastases," said Ji-Xin Cheng, a professor in Purdue University's Weldon School of Biomedical Engineering and Department of Chemistry. "Understanding their unique characteristics and vulnerabilities will enable the development of targeted therapies with the ultimate goal of overcoming tumor relapse and metastasis."

New research focuses on targeting cancer stem cells by inhibiting the activities of enzymes needed to carry out a metabolic process called "desaturation" of lipid molecules.

"Unsaturated lipids in the cancer stem cells are very important to maintain the signaling needed to function," said Cheng, a member of Purdue's Center for Cancer Research. "Researchers have known about cancer stem cells for a while, but lipid metabolism in these cells is a very new topic. Understanding the lipid metabolism in cancer stem cells opens a new way for cancer detection and treatment."

The work was performed by researchers at Purdue, Indiana University School of Medicine, and Northwestern University's Feinberg School of Medicine.

Findings are detailed in a research paper that appeared online Dec. 29 in the journal *Cell Stem Cell*. The paper will be published in the journal's March 2 print issue.

"In this study, we identify and characterize for the first time lipid unsaturation in ovarian cancer stem cells by chemical imaging of single living cells," said Purdue postdoctoral research associate Junjie Li, who was the paper's co-first author along with Salvatore Condello, a research assistant professor in the Feinberg School of Medicine.

The researchers demonstrated that a specific "signaling pathway" directly regulates the production of lipid enzymes, called fatty acid desaturases.

"Collectively, our findings reveal that increased lipid unsaturation is a metabolic marker for ovarian cancer stem cells and a target for therapy focusing on these types of cells," said Cheng, working with the Northwestern University team led by Daniela Matei, a professor in the Feinberg School of Medicine.

Identifying unique metabolic traits, which can be exploited as an Achilles' heel to eliminate cancer stem cells, is an important step forward, said Matei, co-senior author of the paper.

"Here we propose a completely new strategy to eradicate recalcitrant cancer cells responsible for tumor recurrence after standard treatment and elucidate how lipid metabolism contributes to the survival of ovarian cancer stem cells," she said.

The paper was authored by Li; Condello; gynecologic oncologist Jessica Thomes-Pepin, formerly at IU and now at Minnesota Oncology; former Purdue postdoctoral research associate Xiaoxiao Ma; Yu Xia, an associate professor of chemistry at Purdue; Thomas D. Hurley, a

professor in the IU Department of Biochemistry and Molecular Biology; Matei; and Cheng.

Until now, the lack of sensitive single-cell analysis tools has limited the characterization of metabolic activity in cancer stem cells. The imaging methods used in the study were developed by Cheng's group and allow researchers to detect the signature in single cells. Because cancer stem cells represent a tiny population of the total number of cancer cells, the single-cell sensitivity is important for detecting hidden metabolic signatures.

The new approach uses two technologies: hyperspectral stimulated Raman scattering imaging of single living cells and mass spectrometry analysis of extracted lipids.

"We report here significantly increased levels of unsaturated lipids in ovarian cancer stem cells compared to non-cancer stem cells," Cheng said. "Conventional methods can't do single cell analysis. If the signature is localized in a very small area, it is not easily detected by conventional biochemical assay. By stimulated Raman microscopy, we can better pinpoint these cells through the metabolic signature."

The lipid-desaturation signature was identified in laboratory cultures of ovarian cancer stem cells and in cells from human patients. Higher lipid unsaturation levels also were detected in cancer stem cell-enriched laboratory cultures called "spheroids," a three-dimensional culture that mimics tumors in human patients. The researchers used a chemical to inhibit the activities of desaturases and reduce the "stemness" of the cells, rendering them less lethal. Inhibition of lipid desaturases effectively eliminated cancer stem cells, suppressed spheroid formation in laboratory cultures, and blocked tumor initiation capacity in laboratory mice, Cheng said.

"We don't directly block the signaling pathway, but we block fatty acid metabolism so that the unsaturated lipids are reduced, and that actually suppresses the function of the cancer stem cells," Li said.

Some of the research was done in the Bindley Bioscience Center in Purdue's Discovery Park and was supported by the Purdue Center for Cancer Research.

More information: Lipid Desaturation Is a Metabolic Marker and Therapeutic Target of Ovarian Cancer Stem Cells, *Cell Stem Cell*, 2016.

Provided by Purdue University