Suppressing Activity of Common Intestinal Bacteria Reduces Tumor Growth

Mouse studies promising to colon cancer patients who currently have surgery as only option

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A team of University of California, San Diego School of Medicine researchers has discovered that common intestinal bacteria appear to promote tumor growths in genetically susceptible mice, but that tumorigenesis can be suppressed if the mice are exposed to an inhibiting protein enzyme.

The research, said lead author Eyal Raz, MD, a professor of medicine at UC San Diego, could portend an eventual new form of treatment for people with familial adenomatous polyposis or FAP, an inherited condition in which numerous initially benign polyps form in the large intestine, eventually transforming into malignant colon cancer.

The research appears online May 9 in the journal *Nature Medicine*. Raz, with colleagues at the UC San Diego School of Medicine and Wonkwang University in the Republic of Korea, looked at interactions between the vast numbers of bacteria typically found in the gastrointestinal tract and the tract's mucosal lining. Ordinarily, the bacteria and tract establish a kind of homeostasis. "In a normal host, these bacteria actually serve important roles, such as supporting cell production," said Raz. "But in susceptible hosts, the presence of these bacteria turns out to be detrimental."

Specifically, Raz and his co-authors found that mice with an engineered mutation that closely mimics FAP in humans leaves the mice notably vulnerable to inflammatory factors produced by ordinary bacterial activity. The constant inflammation enhances expression of an oncogene called c-Myc. Very quickly, the mice develop numerous tumors in their intestines and typically do not survive past six months of age.

In humans, FAP can be equally devastating. It is a genetic condition in which patients at a young age begin to develop hundreds to thousands of polyps in their intestine. By age 35, 95 percent of individuals with FAP have polyps. The polyps start out benign, but ultimately become malignant without treatment. Current treatment essentially consists of prophylactic surgery -- removal of the polyps before they turn cancerous.

"Right now, people with FAP don't have many options," said Raz. "They develop the cancer relatively early in life and the only treatment is surgery, often a total colectomy - the removal of the entire colon. And that still doesn't preclude the possibility of developing tumors elsewhere in the body."

That's why the second part of the study was especially encouraging, Raz said. When researchers administered a protein enzyme called extracellular signal-related kinase or ERK, it appeared to suppress intestinal turmorigenesis in the mice, causing cancer proteins to degrade more rapidly and increasing the survival time of the mice. If the inhibiting enzyme, which is currently undergoing clinical trials elsewhere, proves to be safe and effective, researchers say it eventually could provide FAP patients with another option other than surgery.

"This is a clear case of nature and nurture in molecular biology," said Raz. "Nature is the host, who in some cases is going to be genetically predisposed to develop certain diseases. Nurture is the environment, which in this case is bacterial activity and its effects. The mechanism for what's happening here with these mice and tumor growth is very clear. We know what we want and need to do."

Co-authors of the paper include Li-Li Hu, Jose Gonzalez-Navajas, Carol Shen, Jonathan Brick, Scott Herdman, Maripat Corr and Jongdae Lee, all from UCSD's Department of Medicine, plus Nissi Varki of the Department of Pathology at UCSD and Sung Hee Lee and Geom Seog Seo at Wonkwang University in Korea. The work was supported with grants from the National Institutes of Health.

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