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Targeting molecules called miR-200s and ADAR2 could prevent tumor metastasis in patients with colorectal cancer

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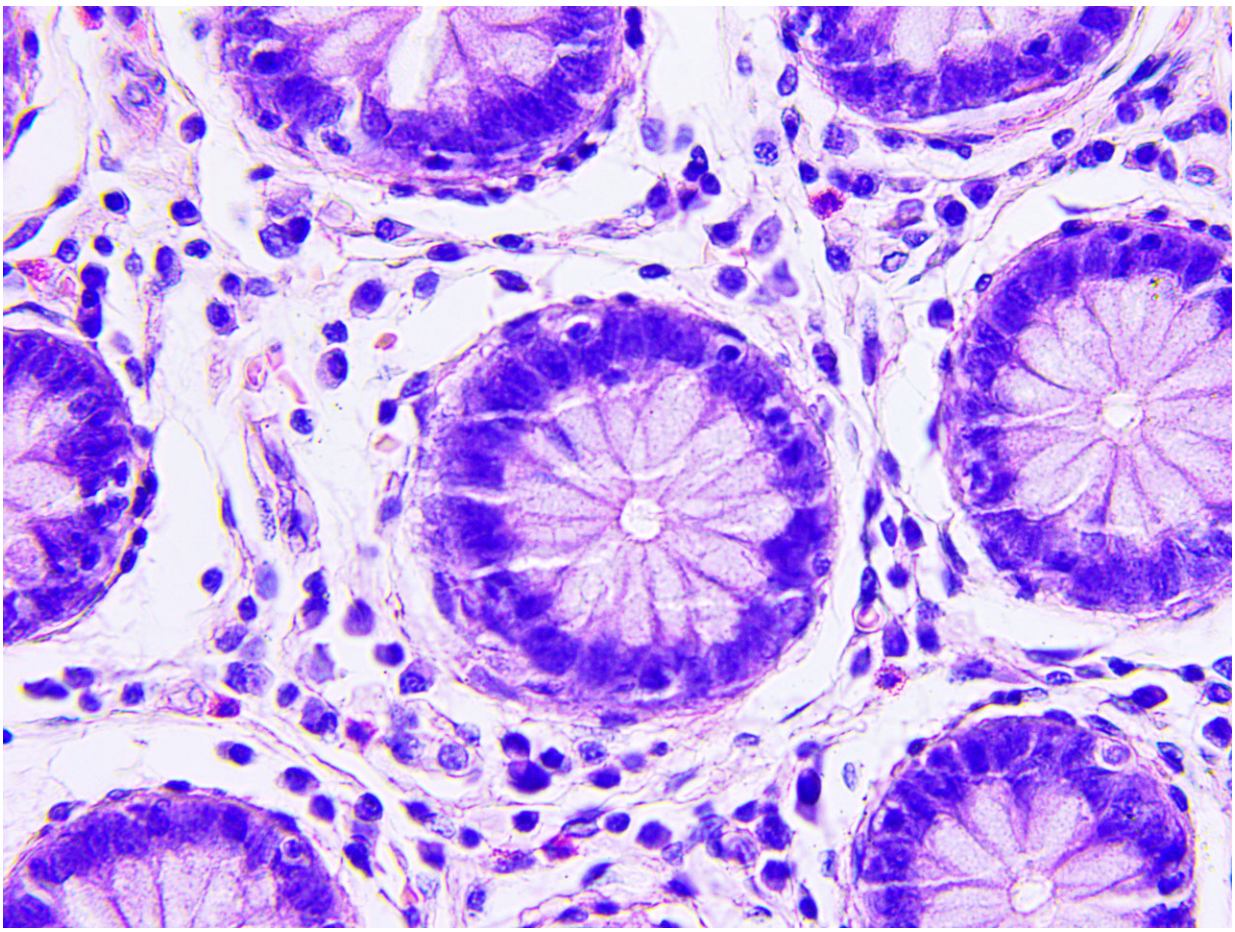

Researchers at SBP target miR-200s and ADAR2 in regulating metastasis of colon cancer cells. Credit: Sanford-Burnham Prebys Medical Discovery Institute

Colorectal cancer is the third most common cancer worldwide and the third-leading cause of cancer-related deaths. The main cause of death in patients with colorectal cancer is liver metastasis, with nearly 70% of patients eventually developing a liver tumor. Recent research has revealed low levels of a tumor suppressor called protein kinase C zeta (PKC zeta) in human colorectal cancer cells and distant metastasis, but it has not been clear how thiscontributes to the spread of tumors and poor prognosis in patients.

