Epigenetic-Metabolic Pathways in Pancreatic Tumor Cells

Can understanding metabolic reprogramming of genetic material in some cancer cells lead to new treatments?

A mutation in the KRAS gene, which plays a role in regulating cell division and survival, is commonly found in human cancers, such as pancreatic and non-small cell lung cancers. While KRAS has been shown to be important in the sustained growth of these tumors, effective KRAS inhibitors have been elusive, and these tumor types remain very difficult to treat. Some researchers propose that effective treatment for such cancers may rely on identifying therapeutic vulnerabilities that result from other mutations the patients might also carry.

Many important cancer genes such as KRAS alter cellular metabolism to support tumor cell growth. The metabolic changes required for a growing tumor can be further modulated by the presence of additional gene mutations. One such gene is LKB1, which encodes a tumor-suppressing enzyme whose normal function is to allow cells to adapt to changing nutrient conditions.

Studies led by Filippos Kottakis, PhD, in the laboratory of Nabeel Bardeesy, PhD, Associate Professor of Medicine, Harvard Medical School and Massachusetts General Hospital Cancer Center, provide a promising advance regarding the understanding and treatment of KRAS-LKB1 mutant tumors. The lab identified an epigenetic-metabolic pathway that drives the formation of pancreatic and lung cancers that carry these mutations. "We have systematically looked at how cell metabolism changes when these mutations are put together, and those efforts led us to uncover a connection to epigenetic control," said Bardeesy, whose findings were published in the November 17, 2016, issue of *Nature*.[1]

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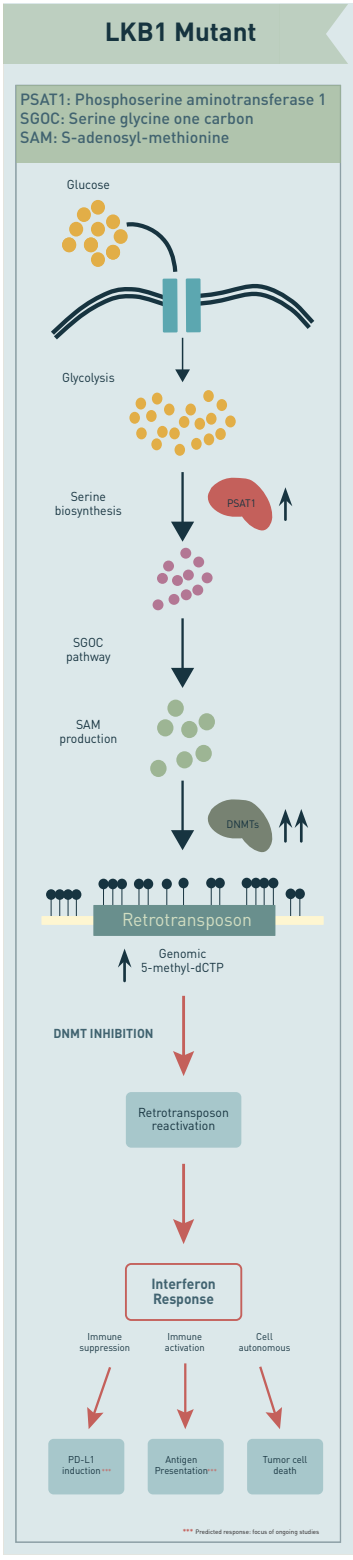
A New Therapeutic Approach

LKB1 mutant cancer cells feature a metabolic process whereby increased glucose uptake leads to a rise in serine production, which boosts methyl donor SAM levels and causes methylation of the DNA via DNMT enzymes. When the DNMT enzymes are inhibited, ancient retroviruses are activated, stimulating an immune response that can lead to tumor cell death.



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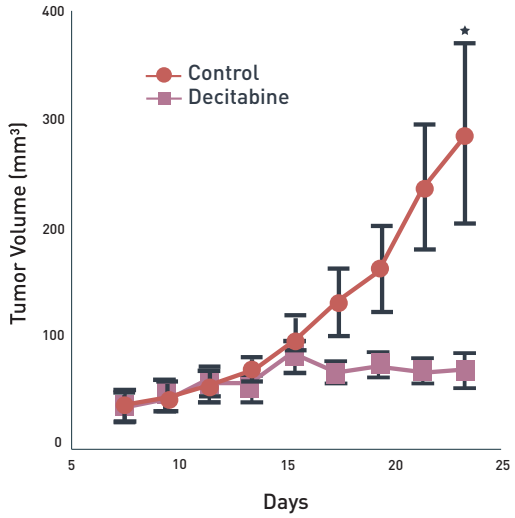
KRAS-LKB1 SYNERGY

Kottakis, Bardeesy and their colleagues set out to look at cancers with mutations in both KRAS and LKB1 genes because these coexist in many lung and pancreatic cancers, the most prevalent and lethal of all cancers. Mutant KRAS is present in more than 90 percent of pancreatic cancers, while mutant LKB1 is found in 5 percent to 10 percent of pancreatic cancers. Cancers with LKB1 mutations tend to be especially aggressive. Heritable mutations in the LKB1 gene are a cause of Peutz-Jeghers syndrome, a disease that is characterized by benign tumors of the gastrointestinal tract that arise at a young age, and by a high rate of malignant tumors, including pancreatic cancer, later in life.

Utilizing mouse models and primary mouse epithelial cells—along with other tools that include metabolic tracing, proteomics/transcriptomics analyses and chromatin studies—the Bardeesy team identified a process by which mutant KRAS and mutant LKB1 cause metabolic reprogramming of a cell that ultimately leads to modifications of the DNA and promotes tumor growth. In particular, these cancer cells showed a marked increase in glucose consumption, which led to accelerated production of the amino acid serine, which in turn boosted DNA methylation, an epigenetic mechanism by which cells control gene expression.



Decitabine Treatment

Treatment with a drug called decitabine, which inhibits DNMT enzymes, leads to a dramatic decrease in tumor growth. Shown: Decitabine treatment of mutant KRAS-LKB1 xenografts (n = 20 tumors per condition).

The Bardeesy team findings suggest that relationships between metabolic and epigenetic activities may play a more general role in tumor growth, and offer potential therapeutic targets for future clinical study.

MECHANISMS OF MUTATION

The group was able to link genetic mutations in KRAS and LKB1 with metabolic changes in glucose consumption and serine production that, in turn, supported increased production of a molecule called SAM, a so-called methyl donor. SAM donates methyl groups, composed of hydrogen and carbon atoms, to other substances. LKB1 mutations also led to rising levels in the cell of enzymes called DNMT1 and DNMT3A, which use SAM to "methylate" certain regions of DNA. The KRAS-LKB1 mutant cells showed particularly evident increases in methylation of regions that code for ancient retroviruses called retrotransposons that have been part of our genome from evolutionary time. In this case, methylation, which changes gene expression along a sequence of DNA without changing the DNA sequence itself, silences the expression of the retrotransposons. Silencing allows a cell to evade the antiviral response that retrotransposon expression usually invites.

Bardeesy and his colleagues further found that disrupting the entire cycle with a drug called decitabine, which inhibits DNMT enzymes, led to a dramatic decrease in tumor growth. Findings suggest

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that it works by reactivating the retrotransposons, which then invite antiviral activity. They are now working with clinicians to design clinical trials with decitabine in combination with immunotherapies, to create what is called a synthetic lethal therapeutic strategy.

[1] Kottakis F, Nicolay B, Roumane A, et al. LKB1 loss links serine metabolism to DNA methylation and tumorigenesis. ***Nature*** 2016; 539: 390-395.

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