East Lancashire Prostate Cancer Support Group Newsletter

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What's Inside

Genome's dark matter offers clues to major challenge in prostate cancer

Researchers identify a lncRNA that provides insight into a key driver of prostate cancer -- and a potential target for future therapy

Date:

May 28, 2018 Michigan Medicine - University of Michigan

Researchers identified a novel gene they named ARLNC1 that controls signals from the androgen receptor, a key player in prostate cancer. Knocking down this long non-coding RNA in mice led to cancer cell death, suggesting this may be a key target for future therapies.

The dark matter of the human genome may shed light on how the hormone androgen impacts prostate cancer.

Researchers at the University of Michigan Rogel Cancer Center identified a novel gene they named ARLNC1 that controls signals from the androgen receptor, a key player in prostate cancer. Knocking down this long non-coding RNA in mice led to cancer cell death, suggesting this may be a key target for future therapies. The study is published in Nature Genetics.

Current prostate cancer treatments aim to block the androgen receptor to stop cancer growth. But most patients become resistance to androgen-specific therapies, developing a challenging form of the disease called metastatic castration-resistant prostate cancer.

"The androgen receptor is an important target in pros-

tate cancer. Understanding that target is important. This study identifies a feedback loop that we could potentially disrupt as an alternative to blocking the androgen receptor directly," says study senior author Arul Chinnaiyan, M.D., Ph.D., director of the Michigan Center for Translational Pathology.

Chinnaiyan's lab identified thousands of lncRNAs in a 2015 paper. Long non-coding RNAs are considered the dark matter of the genome because so little is known about them.

While searching for lncRNAs that might play a role in prostate cancer, the team discovered that ARLNC1 is elevated in prostate cancer relative to benign prostate tissue, which suggests a role in cancer development. And it was associated with androgen receptor signaling, which made it more intriguing.

The researchers found that the androgen receptor actually induces ARLNC1 expression. Then ARLNC1 binds to the androgen receptor messenger RNA transcript. This stabilizes the level of androgen receptor, which then feeds back to sustain ARLNC1.

"At the end of the day, you're creating or stabilizing more androgen receptor signaling in general and driving this oncogenic pathway forward. We're envisioning a potential therapy against ARLNC1 in combination with therapy to block the androgen receptor -- which would hit the target and also this positive feedback loop," Chinnaiyan says.

When researchers blocked ARLNC1 in cell lines expressing androgen receptor, it led to cancer cell death and prevented tumor growth. In mouse models, elevating ARLNC1 caused large tumors to form. Knocking down ARLNC1 in mice caused tumors to shrink.

Researchers plan to continue studying the biology of ARLNC1 to understand how it's involved in prostate cancer progression and androgen receptor signaling.

"We want to further characterize the dark matter of the genome," Chinnaiyan says. "There are a number of these lncRNAs that we don't understand how they functionally work. Some of them will certainly be very useful as cancer biomarkers and we think a subset are important in biological processes."

Story Source:

Materials provided by Michigan Medicine - University of Michigan. Note: Content may be edited for style and length.

Journal Reference:

Yajia Zhang, Sethuramasundaram Pitchiaya, Marcin Cieślik, Yashar S. Niknafs, Jean C.-Y. Tien, Yasuyuki Hosono, Matthew K. Iyer, Sahr Yazdani, Shruthi Subramaniam, Sudhanshu K. Shukla, Xia Jiang, Lisha Wang, Tzu-Ying Liu, Michael Uhl, Alexander R. Gawronski, Yuanyuan Qiao, Lanbo Xiao, Saravana M. Dhanasekaran, Kristin M. Juckette, Lakshmi P. Kunju, Xuhong Cao, Utsav Patel, Mona Batish, Girish C. Shukla, Michelle T. Paulsen, Mats Ljungman, Hui Jiang, Rohit Mehra, Rolf Backofen, Cenk S. Sahinalp, Susan M. Freier, Andrew T. Watt, Shuling Guo, John T. Wei, Felix Y. Feng, Rohit Malik, Arul M. Chinnaiyan. Analysis of the androgen receptor–regulated lncRNA landscape identifies a role for ARLNC1 in prostate cancer progression. Nature Genetics, 2018; DOI: 10.1038/s41588-018-0120-1

"Smell receptor fuels prostate cancer progression" Blocking receptor with drugs or scents might be new prostate cancer treatment

Date: May 29, 2018
Source: Duke University

Researchers have found that an olfactory receptor plays a critical role in the progression of prostate cancer. They found that activating the receptor -- called OR51E2 -- in prostate cancer cells caused the cancer to morph into the more aggressive, castration-resistant form of the disease. The finding suggests that taking the opposite approach -- blocking the receptor with specific molecules, or perhaps even with specific scents -- could provide a new way to treat prostate cancer.

