Epigenetic-Metabolic Pathways in Pancreatic Tumor Cells

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.

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 methylation 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.

Can understanding metabolic reprogramming of genetic material in some cancer cells lead to new treatments?
boosted DNA methylation, an epigenetic mechanism by which cells control gene expression.

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...
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.


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