MedicalXpress

Nerves play key role in triggering prostate cancer and influencing its spread

July 11 2013

Researchers at Albert Einstein College of Medicine of Yeshiva University have found that nerves play a critical role in both the development and spread of prostate tumors. Their findings, using both a mouse model and human prostate tissue, may lead to new ways to predict the aggressiveness of prostate cancer and to novel therapies for preventing and treating the disease. The study published online today in the July 12 edition of *Science*.

Prostate cancer is second to skin cancer as the most common cancer in men. The National Cancer Institute estimates that 238,590 new cases of prostate cancer will be diagnosed in 2013, and 29,720 men will die from the disease.

The study was led by stem-cell expert 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. In earlier research, Dr. Frenette and colleagues had discovered that the sympathetic nervous system regulates hematopoeitic stem cell niches—the sites in the bone marrow where red blood cells are formed.

Nerves are commonly found around tumors, but their role in the growth and progression of cancer has not been clear. "Since there might be similarities between the hematopoeitic stem cell niche and the stem cell niches found in cancer, we thought that sympathetic nerves might also have a role in tumor development," said Dr. Frenette. "It turns out that in

prostate cancer, not only are sympathetic nerves involved, but so too are parasympathetic nerves."

The body's autonomic nervous system (governing functions that we don't consciously control, such as heart rate) is divided into two branches. The sympathetic nervous system, or SNS, modulates the body's "fight or flight response" by, for example, revving up the heart rate and constricting blood vessels. The parasympathetic nervous system, or PNS, generally acts in opposition to the SNS to keep bodily functions in balance.

The researchers discovered the role of nerves in prostate cancer by first injecting human prostate cancer cells into mice and then systematically disabling various parts of the SNS and PNS and observing how the cells fared. A control group of mice were administered the cancer cells but underwent no further interventions.

The study found that the autonomic nervous system's two branches have complementary functions in the development and spread of prostate cancer. The SNS helps initiate the early phases of the disease, while the PNS is involved in the later stages when the cancer spreads.

More specifically, the researchers found that the SNS promotes tumor growth by producing the neurotransmitter norepinephrine, which then binds to and stimulates two types of adrenergeric receptors (beta-2 and beta-3) on the surface of the stromal cells in the tumor (adrenergic receptors are targeted by adrenaline and noradrenaline, also known respectively as epinephrine and norepinephrine). "This is consistent with recent epidemiological studies showing that the use of beta-blockers, which lower blood pressure by blocking beta-adrenergic receptors, is associated with improved survival of prostate cancer patients," said Dr. Frenette.

As for the PNS's role in cancer progression, it makes tumor cells invade other tissues and travel to distant parts of the body (tumor metastasis) when its nerve fibers release acetylcholine, which activates a signaling pathway in stromal cells of the tumor microenvironment. (Stromal cells make up connective tissue.)

"Our findings raise the tantalizing possibility that drugs targeting both branches of the autonomic nervous system may be useful therapies for prostate cancer," Dr. Frenette added.

To see whether their findings were relevant to human cancer, the researchers analyzed nerve fiber densities in prostate tissue specimens taken from 43 patients with prostate cancer who had not undergone any treatment.

Patients who turned out to have aggressive prostate cancers had a higher density of nerve fibers within tumors and in normal prostate tissue surrounding their tumors compared with patients who had less aggressive tumors. "More work needs to be done, but the findings suggest that nerve density assessment merits further study as a possible predictive marker of prostate cancer aggressiveness," said Dr. Frenette.

Whether these findings apply to other forms of cancer is uncertain. "Clinical studies show that breast cancer patients who took beta blockers did better than those who were not taking beta blockers," said Dr. Frenette. "This suggests that the same mechanisms are involved, but that remains to be seen."

The paper is titled "Autonomic Nerve Development Contributes to Prostate Cancer Progression." Other Einstein authors are Claire Magnon, Ph.D. Juan Lin, Ph.D., and Xiaonan Xue, Ph.D. Additional contributors are Simon J. Hall, M.D., at Icahn School of Medicine at Mount Sinai, New York, NY; Leah Gerber and Stephen J. Freedland, M.D., both at

Durham VA Medical Center and Duke University, Durham, NC.

The study was supported by an Idea Development award from the Department of Defense (W81XWH-07-1-0165) and grants from the National Institutes of Health.

Albert Einstein College of Medicine has a pending U.S. patent application relating to the use of adrenergic and muscarinic receptors antagonists for cancer therapy, which is currently available for licensing.

More information: "Autonomic Nerve Development Contributes to Prostate Cancer Progression," by C. Magnon et al *Science*, 2013.

Provided by Albert Einstein College of Medicine