Oncology -- Genitourinary Oncology.

Olfactory receptors belong to a family of proteins called G protein-coupled receptors or GPCRs, which are the most commonly exploited drug target in modern medicine. These receptors act by a lock and key mechanism. When the right molecular "key" fits into the receptor's "lock," it sets off a cascade of biochemical reactions that culminate in a specific biological activity, such as the brain recognizing the scent of freshly cut grass.

Thus far, Matsunami's lab has identified the molecular keys or "ligands" that activate more than 50 different olfactory receptors, most involved in smell and other senses.

But Tatjana Abaffy, Ph.D., a research assistant professor working with Matsunami, was interested in olfactory receptors that are present outside the nose. She found repeated mentions in the scientific literature of a receptor called OR51E2 present in such unusually high levels in prostate cancer cells that it earned the alternate moniker Prostate-Specific G Protein-Coupled Receptor（PSGR）.

To find the ligands that bind OR51E2 -- the first step to figuring out what role it might play in pros-

tate cancer cells -- Abaffy made a virtual model of the olfactory receptor. She then trained a computer to screen a library of 2,516 different human metabolites and pick out the ones most likely to unlock the virtual receptor. Abaffy took the top 100 most promising candidates from that virtual screen and added them to living cells to see which ones activated the receptor.

A couple dozen ligands, including a steroid called 19-hydroxyandrostenedione or 19 OH-AD, caused the cancer cells to take on the characteristics of neuroendocrine cells. Most deaths from prostate cancer are due to the progression of localized disease into metastatic, castration-resistant prostate cancer, which is characterized by an increased number of these neuroendocrine-like cells.

"The typical therapy for patients with prostate cancer involves eliminating cancer-fueling hormones like testosterone by chemical or surgical castration," said Abaffy, who is lead author of the study. "This approach slows down the cancer, but resistance typically develops after a year or two, resulting in castration-resistant prostate cancer. We believe the olfactory receptor is involved at this stage of the disease."

Abaffy also found that cancer cells secrete 19 OH-AD, which acts as a critical intermediate in the chemical conversion of testosterone into estrogen, essentially feeding their own progression. But when she eliminated the olfactory receptor from the cells, 19 OH-AD lost its effect, and the progression stalled.

"By identifying molecules that can activate or block this receptor, we could change the course of prostate cancer," Matsunami said.

With that goal in mind, the researchers are currently conducting follow-up experiments with the other compounds uncovered in this study.

Story Source:

Materials provided by Duke University. Note: Content may be edited for style and length.

Journal Reference:

Tatjana Abaffy, James R. Bain, Michael J. Muehlbauer, Ivan Spasojevic, Shweta Lodha, Elisa Bruguera, Sara K. O ' Neal, So Young Kim, Hiroaki Matsunami. A Testosterone Metabolite 19-Hydroxyandrostenedione Induces Neuroendocrine Trans-Differentiation of Prostate Cancer Cells via an Ectopic Olfactory Receptor. Frontiers in Oncology, 2018; 8 DOI: 10.3389/fonc.2018.00162

Prostate cancer management has structural weakness that may hit thousands of men

by **Jill Margo**

May 29 2018 at 9:27 AM
Updated May 29 2018 at 1:28 PM FINANCIAL REVIEW

A structural weakness in the way Australia manages prostate cancer may affect thousands of men across the country.

The weakness has been uncovered by a study published in the *Medical Journal of Australia* and affects those who are on "active surveillance", a program designed to keep a close watch on men with prostate cancer.

Most, but not all men on this program have been diagnosed with low risk cancer and are under surveillance in case their cancer should become more active.

