Study shows how nerves drive prostate cancer

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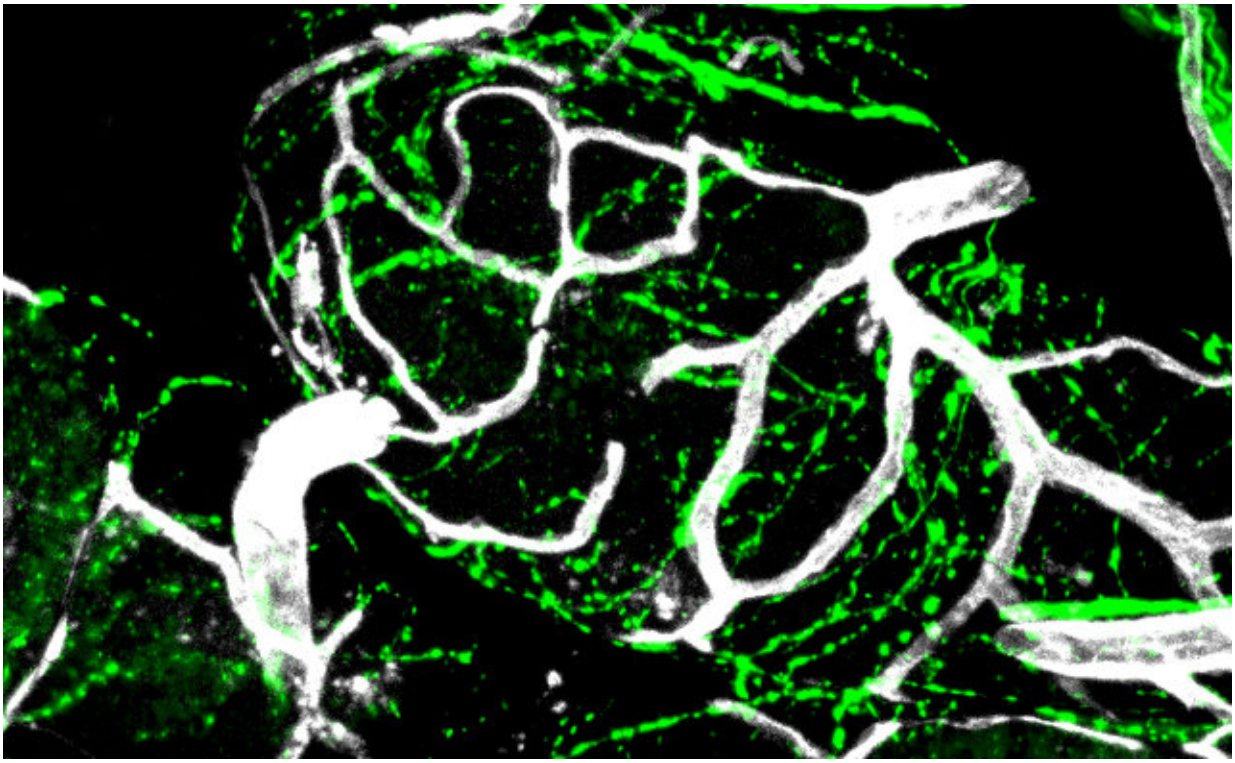


Tissue from an early-stage tumor developing in a mouse model of prostate cancer. Sympathetic-nerve fibers (green) are closely intertwined with blood vessels (white). Norepinephrine released by nerve fibers stimulates vessel proliferation that fuels tumor growth.Image courtesy Albert Einstein College of Medicine Credit: Albert Einstein College of Medicne

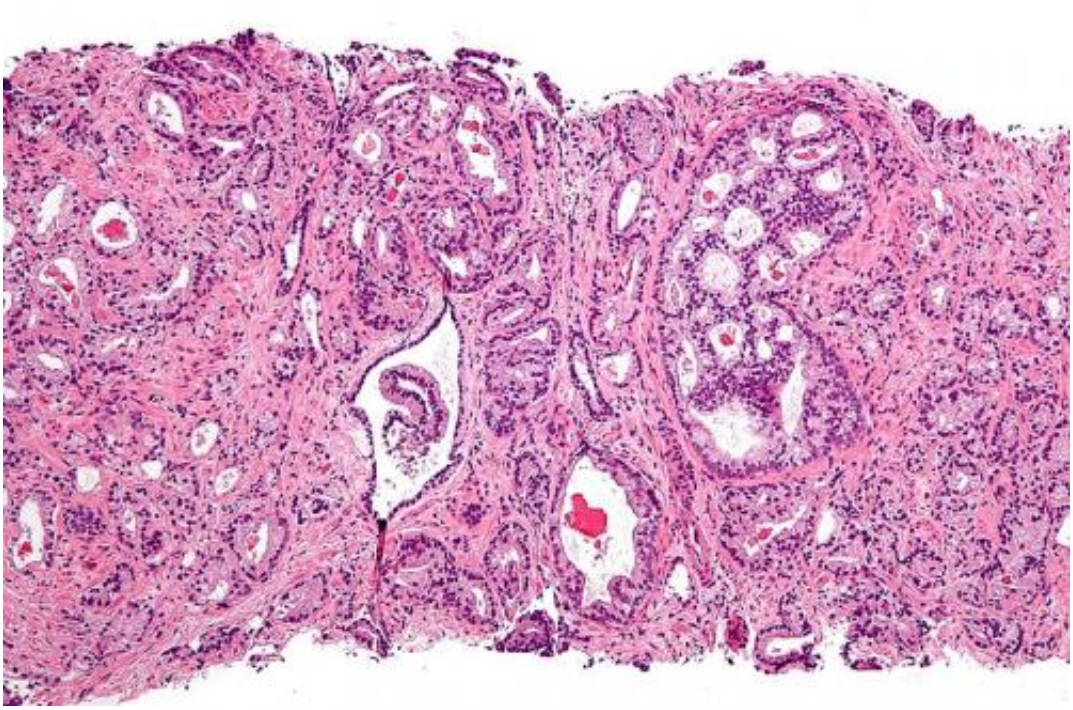
In a study in today's issue of *Science*, researchers at Albert Einstein College of Medicine, part of Montefiore Medicine, report that certain

