

A New Therapeutic Target for Pancreatic Cancer

Can better understanding an epigenetic pathway lead to clues in one of the most lethal cancers?

Pancreatic ductal adenocarcinoma (PDAC) accounts for 90% of all pancreatic cancers, and is one of the most lethal cancers in humans. PDAC is characterized by mutant KRAS, a gene involved in regulating cell division, but little is known about the molecular processes governing initiation, progression and metastasis in PDAC. As a consequence, no good

new therapeutic targets have been identified for the cancer in three decades. Despite active research in this field, standard chemotherapy remains the primary treatment available for PDAC, and survival rates are under 5% after a year.

But understanding the mechanics at play in those tumors may lead to better treatments. **Raul Mostoslavsky, MD, PhD**, the Kristine and Bob Higgins Massachusetts General Hospital Research Scholar at Massachusetts General Hospital Cancer Center and the Laurel Schwartz Associate Professor of Oncology at Harvard Medical School, has identified an epigenetic pathway that is responsible for cancer growth in 30 to 40% of PDAC patients. In this subset of patients, the researchers found, growth of the carcinoma depends on expression of a protein

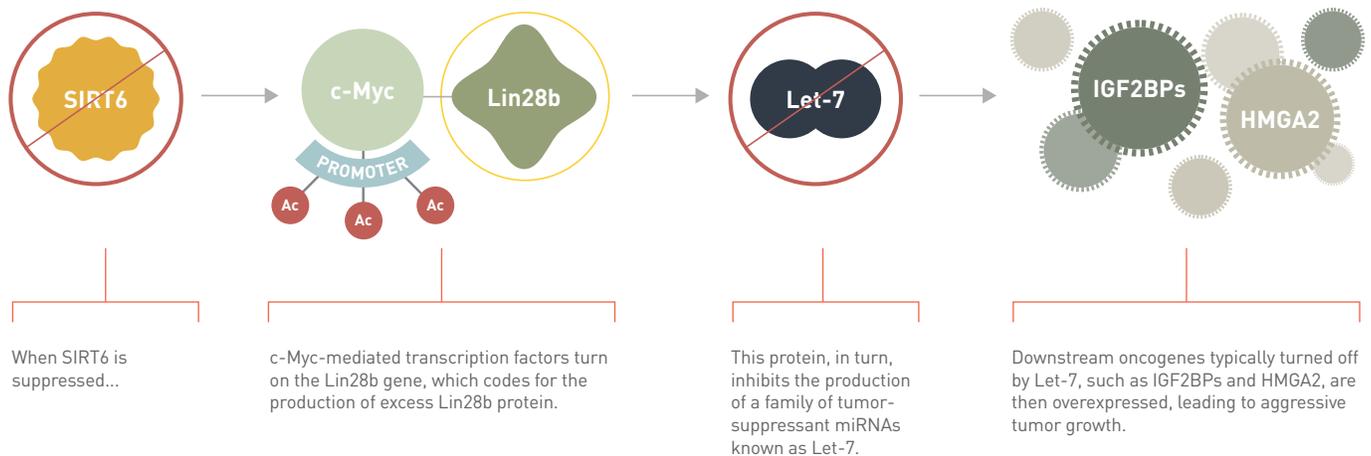
called lin28b, which is regulated by an epigenetic enzyme called sirtuin 6 (SIRT6). Mostoslavsky's findings, published in the June 2, 2016 issue of *Cell*, indicate that the loss of SIRT6 can result in the activation of lin28b protein in both humans and mice PDAC cells, which kicks progression of the cancer into high gear and stimulates metastasis.¹ When Mostoslavsky and colleagues knocked out the gene that codes for the Lin28b protein, they found that they were able to completely halt growth in the cancer cells, suggesting a strong therapeutic target for this particular type of cancer.

EPIGENETIC CONTROL

Mostoslavsky looked into the role played by SIRT6 in PDAC for several reasons. SIRT6 is involved in chromatin-remodeling functions,

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KrasG12D Pancreatic Cells.



SIRT6

The enzyme sirtuin 6 (SIRT6) plays a number of roles, and SIRT6-deficiencies can play a critical part in the growth of colon cancer

