K-Ras in cancer metabolism

By Lauren Martz, Staff Writer

Researchers from the **Dana-Farber Cancer Institute** have identified two glucose metabolism pathways that are activated by the *K-Ras* oncogene in pancreatic tumors.[1] Based on the findings, it may be possible to target proteins in the pathways to block proliferation of K-Ras-driven cancers.

Tumors typically grow and proliferate by dramatically increasing their rate of glycolysis compared with that in normal cells. Cancers rely on the process, called the Warburg effect, because it supplies energy and intermediates to sustain tumor growth. Thus, blocking glycolysis and potentially other metabolic pathways in tumors could cut off the malignancy's energy and nutrient supply.

Indeed, potential therapeutic targets in cancer metabolism pathways include pyruvate kinase M2 isoenzyme (PKM2) and isocitrate dehydrogenase 1 (IDH1).[2,3] Several oncogenes have also been implicated in the activation of cancer metabolism pathways, including *PTEN* (*MMAC1*; *TEP1*), *c-Myc* (*MYC*), and *phosphoinositide 3-kinase* (*PI3K*) and *protein kinase B* (*PKB*; *PKBA*; *AKT*; *AKT1*).[4–6]

Now, Alec Kimmelman and colleagues at Dana-Farber have shown that the *K-Ras* oncogene upregulates two glucose metabolism pathways in pancreatic tumors. The team also identified enzymes in each of the pathways that could become new therapeutic targets for pancreatic cancer.

K-Ras mutations are best known as drivers of resistance to epidermal growth factor receptor (EGFR) inhibitors. Activating mutations in *K-Ras* are found in more than 90% of patients with pancreatic cancer. Although the gene is a driver for cancer initiation and progression, there are no disclosed small molecule inhibitors selective for mutant *K-Ras* in development because attempts to target the complex biology and interactions of the mutant form of the protein have been unsuccessful.

Prior work had shown that mutant *K-Ras* drives tumor growth in part by hijacking metabolic pathways in tumors. Those results suggested it might be possible to block the effects of K-Ras by going downstream and targeting proteins in a protumorigenic metabolic pathway. The challenge was identifying which metabolic pathways mutant *K-Ras* hijacked.

To find those pathways, the Dana-Farber team designed a mouse model of pancreatic ductal adenocarcinoma (PDAC) that expressed K-ras in the pancreas only in the presence of doxycycline. To further increase the number of pancreatic lesions that progressed to PDAC, the team also knocked out the tumor suppressor p53.

In the mice, doxycycline withdrawal caused tumor regression through increased apoptosis and decreased cancer cell proliferation compared with continued doxycycline exposure, confirming that maintenance of pancreatic tumors required K-ras.

Genetic and metabolic studies showed glycolytic metabolites and enzymes were downregulated in the absence of K-Ras. Downregulated enzymes included glutamine–fructose-6-phosphate transaminase 1 (Gfpt1), ribose 5-phosphate isomerase A (Rpia) and ribulose-5-phosphate-3-epimerase (Rpe).

Finally, the team showed that treatment of the K-ras-mutant tumors with a MEK inhibitor downregulated the same set of metabolism genes. However, treatment with inhibitors of mammalian target of rapamycin (mTOR; FRAP; RAFT1) or the PI3K and AKT pathway did not reduce gene expression.

Those findings suggest the MEK pathway downstream of K-Ras is the relevant mechanism that promotes cancer metabolism in pancreatic tumors, whereas other pathways such as the PI3K and mTOR pathway do not affect cancer metabolism.

Kimmelman is an assistant professor of radiation oncology at Dana-Farber and **Harvard Medical School**. The paper also included researchers from **Beth Israel Deaconess Medical Center**, **Massachusetts General Hospital** and **The University of Texas MD Anderson Cancer Center**.

Results were published in *Cell*.

"The fact that many oncogenic or tumor suppressor pathways have an impact on cell metabolism has been one of the key factors underpinning the recent resurgence in cancer metabolism research," said Neil Jones, senior principal target validation scientist at **Cancer Research UK**'s **Cancer Research Technology Ltd.** commercial arm.

