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Researchers discover two key events that turn normal cells into cancer

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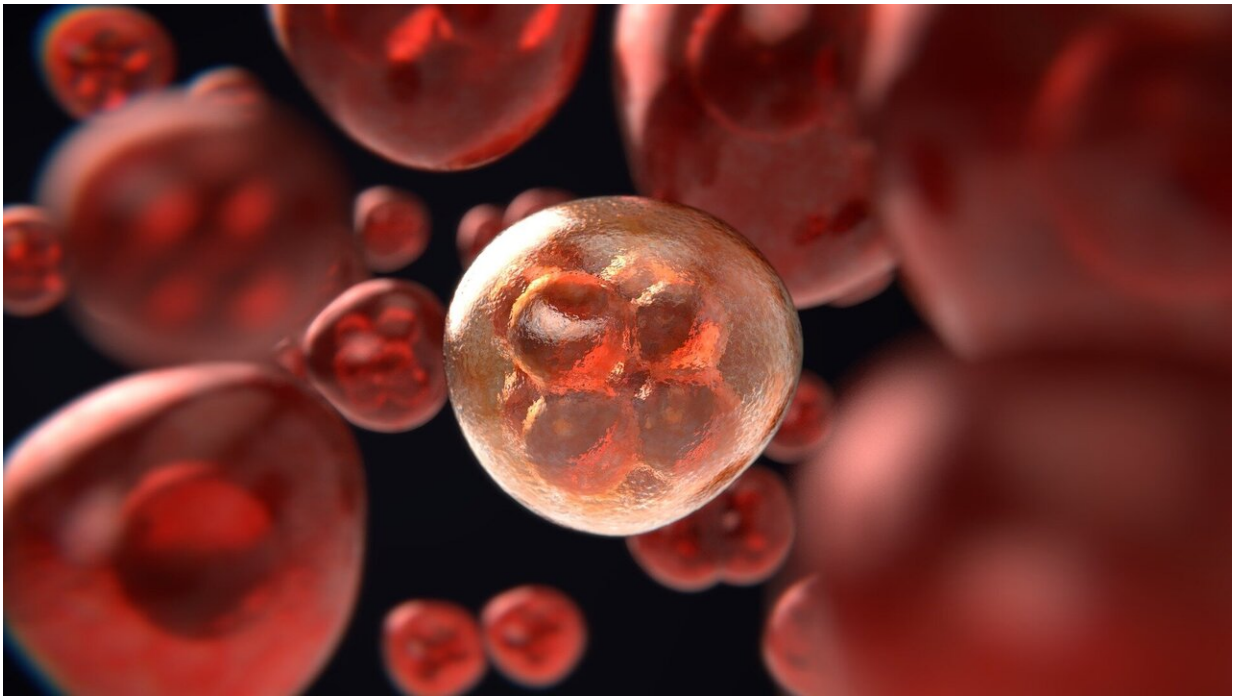

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More than 100 cancer types can arise all over the body, but two universal metabolic pathways may tie them all together, researchers from the Perelman School of Medicine at the University of Pennsylvania report in a new study published today online in *Cell Metabolism*. Researchers have long believed all cancers are governed by a common set of fundamental processes. Exactly what those were, however, has remained elusive.

Having a unifying mechanism could inform new therapeutic approaches to prevent normal cells from transforming into any type of tumor, be it breast, prostate, or colon, for example.

The team discovered how the transformation from a phenotypically normal cell to a cancerous one involves the enhancement of two key elements: antioxidant defense and nucleotide synthesis. Genes associated with cancer, they found, are super charging some cells to fight off oxidative stress and synthesize nucleotides, which cells need to survive and rapidly grow, respectively.

"Since the early 1980s, numerous cancer genes have been identified. However, they often affect multiple cellular processes, which makes it very hard to really summarize what exactly turns cells cancerous," said senior author Xiaolu Yang, Ph.D., a professor of Cancer Biology in the Perelman School of Medicine at the University of Pennsylvania. "We took a unique approach and looked at the cellular changes driven by a particular metabolic enzyme, which turned out to be the key here. Strikingly, we found that for a phenotypically normal cell to become a cancer cell, all it needs to do is to be equipped with the extra capacity to endure oxidative stress and produce nucleotides."

Shut down these metabolic pathways, the study suggests, and the cells don't become cancerous.

The researchers first overexpressed the gene G6PD, which makes the enzyme glucose-6-phosphate dehydrogenase, in mice and human cells. That enzyme is active in nearly all cells in the body and involved in the normal processing of carbohydrates. They showed that this overexpression alone turned human cells cancerous and led to tumors in the mice.

Next, they analyzed the mechanisms involved in that overexpression to

pinpoint what pathways were critical to the transformation. They found that G6PD stimulates production of new NADPH, a crucial co-enzyme for maintaining redox balance (which keeps the cell from being damaged and dying off), as well as more nucleotide precursors to keep them multiplying. Under conditions that elicit oxidative stress, which are often encountered by cancer cells due to their relentless proliferation, often in a wrong place, a normal cell would buckle, but a cancer cell armed with these additions presses on.

The findings also lend further evidence shown in clinical trials and other studies that antioxidants in fact support tumor growth, not decrease it. For a tumor to form, it needs a robust antioxidant defense; giving it more antioxidants provides an ideal environment for it to do that. The findings also provide an explanation for the observation that compounds interfering with nucleotide biosynthesis are among the most successful chemotherapeutic drugs for cancer.

Importantly, the study reveals a molecular framework to better understand the process of oncogenesis and a potential road map for new approaches to treat cancer, the authors said.

"Now we can say that the oncogenic transformation comes from two fundamental steps," Yang said. "Our study also suggests that combining therapeutics that affect both events, some which are already in clinics, would be more effective at preventing normal cells from becoming cancerous."

More information: Yang Zhang et al. Upregulation of Antioxidant Capacity and Nucleotide Precursor Availability Suffices for Oncogenic Transformation, *Cell Metabolism* (2020). DOI: 10.1016/j.cmet.2020.10.002

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