Manitoba Prostate Cancer SUPPORT GROUP

Newsletter

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Scientists Identify Gene Contributing to Prostate Cancer Drug Resistance

The GREB1 gene promotes resistance to prostate cancer treatments, making it a potential target for future therapies.

Researchers have discovered how a gene involved in regulating hormone receptors may contribute to drug resistance in some prostate cancer patients.

Their findings, published in eLife, suggest that disrupting specific activity of the GREB1 gene could be explored for developing more effective therapies in future.

Androgens, a male hormone, encourage the growth of prostate cancer cells. Hormone therapies (or 'antiandrogens') have been developed to counter this activity. These treatments, which target a protein molecule activated by the hormone – the androgen receptor (AR) – are effective against advanced prostate cancer but are hindered by a type of drug resistance called castration-resistant prostate cancer (CRPC). The most common cause of this resistance is an increase in both the amount and activity of AR. Previous studies have shown that increases or mutations in AR are present in over 50% of CRPC patients, and that increases in AR are associated with greater resistance to the next-generation AR inhibitors: abiraterone and enzalutamide.

"Studies have also revealed several differences in AR activity in prostate cancer," explains first author Eugine

(Continued on page 2)

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Thanks!

Next Meeting:

Wednesday, February 20, 2019

Speaker: Jonathan Doherty (Delta 9 Cannabis Inc.)

Title: *"Cannabis 101: An introduction to cannabis as medicine"*

Location: The First Unitarian Universalist Church of Winnipeg, 603 Wellington Crescent

Time: 7 – 9 pm.
(First hour for general discussion; second hour for expert guest speaker)

Free Admission Everyone Welcome
Plenty of free parking

SHARING IS CARING SHARING IS CARING

The Manitoba Prostate Cancer Support Group offers support to prostate cancer patients but does not recommend any particular treatment modalities, medications or physicians ; such decisions should be made in consultation with your doctor.

MPCSG – active since 1992.

Thought of The Day

Believe in yourself, take on your challenges, dig deep within yourself to conquer fears. Never let anyone bring you down. You got to keep going. – *Chantal Sutherland*

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Lee, Research Fellow in Charles Sawyers' lab at Memorial Sloan Kettering Cancer Center, US. "Notably, these differences occur in the absence of genetic alterations in AR, which are generally found only in CRPC. A possible explanation is that AR activity is encouraged by coactivators – other genes and proteins that help the function of AR – and we wanted to see if this is the case."

Lee and her team first isolated prostate cancer cells with low versus high AR activity. They found that those with high AR output have reduced sensitivity to enzalutamide, in the absence of changes in AR protein expression.

"They next identified three genes that were most active in cells with high AR output: GREB1, KLF8 and GHRHR. "Of these genes, we prioritised GREB1 for further investigation because it has higher expression levels in primary prostate tumours with high AR activity," says Lee.

Their analysis showed that GREB1 increases AR activity through a novel two-part mechanism: it binds AR and promotes its activity by recruiting AR coactivators (enzymes such as EP300/CBP); and it improves the efficiency of AR binding to DNA, which further enhances AR activity. Importantly, the team found that inhibiting GREB1 converted cells with a high AR output to a low-output state, and improved the effectiveness of enzalutamide treatment.

"Collectively, our results implicate GREB1 as an amplifier of AR activity that contributes to prostate cancer progression and promotes antiandrogen resistance in disease models," concludes senior author and Howard Hughes Medical Institute Investigator Charles Sawyers, Chair of the Human Oncology and Pathogenesis Program at Memorial Sloan Kettering Cancer Center.

"For now, further research is needed to understand the clinical implications of this work – particularly whether GREB1 levels in CRPC patients can be used to predict their response to next-generation AR therapy."

Jan 15, 2019

https://elifesciences.org/for-the-press/2600db7f/scientists-identify-gene-contributing-to-prostate-cancer-drug-resistance

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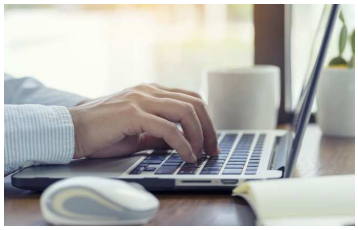
Did You Know?

