Prostate cancer's nerves

By Lauren Martz, Staff Writer

In prostate cancer, a handful of companies are racing to develop third-generation antiandrogen therapeutics that overcome resistance mechanisms that render first- and second-generation molecules ineffective.[1,2] The problem is that any direct attack on the tumor is likely to lead to resistance mutations in a short stretch of time.

Now, a team from the **Albert Einstein College of Medicine of Yeshiva University** has taken a new approach for treating the disease. The group has evidence that blocking nerve signaling pathways with marketed β-adrenergic receptor and muscarinic receptor antagonists can inhibit prostate tumor initiation and metastasis.[3] The team plans to study the drugs in the new indication, although it is not yet clear whether the approach can treat established disease.

Previous studies have reported a link between prostate cancer progression and nervous system stimulation. For example, a 2001 study found that sensory neurons stimulate prostate cancer proliferation *in vitro*.[4]

This year, researchers at **Oslo University Hospital** reported that patients with prostate cancer who were taking β-blockers had a lower incidence of recurrence and mortality than patients who did not take the medication.[5,6]

The Albert Einstein College of Medicine team inhibited sympathetic nerve signaling in mice by knocking out *adrenergic receptor* β_2 (*Adrb2*) and *Adrb3* and saw less tumor initiation than that in wild-type controls.

In addition, inhibition of parasympathetic nerve signaling by blocking muscarinic acetylcholine receptor M1 (CHRM1; HM1) helped block tumor invasion and metastasis.

β-Blockers are marketed to treat cardiovascular conditions including hypertension, myocardial infarction (MI) and heart failure. CHRM1 antagonists are marketed to treat incontinence and drooling.

Building on the previous work, Claire Magnon, Paul Frenette and colleagues set out to determine whether blocking signaling of the autonomic nervous system in the prostate could help treat or prevent the disease.

Magnon is an assistant professor at the Albert Einstein College of Medicine. Frenette is director and chair of the Ruth L. and David S. Gottesman Institute for Stem Cell and Regenerative Medicine Research and a professor of medicine and cell biology at the college. The group also included researchers from **Duke University**, the **Icahn School of Medicine at Mount Sinai** and the **Durham VA Medical Center**.

The team injected luciferase-expressing human prostate cancer cells into the prostates of immunocompromised mice to bioluminescently model the disease. The number of tumor-infiltrating sympathetic plus parasympathetic nerve fibers within the tumor increased with cancer development, which suggested the tumors recruited new nerves to the stroma.

In the mice, elimination of sympathetic nerve fibers prevented development of prostate cancers.

The group then hypothesized that because sympathetic neurons signal through β-adrenergic receptors, antagonizing the receptors might help prevent prostate cancer. Indeed, genetic deletion of *Adrb2* or *Adrb3* in the mice delayed tumor development. The effect was even more pronounced in double knockout animals.

Parasympathetic signaling also played a role in tumor development and progression.

In the bioluminescent mouse model, a nonspecific agonist of muscarinic cholinergic receptors, which are activated by parasympathetic neurons, increased tumor cell invasion into lymph nodes compared with no treatment. A nonspecific CHRM antagonist, a specific CHRM1 antagonist or genetic *Chrm1* knockout prevented the increase in invasion, decreased metastasis and improved survival.

Finally, an analysis of prostate tumor and tissue samples from 43 treatment-naïve patients showed that high nerve fiber densities in and around tumors correlated with poor prognosis.

Results were published in *Science*.

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> ***—Kristin Austlid Taskén, Oslo University Hospital***

Drug repurposing

Researchers agree that β-adrenergic receptor antagonists and CHRM1 antagonists could be repurposed to prevent and possibly treat prostate cancer.

Ian Barron, a postdoctoral research fellow at **Trinity College Dublin**, told *SciBX* that "a number of drugs that inhibit these targets are already available. Their safety profiles are well understood."

"Since such blockers are in routine clinical use, their employment in prostate cancer treatment should be relatively seamless," added Norman Maitland, director of the YCR Cancer Research Unit and a professor of molecular biology at **The University of York**.

Maitland and Kristin Austlid Taskén, an adjunct professor of urology at Oslo University Hospital, both liked that the antagonists target the nerves in the tumor microenvironment rather than the tumor cells themselves. Taskén was the group leader on the retrospective study linking β-blockers with improved prostate cancer prognosis.

Androgen receptor–targeting drugs and chemotherapies for prostate cancer target the cancer cells themselves. "Drug resistance is a major problem in cancer drug development. Assuming that the high plasticity

of the cancer cells makes them more prone to develop resistance, targeting the stromal cells like the nerves instead may slow down or block the resistant development," said Taskén.

An unanswered question is whether blocking nerve signaling pathways can treat established disease.

"It is difficult to see how this mechanism of action fits into a postdiagnosis treatment paradigm, as by the time that most patients present with their cancer, tumor dissemination will have already happened," said Barron.

Maitland added that most prostate cancer chemotherapies are used when the disease has penetrated the prostatic capsule or the cancer cells have metastasized to the local lymph nodes.

"Would such a nervous system treatment affect these cells at all? By this time, the tumors have become largely independent of the prostate stroma influence and have adapted to the bone environment, for example," he said.

Despite the concerns, Magnon expects that ADRB2, ADRB3 and CHRM1 inhibitors may prevent and treat both early and late stage cancers.

"Targeting the sympathetic nervous system may help to treat early prostate cancer. However, after surgery of advanced cancers, administration of selective β-blockers targeting ADRB2 and ADRB3 might block potential recurrence at the primary site. Adjunction of a CHRM1 inhibitor may prevent perioperative tumor dissemination and then metastasis," she said.

Hagop Youssoufian, EVP of R&D at **Progenics Pharmaceuticals Inc.**, thinks the best uses for nervous system–targeting therapeutics will likely be in patients predisposed to prostate cancer, patients who had primary tumors removed by surgery and patients with minimal residual disease after primary therapy.

Progenics' PSMA ADC, an antibody-drug conjugate targeting prostate-specific membrane antigen (PSMA; FOLH1; GCPII), is in Phase II testing to treat prostate cancer.

Magnon thinks combining ADRB2, ADRB3 and CHRM1 antagonists plus chemotherapy could treat established disease while preventing recurrence. Before studying such a combination in mice, Magnon hopes to better characterize the nerve signaling processes in the tumor microenvironment.

"I would like to dissect further nerve interactions with other components of the stroma in order to design the best targeted therapies," she said.

Magnon said the Albert Einstein College of Medicine has patented the work and the IP is available for licensing.

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