nerves sustain prostate cancer growth by triggering a switch that causes tumor vessels to proliferate. Their earlier research—which first implicated nerves in fueling prostate cancer—has prompted Montefiore-Einstein to conduct a pilot study testing whether beta blockers (commonly used for treating hypertension) can kill cancer cells in tumors of men diagnosed with prostate cancer.

"Solid tumors depend on an expanding blood supply to thrive," says study leader Paul Frenette, M.D., professor of medicine and of cell biology and director of the Ruth L. and David S. Gottesman Institute for Stem Cell and Regenerative Medicine Research at Einstein and a member of the NCI-designated Albert Einstein Cancer Center. "Here we show that nerves stimulate the new blood vessels that encourage prostate tumor growth—and that we can short-circuit nerve stimulation to prevent new vessels from forming. This opens up an entirely new strategy for treating prostate cancer—one that we may be able to pursue using existing drugs."

Prostate cancer is second to skin cancer as the most common cancer in men. The National Cancer Institute estimates that 161,360 new cases of prostate cancer will be diagnosed in 2017, and 26,730 men will die from the disease, accounting for 4.4 percent of all cancer deaths.

In a 2013 paper, also in *Science*, Dr. Frenette and colleagues showed that nerves play a critical role in helping prostate tumors develop and spread. More specifically, the researchers found that nerves of the sympathetic nervous system, (responsible for activating the "fight or flight" response,) promote tumor growth by producing norepinephrine, which encourages tumor growth by binding to and stimulating receptors on tumor connective- tissue cells.



Micrograph showing prostatic acinar adenocarcinoma (the most common form of prostate cancer) Credit: Wikipedia, CC BY-SA 3.0

In the current study, the researchers used a mouse model of prostate cancer to determine precisely how nerves within connective tissue drive tumor growth. After being released by nerve fibers, norepinephrine binds to receptors on endothelial cells that line the inner surface of blood vessels. The researchers found that the binding of norepinephrine to those receptors triggers an "angio-metabolic switch" that changes how cells metabolize glucose. To make new blood vessels, the endothelial cells—which ordinarily use oxidative phosphorylation to obtain energy from glucose—were now relying almost exclusively on glycolysis. Using glycolysis to metabolize glucose is a phenomenon that had previously been observed in cancer cells.

To confirm norepinephrine's role in triggering this metabolic switch, the researchers deleted a gene in their animal model that codes for

norepinephrine's receptor on vessel cells, thereby eliminating norepinephrine's binding target. They then observed that cells lacking the receptor were using oxidative phosphorylation rather than glycolysis. As a result, the formation of new vessels was inhibited.

"Oxidative phosphorylation generates more energy than glycolysis," says Dr. Frenette. "It may seem counter-intuitive, but this energy boost provided by oxidative phosphorylation diminishes endothelial cell function and inhibits angiogenesis—the formation of new blood vessels that sustains tumor growth." In Dr. Frenette's mouse model of prostate cancer, stimulation from norepinephrine released by nerves had allowed endothelial cells to maintain use of glycolysis, enabling the rapid progression of prostate cancer from a low-grade precancerous stage to a high-grade malignant stage.

"While we need to learn more about the role that norepinephrine-releasing nerves play in prostate cancer, it's certainly worth exploring whether beta-blockers can improve disease outcomes," says Dr. Frenette, noting that beta-blockers work by blocking the effects of norepinephrine and similar compounds. Retrospective epidemiological studies, he says, have found that use of these drugs by men with prostate cancer was associated with reduced metastasis and increased survival.

The 2017 *Science* paper is titled "Adrenergic nerves activate an angio-metabolic switch in prostate cancer."

More information: A.H. Zahalka el al., "Adrenergic nerves activate an angio-metabolic switch in prostate cancer," *Science* (2017). science.sciencemag.org/cgi/doi … 1126/science.aah5072

Provided by Albert Einstein College of Medicine