Did you know that this newsletter is available in a colour version one to two weeks before you receive the black and white printed version via Canada Post? All you have to do is go to our website **www.manpros.org** to the home page and click on newsletters. Unlike many other organizations there is free public access to the newsletter. You don't need a password or code to access the newsletters. The colour makes the newsletter more reader friendly and the reading easier. The illustrations are much more informative



than in the black and white newsletter. Not only is the current newsletter available but also all the newsletters going back to January, 2013. While you're at it look to left side of the home page and click on History and read how the support group was formed and the history of its first 20 years.

We would appreciate receiving your comments on the on-line newsletter by sending them to our e-mail mail box at manpros@mts.net.

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You're a Cancer Survivor. Now What?

The National Cancer Institute says that in 2016, 15.5 million adult Americans were alive after a diagnosis of cancer. That number will hit 20.3 million by 2026.

And a report from the Institutes of Medicine, "From Cancer Patient to Cancer Survivor: Lost in Transition," found that while 62 percent of cancer survivors had their cancer diagnosed within the previous 10 years, 19 percent of female cancer survivors were diagnosed 20 or more years ago. Eight percent of male cancer survivors were diagnosed that long ago.

Clearly, there are a lot of folks dealing with the physical and emotional repercussions of cancer diagnosis, treatment and survivorship. If that's you or a loved one, it's vital that the emotional toll it can take is addressed and managed, just like you manage ongoing medical care by getting regular exams/screenings to check for recurrence or another health issue.

Unfortunately, you don't all attend to the ongoing medical supervision that's so essential to head off any developing problems or recurrence. Researchers at the Mayo Clinic Cancer Center found that one year after surgery for breast cancer, 13 percent of the women had not had a follow-up mammogram. After five years, only 50 percent of the women had had at least one mammogram each year.

What everyone needs to understand is that challenges to your emotional well-being also challenge your physical health. Stress fuels inflammation, immune system problems and heart disease, and may make you reluctant to get those follow-ups.

It's estimated that up to 58 percent of cancer survivors deal with depression and up to 23 percent experience bouts of anxiety. According to a 2014 study by researchers from Wake Forest School of Medicine, "Cancer diagnosis and treatment may be accompanied by profound physical, emotional, social, occupational and financial stressors, as well as associated increases in anxiety and depressive symptoms."

Many folks also contend with what the Harvard Mental Health Letter calls the "Damocles syndrome": Like a sword hanging over your head, you may worry about recurrence.

That makes every checkup scary, and every insignificant skin bump or gurgle in your gut seem like a bad sign of something.

That's why it's important to embrace the following three ways to help you make surviving a time for thriving:

1. Upgrade your lifestyle habits. The Centers for Disease Control and Prevention recommends you stay away from tobacco (including second- and third-hand smoke); limit alcohol intake, eat lots of fruits and vegetables; maintain a healthy weight; and be physically active.

2. Stay in touch with your docs and get all recommended follow-up and screening tests.

3. Practice stress-management techniques like meditation, guided imagery or deep breathing, etc., at least once a day. Consider group or individual talk therapy.

There are patient- and counselor-led groups at medical centers. Online, CancerCare.org offers support groups lead by oncological social workers. Some institutions, such as the Penn State Cancer Center, also recommend creative writing or art classes to help you express your feelings.

There also are adjunct activities that help ease emotional distress, like a reflection program (many cancer centers have setups) where you can experience reiki, reflexology, oncology massage, plus facials and makeup lessons to help deal with appearance-related side effects of treatments. In addition, some hospitals offer shared medical appointments for patients after breast, prostate and other cancers (these are covered by almost all insurance programs). In six or seven sessions, you'll learn survivorship behaviors.

Programs like this exist all throughout the U.S. and Canada, but you have to ask about them.

Take advantage, survivors!

