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New hope for cancer comes straight from the heart

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Digitalis-based drugs like digoxin have been used for centuries to treat patients with irregular heart rhythms and heart failure and are still in use today. In the Dec. 16 issue of the *Proceedings of the National Academy of Sciences*, researchers at the Johns Hopkins University School of Medicine now report that this same class of drugs may hold new promise as a treatment for cancer. This finding emerged through a search for existing drugs that might slow or stop cancer progression.

"This is really exciting, to find that a drug already deemed safe by the FDA also can inhibit a protein crucial for cancer cell survival," says Gregg L. Semenza, M.D., Ph.D., director of the vascular program at the Johns Hopkins Institute for Cell Engineering and a member of the McKusick-Nathans Institute of Genetic Medicine.

Semenza and his team have long studied the hypoxia-inducible factor, or HIF-1, protein, which controls genes that help cells survive under low-oxygen conditions. HIF-1 turns on genes that grow new blood vessels to help oxygen-starved cells survive. Regions of low oxygen are common within the environment of fast-growing solid tumors.

"Oxygen-deprived cancer cells increase their HIF-1 levels to survive in these unfavorable conditions," says Semenza. "So turning down or blocking HIF-1 may be key to slowing or stopping these cells from growing."

The researchers took advantage of the Johns Hopkins Drug Library, a

collection of more than 3,000 drugs already FDA approved or currently being tested in phase II clinical trials, assembled by Hopkins pharmacology professor Jun O. Liu. In this study, the research team tested every drug in the library for its ability to turn down HIF-1in cancer cells. The top 20 candidates identified were able to reduce HIF-1 by more than 88 percent, and more than half of these 20 belong to a class of drugs already commonly used for treating heart failure, and included digoxin.

The researchers focused on digoxin because of its already well-established clinical use. They treated prostate cancer cells grown at normal and low-oxygen levels with digoxin for three days and counted the number of cells each day. They found that cells treated with digoxin significantly slowed their growth, with fewer total cells after three days and increased numbers of cells that had stopped growing when compared to untreated cells.

"Many drugs may appear promising when used to treat cancer cells in a dish in the lab, but may have little or no effect on tumors in living animals," says Huafeng Zhang, Ph.D., a research associate in the Department of Oncology and the Institute for Cell Engineering at Hopkins.

To see if digoxin had the same effect on cancer cells in the physiological context of a whole animal, the team administered daily injections of digoxin to mice with tumors. In untreated mice, tumors were large enough to be felt within nine days, but in treated mice, tumors could first be felt only after as long as 15 to 28 days. The team then examined tumors from the mice and found that HIF-1 levels were lower than tumors from untreated mice. The team then went on to show that it is digoxin specifically reducing HIF-1 that leads to the anti-tumor results they saw.

While Zhang thinks it is possible that drugs like digoxin could someday be used for treating cancer, she cautions that a great deal of work remains to be done to understand in detail how these drugs inhibit HIF-1 and slow or stop tumor growth. Also, since this class of drugs acts by both strengthening and slowing down the rhythm of the heart, she notes that patients can safely tolerate them in only a limited dosage range—a range that is lower than the concentrations of digoxin used in this study. "We're trying to kill a tumor," she says, "We don't want to stop a heart."

Source: Johns Hopkins Medical Institutions

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