The problem is that about 75 per cent of them are not receiving proper surveillance and are at risk of their cancer silently advancing.

They risk slipping through the cracks and missing the opportunity for curative treatment.

While it is unclear how non-compliance affects the death rate, for many this could mean more burdensome treatment down the track.

The study is a call to action for both men under surveillance and their doctors, to ensure the criteria are being diligently met.

"We may need to create tools – with an app, a tracking or a messaging system – to prompt men and their clinicians to action," says Associate Professor Declan Murphy, Director of Genitourinary Oncology at the Peter MacCallum Cancer Centre in Melbourne.

Like a dental check-up, he says a surveillance check can slip the mind – but the consequences can be more serious.

The study was performed in Victoria, but he says it can be extrapolated to the rest of the country.

Of the 20,000 new cases of prostate cancer diagnosed nationally every year, about 5000 have low risk cancer and about 60 per cent of them opt for active surveillance.

This is a good thing because only a minority of low risk tumours become life threatening and these men avoid invasive treatments such as surgery or radiation which carry undesirable side effects.

Broadly, a low risk cancer is in the grade group 1（of 5） with the blood marker for prostate cancer, PSA below 10.

But Murphy says some men, who have favourable intermediate disease, also opt for active surveillance. In this study some men were in grade group 2, and 5 per cent were in grade group 3.

"They wanted active surveillance and were prepared to accept a little uncertainty, but it's incumbent on them and their doctors that there is compliance," says Murphy, a co-author of the study.

In general, he says in the first year after a repeat biopsy, 17 per cent of men will be reclassified and will transition to active treatment.

By five years, the number could reach 30 per cent.

While various active surveillance programs exist around the world, the Australian one used in this study requires three PSA tests, physical examinations and one repeat biopsy in the first two years.

Inexplicably, it showed men who had a trans-rectal biopsy（needle passes through the back passage into the prostate） were more likely to adhere to the protocols of surveillance than those who trans-perineal one（needle passes through the skin of the perineum）.

But Murphy says rectal biopsies are far less reliable and "miss up to 50 per cent of clinically significant cancer compared to trans-perineal biopsies".

He cites a British study that admitted men to a surveillance program after a rectal biopsy showed they had low-risk cancer. Within six months, all had a follow up trans-perineal biopsy.

"A third of them had higher risk disease, not because they had suddenly progressed, but because the rectal biopsy got it wrong," he says.

"We did this study because we were uncertain if Australian men suitable for active surveillance were actually getting reasonable levels of surveillance."

The study, led by Melanie Evans of Monash University, analysed 1600 men diagnosed with prostate cancer between 2008 and 2014.

They had all been on active surveillance for at least two years but only 26 per cent had adhered to the protocol. Those diagnosed in public hospitals were less likely to adhere.

Nearly 40 per cent of all participants did not have a repeat biopsy in the two-year period.

"Concerning", is how the results were described by senior author of the study, Associate Professor Sue Evans, who is not related to Melanie. They can be heard discussing the issue on an open access podcast.

Professor Evans is head of the Clinical Registry Unit, and Director of the Centre of Research Excellence in Patient Safety at Monash University. She says possible confusion may arise from the Medicare item numbers used by GPs for PSA testing.

Men who have not been diagnosed are restricted to one PSA test per year. Those already diagnosed can have more. She told MJA Insight it may be useful to provide men with a system that

From Left to Right Hazel Goulding (Treasurer) Leon D Wright (IT Admin) Stuart Marshall (Secretary) Steve Laird (Vice Chairman) Dave Riley (Chairman)

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We are a group of local people who know about prostate cancer. We are a friendly organisation dedicated to offering support to men who have had or who are experiencing the effects of this potentially life threatening disease.

The East Lanc's Prostate Cancer Support Group offers a place for free exchange of information and help for local men and their supporters (family and friends) who may be affected by this increasingly common form of male cancer.

At each meeting we strive to be a happy, supportive and upbeat group of people; encouraging open discussion on what can be a very difficult and perhaps for some an

Next Meeting
Thursday 7th June 2018
The Mackenzie Building
Burnley General Hospital
2:00pm—4:00pm