Cancer's metabolism subject of trailblazing study

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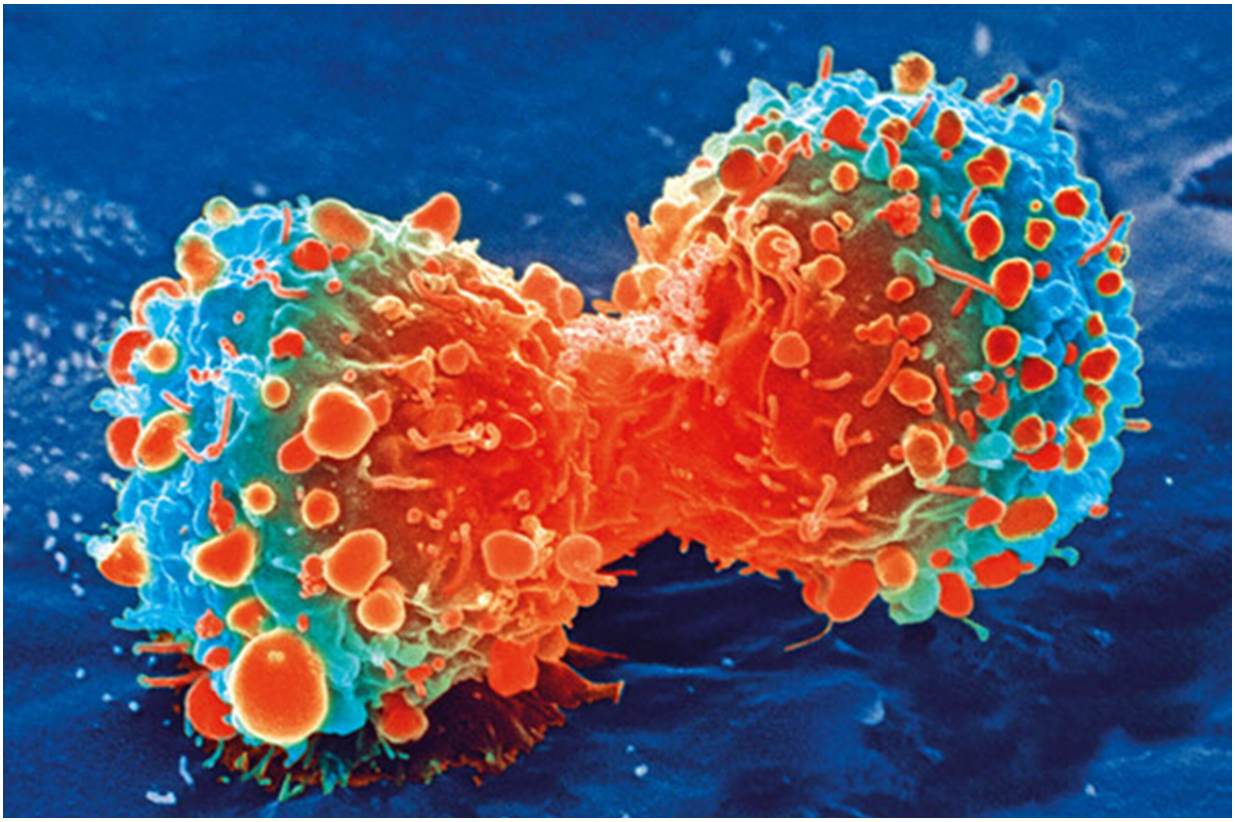

Cancer cell during cell division. Credit: National Institutes of Health

No matter what form cancer takes in the body, it starts at the cellular level and grows via metabolism run amok.

Understanding that altered metabolism in cancer has received renewed research interest, according to Abe Stroock, the William C. Hooey Director and Gordon L. Dibble Professor in the Smith School of Chemical and Biomolecular Engineering. His latest research examines cancer metabolism at multiple scales, and lays theoretical groundwork for future studies.

"Cancer has distinct metabolism, in some sense, and it's one of the earliest characteristics [of the disease] at the cellular and sub-cellular scale that was identified," said Stroock, senior author of "Multi-Scale Computational Study of the Warburg Effect, Reverse Warburg Effect and Glutamine Addiction in Solid Tumors," published recently in *PLOS Computational Biology*.

Mengrou Shan, Ph.D., a former Samuel C. Fleming Family Graduate Fellow in the Stroock lab, is lead author.

Nearly 100 years ago, German physiologist and Nobel laureate Otto Warburg hypothesized that cancer growth is caused by mitochondria consuming abnormal amounts of glucose, even in the presence of oxygen. Healthy cells only consume glucose in the absence of oxygen. This phenomenon of altered metabolism in cancer has been termed the Warburg effect.

Warburg surmised that cancer was a metabolic disease, first and foremost, but subsequent research has put forth the idea that genetic mutations are at the root of cancer.

"The Warburg claim that this metabolic defect is the origin of cancer has, in important ways, been dismissed today," Stroock said. "But we still don't cure cancer, so the questions about metabolisms as they relate to the genetics of cancer are back on the table."

When cancer cells consume glucose, Stroock said, they do it through a process called glycolysis, in which a significant amount of glucose is turned into lactic acid. It's a very inefficient way to use glucose—the same phenomena that occurs when fatigued muscles consume sugar anaerobically, leading to lactic acidosis if left unchecked.

One of the goals of the research was to find out if and how oddities in cancer's metabolism, like the Warburg effect, help or hurt tumor growth. For example: Given the intrinsic inefficiency of glycolysis, tumor cells should be disadvantaged relative to healthy tissues.

"One of the reasons that's a pressing question is, our current understanding of a tumor is based on survival of the fittest," Stroock said. "It [cancer] wins because cancerous cells defy the rules of good tissue cells, which are, 'Do what you're told,' and 'Have genetic integrity.' In doing this, the tumor out-competes healthy tissues."

Stroock aimed to determine the strengths and weaknesses of this rewired metabolic process at multiple scales—intracellular, cellular, multicellular—and created tools for doing so. The group modeled these processes in three metabolic scenarios:

- The Warburg effect (aerobic consumption of glucose);
- Glutamine addiction, which had been seen as a hallmark of cancer metabolism, and;
- The reverse Warburg effect, in which cancer cells "hijack" noncancerous cells in the tumor's microenvironment and force them to consume glucose like cancer cells do.

One of the tools the group utilized was flux-balance analysis (FBA), a computational method for determining the utilization of nutrients throughout the metabolic process within individual cells.

Using the results of FBA in models of populations of cells in the form of solid tumors, the group confirmed that the Warburg effect provides a growth advantage for the tumor, but that glutamine addiction does not benefit tumor cells' growth. "We show that it's not helpful [for the tumor] to be glutamine-addicted," Stroock said. "The community will have to find other ways in which glutamine is important."

Stroock's team also offered insights into the relationship between healthy cells and tumor cells under the reverse Warburg effect, which allows more oxygen to penetrate the cancerous mass in resource-limited microenvironments.

Stroock said the group's work, while opening doors to future study, also confirms a nearly 100-year-old theory. "It puts this ancient hypothesis on more solid footing," he said, "and we now know more quantitatively ... how cancer cells use this Warburg mechanism."

More information: Mengrou Shan et al, Multi-scale computational study of the Warburg effect, reverse Warburg effect and glutamine addiction in solid tumors, *PLOS Computational Biology* (2018). DOI: 10.1371/journal.pcbi.1006584

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