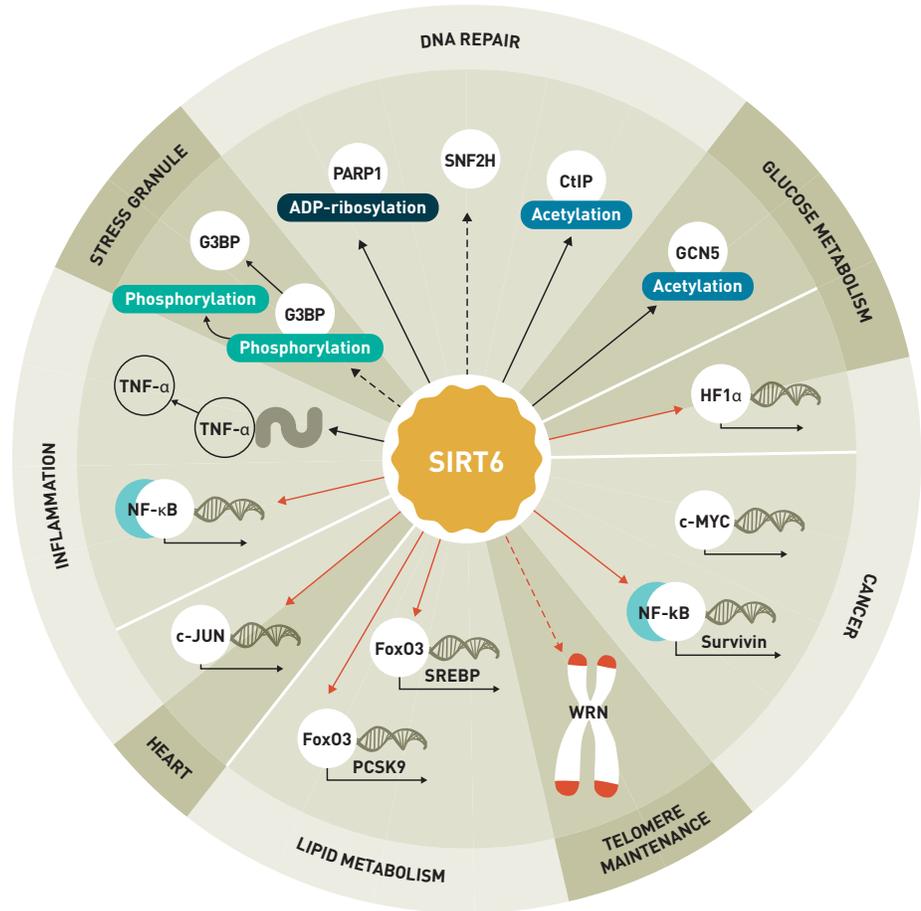
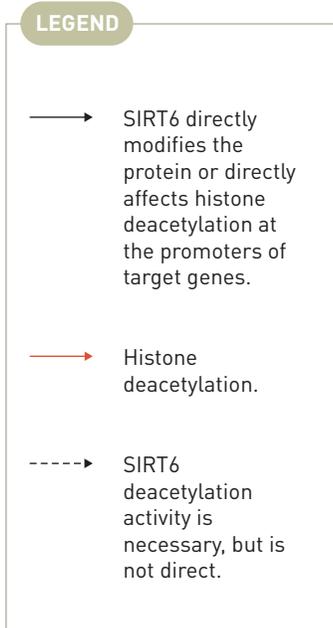


Image from Mostoslavsky paper, "Chromatin and beyond: the multitasking roles for SIRT6" [http://www.cell.com/trends/biochemical-sciences/fulltext/S0968-0004\(13\)00201-6](http://www.cell.com/trends/biochemical-sciences/fulltext/S0968-0004(13)00201-6)

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which control epigenetic gene expression and are dysregulated in a number of human cancers. He and his colleagues also recently found that, at a cellular level, SIRT6-deficiencies play a critical part in the growth of colon cancer. Further, around 60% of pancreatic cancer cell lines seemed to possess

fewer than normal copies of SIRT6. They also found low SIRT6 levels to be associated with stomach, skin and squamous cell carcinomas, suggesting that the enzyme may have evolved as a broad tumor suppressor.²

To identify SIRT6's specific relationship to cancer growth in

PDAC, the researchers conducted a genome-wide analysis of chromatin changes in PDAC. They were surprised to find that SIRT6 does not play the same role in PDAC as it does in colon cancer, where it enhances tumor growth by stimulating excess glucose uptake, something called the Warburg effect.

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THE ROLE OF LIN28B

Though the lin28b protein has been associated with advanced disease and poor prognosis in few human cancers, its functional role and the way in which it is activated are poorly understood and it had not been previously studied in relation to PDAC.

One hint to understanding its mechanisms, says Mostoslavsky, is that lin28b is an oncofetal protein. It is usually expressed only during early development—and the proteins can typically only be found in embryonic stem cells. “One possibility is that these cells are up-regulating these [lin28b] fetal proteins to make the cells look more embryo-like,” he says. Embryonic stem cells are poorly differentiated. And as a rule, the less specialized a cancer cell is, the more aggressive its growth.

Lin28b is also known to inhibit the production of a family of 12 tumor suppressor microRNAs (MiRNAs) that are collectively referred to as let-7. Mature let-7 miRNAs tend to be suppressed in embryonic tissues, and highly expressed in normal adult cells—the converse of lin28b.

Because lin28b is not normally expressed in adult cells, drug treatments that target it might have an easier job. A lin28b inhibitor would likely have limited toxicity

for the targeted cells. Mostoslavsky says he is already working on developing lin28b inhibitors, as a result of this recent work. “We’ve started a couple of collaborations with chemistry labs to develop small molecule compounds. I strongly believe that inhibiting lin28b with small molecules will have a major effect at least on this particular subset of pancreatic cancer.” The challenge with pancreatic cancer is getting the drug to the tumor—the pancreas can be difficult to access—but there are many laboratories developing tools for this problem as well, he says.

¹ Sita Kugel, Carlos Sebastian, Julien Fitamant, Vikram Deshpande, Nabeel Bardeesy, Raul Mostoslavsky. “SIRT6 Suppresses Pancreatic Cancer through Control of Lin28b.” *Cell* 165, 1401–1415 June, 2016.

² Sebastian, C., Zwaans, B.M., Silberman, D.M., Gymrek, M., Goren, A., Zhong, L., Ram, O., Truelove, J., Guimaraes, A.R., Toiber, D., et al. [2012]. “The histone deacetylase SIRT6 is a tumor suppressor that controls cancer metabolism.” *Cell* 151, 1185–1199. Dec., 2012.

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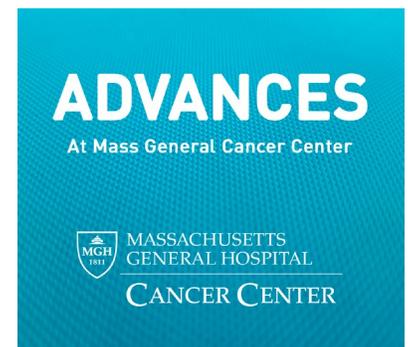
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