A new study by Sanford Burnham Prebys Medical Discovery Institute (SBP) researchers helps explain the connection between PKC zeta and metastatic colorectal cancer. Published in *Cell Reports*, the research describes how PKC zeta deficiency promotes liver metastasis through the inactivation of an enzyme called ADAR2 and the subsequent secretion of molecules called miR-200s from cancer cells into the blood. In addition, treatment with a compound that inhibits the secretion of miR-200s significantly reduced liver metastasis in mice with colorectal cancer.

"Our findings suggest that elevated blood levels of miR-200s could serve as a non-invasive diagnostic marker for patients at risk of metastasis," says senior study author Jorge Moscat, Ph.D., director of Metabolism Initiatives and director and professor of the Cancer Metabolism and Signaling Networks Program at SBP's NCI-designated Cancer Center. "Moreover, our study is of great potential therapeutic relevance because it providesproof of concept that targeting signals that are activated by the loss of PKC zeta can be useful anti-metastatic therapies."

Unleashed signaling pathways

In a previous study, Moscat and his collaborators identified PKC zeta as a tumor suppressor in colorectal cancer. As reported in 2013 in the journal Cell, they found that loss of PKC zeta leads to metabolic changes

that allow cancer cells to survive and proliferate under conditions of nutrient deprivation, resulting in tumor formation in mice and poor prognosis in human patients. But it has been challenging todevelop therapies that targetPKC zetato restore tumor suppressive activity.

"An alternative approach is to look for cell vulnerabilities created by the loss of the tumor suppressor's function," saysstudy author Maria Diaz-Meco, Ph.D., a professor in the Cancer Metabolism and Signaling Networks Program at SBP. "This is the rationale behind investigatingthe signaling pathways unleashed during PKC zeta inactivation in cancer."

Jorge Moscat, Ph.D., professor and director of Metabolism Initiatives at SBP. Credit: Sanford Burnham Prebys Medical Discovery Institute

To address this question, Moscatand Diaz-Meco focused on the potential involvement of miRNAs—molecules that play an important role in regulating gene activity. An increasing body of evidence has shown that dysregulated miRNAs are associated with certainhallmarks of cancer, including sustained proliferation, resistance of cell death, and metastasis.

"Understanding the mechanisms controlling the expression of miRNAs is emerging as a novel approachto design better strategies to treat metastasis," Moscat says. "Whether PKC zeta isinvolved in the repression of tumor initiation and survival—and also restrains metastasis through the regulation of the expression of miRNAs, had not previously been explored."

Cancer's Achilles' heel

In the new study, the researcher teamscreened PKC zeta-deficient human colorectal cancer cells for changes in miRNAs. They found that loss of PKC zeta is most prominently associated with decreased levels of the miR-200 family. Additional experiments showed that PKC zeta deficiency promotes liver metastasis of colorectal cancer cells through ADAR2 inactivation, which increases the loading of miR-200s into vesicles that are subsequently secreted by the cells.

Consistent with this finding, colorectal cancer patients with metastatic tumors have increased blood levels of vesicles containing miR-200s. In mice with colorectal cancer, injection of a compound that inhibits the secretion of miR-200s significantly reduced liver metastasis.

"Altogether the results reported here highlight the importance of identifyingsignaling vulnerabilities unleashed upon the inactivation of tumor suppressors and establish PKC zeta-derived signals controlling

miR-200s as potentially important therapeutic targets in cancer metastasis," Diaz-Meco says.

Moreover, the discovery that ADAR2 is a key vulnerability of PKC zeta-deficient cells could have broad clinical relevance, in light of past studies showing that this enzyme acts as a tumor suppressor in brain cancer, stomach cancer, liver cancer, and esophageal cancer. Despite the importance of ADAR2 in a wide range of cancers, little is known about how it inhibits tumor growth and migration.

In future studies, Moscat and his collaborators will address this question by investigating how ADAR2 regulates the secretion of miR-200s. "Given thatmetastasis accounts for more than 90% of all cancer-related deaths, identifying a therapeutic target that regulates the spreadof multiple types of tumors could have a tremendous impact on patient survival," Moscat says.

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