Cancer Research Technology and **AstraZeneca plc** are identifying cancer metabolism targets and developing therapeutics against them under a three-year deal.

"The research area of cancer metabolism is undergoing a renaissance driven by a greater understanding of how genetic drivers reprogram metabolic pathways," added Patrick O'Connor, VP and head of oncology at **Ruga Corp.** The company has multiple preclinical programs focused on tumor-selective adaptive responses including tumor metabolism.

"Because it is difficult to inhibit the *Ras* oncogene directly, this paper provides a number of downstream mediators that could become alternative therapeutic targets for Ras-driven tumors. The goal is to engineer potent and selective inhibitors impacting various points in the pathways uncovered in this manuscript as a step toward therapeutic intervention in the clinic," said O'Connor.

"The research area of cancer metabolism is undergoing a renaissance driven by understanding the genetic drivers and how they turn on and drive metabolic pathways."

—Patrick O'Connor, Ruga Corp.

Based on the new findings, GFPT1 "could be a potential target, as glycosylation is an intriguing area of cancer research, with this post-translational modification playing a fundamental role in many tumor-related responses including proliferation, invasion, immune response and angiogenesis," added Jones.

O'Connor said the findings should also encourage "further preclinical investigation of MEK inhibition with inhibitors of glucose uptake or inhibitors of glucose utilization through the various pathways identified."

Next steps

Kimmelman told *SciBX* his team is performing further mechanistic studies on the key pathways elucidated in the paper and is designing inhibitors of the newly identified targets.

Jones said a key area of investigation "would be to evaluate the role of different *K-Ras* mutations in tumor metabolism. There is evidence that different *K-Ras* mutants utilize different effector pathways that could give rise to an alternative metabolic phenotype."

"It will also be important to evaluate the expression and significance of some of the identified targets in clinical samples of K-Ras-dependent prostate cancers to see if the identified metabolism enzyme signature translates into clinical samples," said Jones.

He said it also will be necessary to study "potential bypass mechanisms of alternative metabolic pathways and any toxicity implication in rapidly proliferating normal tissues."

Finally, because the potential cancer metabolism targets described in the paper were identified primarily through genetic studies, a key next step will be to determine whether selective and potent pharmacologic inhibitors of these reprogrammed pathways can safely reproduce the same results, said O'Connor.

Kimmelman said Dana-Farber has filed a patent application covering the findings and the new targets. The IP is available for licensing.

Martz, L. *SciBX* 5(20); doi:10.1038/scibx.2012.513
Published online May 17, 2012

REFERENCES

1. Ying, H. *et al. Cell*; published online April 27, 2012; doi:10.1016/j.cell.2012.01.058
   Contact: Ronald A. DePinho, The University of Texas MD Anderson Cancer Center, Houston, Texas
   e-mail: rdepinho@mdanderson.org
   Contact: Alec C. Kimmelman, Dana-Farber Cancer Institute, Boston, Mass.
   e-mail: alec_kimmelman@dfci.harvard.edu
2. Christofk, H.R. *et al. Nature* **452**, 230–233 (2008)
3. Thompson, C.B. *N. Eng. J. Med.* **360**, 813–813 (2009)
4. Shim, H. *et al. Proc. Natl. Acad. Sci. USA* **94**, 6658–6663 (1997)
5. Doe, M.R. *et al. Cancer Res.* **72**, 949–957 (2012)
6. Govindarajan, B. *et al. J. Clin. Invest.* **117**, 719–729 (2007)

COMPANIES AND INSTITUTIONS MENTIONED

AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.
Beth Israel Deaconess Medical Center, Boston, Mass.
Cancer Research Technology Ltd., London, U.K.
Cancer Research UK, London, U.K.
Dana-Farber Cancer Institute, Boston, Mass.
Harvard Medical School, Boston, Mass.
Massachusetts General Hospital, Boston, Mass.
Ruga Corp., Palo Alto, Calif.
The University of Texas MD Anderson Cancer Center, Houston, Texas