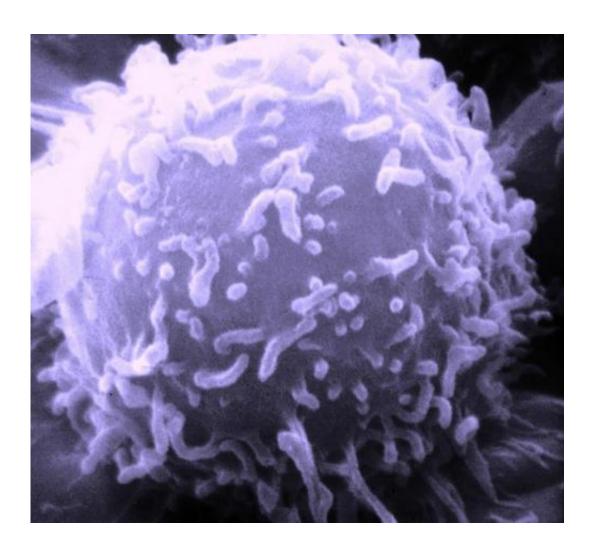


Cancer, bioelectrical signals and the microbiome connected

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Electron microscopic image of a single human lymphocyte. Credit: Dr. Triche National Cancer Institute



Developmental biologists at Tufts University, using a tadpole model, have shown that bioelectrical signals from distant cells control the incidence of tumors arising from cancer-causing genes and that this process is impacted by levels of a common fatty acid produced by bacteria found in the tadpole and also in humans.

"Genetic information is often not enough to determine whether a cell will become cancerous; you also have to take into account the physiology of the cell and the bioelectrical signals it receives from other tissues. This has huge implications for diagnostic technology as well as our basic understanding of the role of genetics and physiology in oncology," said Michael Levin, Ph.D., Vannevar Bush Professor of Biology and corresponding author of the paper in the journal *Oncotarget* that describes the research. The paper appeared online in advance of print on May 1.

"These data also suggest a number of ways we might prevent, detect and treat <u>cancer</u>," Levin added, "for example, by using ion channel drugs – "electroceuticals"—to target the bioelectric state of distant sites in the body. Ion channel agents, such as anti-epileptic drugs, are already approved for human use. "

Levin and Brook T. Chernet, Ph.D., injected Xenopus laevis tadpoles with oncogenes associated with many human cancers. The oncogenes caused tumor-like structures to form in these locations. Levin and Chernet's study showed that the incidence of tumor formation could be significantly reduced through misexpression of hyperpolarizing ion channels, which control current flow across a <u>cell membrane</u>, even when these electrical signals originated far from the oncogene-expressing cells. "These distant bioelectric signals suppressed tumor growth, despite the cells' continued high levels of oncogene protein," said Chernet, a former doctoral student in Levin's lab.



Further investigation revealed that the tumor-suppressing effects of hyperpolarization were regulated by a mechanism involving the short chain fatty acid butyrate and its target, the enzyme histone deacetylase. In humans, butyrate is produced in the colon by natural bacterial fermentation of carbohydrates, and butyrate has been shown to protect against colorectal cancer. To confirm that bacterial butyrate was also involved in regulating distant tumor formation in tadpoles, the researchers administered antibiotics; they found that the drugs indeed reduced butyrate production and thereby stopped membrane-voltage-based tumor suppression.

Programming Bacteria to Prevent Tumors

"Our research uncovers a promising connection between the microbiome and cancer that is controlled by alterations in bioelectric signaling and also opens up exciting possibilities for biomedicine. Imagine bacteria that are metabolically programmed to produce butyrate levels appropriate to prevent tumors," said Levin.

The distance over which carcinogenesis can be predicted and controlled has been addressed in a handful of earlier studies, including work by Levin and colleagues. Levin and Chernet have shown that aberrant bioelectrical properties of tissue revealed the location where tumors were likely to form and that melanoma-like growth could be triggered by bioelectrical signaling of instructor cells far from the melanocytes. The two biologists say that more research is needed to determine whether such signaling occurs in mammalian cancer models and over what distance.

The Tufts biologists are also intrigued by the question of whether cancers emit bioelectrical information that could be detectable at a distance from the tumors themselves. "It is tempting to speculate that the long-range signaling connections are bi-directional," says Levin.



More information: Chernet, B., & Levin, M. (2014). Transmembrane voltage potential of somatic cells controls oncogene-mediated tumorigenesis at long-range. *Oncotarget*, 5. This work was published May 1, 2014, online in advance of print.

Provided by Tufts University

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