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Exposing Cancer's Metabolic Addictions

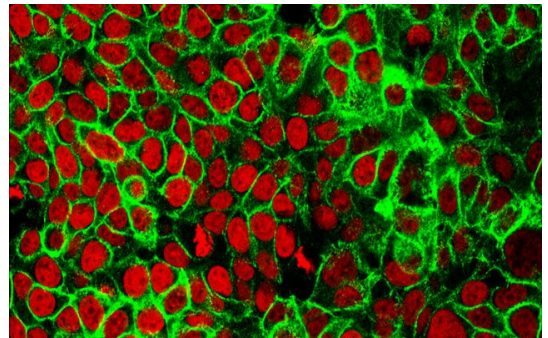
Real estate is important: where a tumor arises dictates specific metabolic vulnerabilities, identifying potential targets for effective cancer treatments

Cancerous tumors are classified primarily based on their tissue of origin. However, the sequencing of the human genome and the development of powerful and affordable DNA sequencing technologies has ushered in a new era of precision oncology, in which patients are treated with customized therapies designed to target the specific mutations within their tumor.

This new treatment approach has yielded some important successes but, recently many cancers experts have begun to suspect that where a cancer arises in the body may influence how specific mutations behave, playing a major role in determining how patients respond to targeted treatments. Currently, the ways in which the tissue environment shapes the tumors genetic makeup are not well understood.

In a new paper, publishing April 24, 2019 in *Nature*, a team of researchers headed by scientists at University of California San Diego School of Medicine and the Ludwig Institute for Cancer Research at UC San Diego, describe a new set of “rules” that predict how the tissue of origin influences critical aspects of the genetic makeup of tumors, with potentially important therapeutic implications.

Focusing on an essential cellular molecule called nicotinamide adenine dinucleotide (NAD), a critical co-factor required for many cellular reactions, including energy metabolism, epigenetic regulation and DNA damage response, the team, headed by senior author Paul S. Mischel, MD, professor in the UC San Diego School of Medicine Department of Pathology and Ludwig member, in collaboration with Bing Ren, PhD, professor of cellular and molecular medicine;



A colorized micrograph depicting colon cancer cells. Image courtesy of the [National Institutes of Health](#)

Vineet Bafna, PhD, professor of computer science and engineering; postdoctoral research fellow Sudhir Chowdhry, PhD, and others identified a surprising role for tissue of origin in determining how cells make NAD, with important consequences for cancer treatment.

Normal cells make NAD by using any of three biochemical pathways. The team discovered that cancer cells behave in a very different way. By analyzing more than 7,000 tumors and 2,600 matched normal samples of 19 different tissue types, coupled with mathematical modelling and extensive studies in cells and in mice, the researchers found that where a cancer arises is the major determinant of how cancer cells make NAD.

In contrast to normal cells that can use any of the three pathways if needed, cancer cells can use only one NAD synthesis pathway, rendering them addicted to that pathway and highly vulnerable to targeted pharmacological intervention.

Specifically, in certain body organs, an enzyme called nicotinic acid phosphoribosyltransferase or NAPRT, a key regulator of one of the three pathways, is highly expressed. Cancers that arise from organs that highly express NAPRT include the prostate, ovaries, gastrointestinal tract and pancreatic tissues. They have a high frequency of NAPRT amplification and are completely and irreversibly dependent upon NAPRT for survival.

The researchers showed that a drug that targets this pathway is very effective at killing tumors that arise from these organs, while sparing normal tissue, suggesting a promising new way to treat a large number of cancer patients.

The study also demonstrate that cancers that don't arise from these organs become dependent on a different pathway for making NAD, via a change in epigenetic regulation, which indicates that patients who have these other types of cancer need to be treated with a different set of therapies targeting NAD metabolism.

“This work — identifying and targeting cancer cell specific pathways of NAD metabolism in multiple different tumor types — lays the groundwork for a new set of specific, selective and highly promising new cancer treatments that spare normal tissue,” said Mischel.

Co-authors include: Ciro Zanca, Tomoyuki Koga, Ramya Raviram, Kristen Turner, Huijun Yang, Elizabeth Brunk and Junfeng Bi, Ludwig Institute for Cancer Research, UC San Diego; Utkrisht Rajkumar and Yarui Diao, UC San Diego; Frank Furnari, Ludwig Institute for Cancer Research and UC San Diego; and Feng Liu, Ruijin Hospital, China.

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Disclosure: Paul Mischel and Vineet Bafna are co-founders of Pretzel Therapeutics. They have equity in the company and serve as consultants.

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