By Mehmet Oz and Mike Roizen,
Special to the Star-Advertiser
January 9, 2019

Mehmet Oz, M.D., is host of "The Dr. Oz Show," and Mike Roizen, M.D., is Chief Wellness Officer and Chair of Wellness Institute at Cleveland Clinic. Email questions to youdocsdaily@sharecare.com

https://www.staradvertiser.com/2019/01/09/features/youre-a-cancer-survivor-now-what/

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Genetic Finding Can Guide Immunotherapy for Prostate Cancer

Summary

Immunotherapy drugs called checkpoint inhibitors can be very effective but don't work for most people with prostate cancer. A small subset of men whose prostate tumors have a genetic abnormality called high microsatellite instability do respond to the drugs. A new study shows that genetic sequencing can identify these men, allowing them to benefit from immunotherapy.

Immunotherapy drugs called checkpoint inhibitors hold great promise for cancer treatment. But only a minority of people respond to them. Researchers are trying to develop better therapies and figure out ways to identify who will respond to the drugs that already exist.

Checkpoint inhibitors tend to work well in people whose cancer cells are deficient in a DNA-repair process called mismatch repair (MMR). MMR-deficient cells can have hundreds or even thousands of mutations. A typical cancer cell has just a few dozen. Tumors with an MMR deficiency frequently display a characteristic called high microsatellite instability (MSI-H). Cells with MSI-H have repeated sequences of DNA, showing that something has gone awry in the repair process.

In 2017, the US Food and Drug Administration approved the checkpoint inhibitor pembrolizumab (Keytruda®) for MSI-H cancers. It was the first time that a drug was approved based on a tumor's genetic profile rather than where the cancer originated.

Now a team of Memorial Sloan Kettering researchers has published findings in JAMA Oncology that show how people with MSI-H prostate cancer respond to these drugs. We spoke with MSK medical oncologist Wassim Abida, who led the research, on what this means for people with this specific type of prostate cancer.

What did this study reveal about MSI-H in prostate cancer, and why is this important?

Checkpoint inhibitors have had less impact in prostate cancer compared with many other cancers. There was not a clear sense of how many prostate cancers harbor evidence of MSI-H.

We wanted to see if DNA sequencing was an effective way to detect the presence of MSI-H or MMR deficiency. We used MSK-IMPACT™, a genetic test that looks for cancer-related mutations. We sequenced tumors from slightly more than 1,000 people having treatment for prostate cancer at MSK. The goal was to identify people who could enroll in clinical trials based on specific mutations. In this group, only 32 had cancer cells with MSI-H. This comes to a frequency of just over 3%, so it's a small subset.

Of those 32 people, 11 received pembrolizumab or a similar immunotherapy drug. Half of those receiving these drugs showed a lasting benefit. This was true even in some people who had to stop taking the drugs because of side effects. So though the overall number of people responding to the treatment is small, the benefit can be durable.

How could this discovery change treatment for people with MSI-H prostate cancer?

First, this finding suggests that everyone with advanced prostate cancer should be considered for testing for MMR deficiency or MSI-H status. This is now possible with sequencing tools such as MSK-IMPACT. One conventional way to look for MMR deficiency has been a process called immunohistochemical staining, which uses antibodies to test for certain markers in a tissue sample. It is not feasible to do that kind of testing to identify the relatively small number of men who have MMR-deficient high or MSI-H cancers.

But DNA sequencing can be done to look for different targetable mutations, and this study shows that it is a practical way to test for MSI-H cancers. We are already using MSK-IMPACT to sequence tumors from all people with advanced cancers, so adding MSI testing to the panel, which we did in 2017, was straightforward. This is a good way to identify the 3 to 4% of men who might respond to pembrolizumab or a similar drug.

Although a response rate of about 50% is good, we need to investigate why these drugs don't work for everyone. This is true not just in prostate cancer but for all solid tumors. The presence of MSI-H alone doesn't necessarily mean they will respond, so we need a better

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understanding of which other factors are driving the cancer.

Does the presence of MSI-H in someone with prostate cancer have any impact beyond immunotherapy treatment?

In our study, seven of the 32 MSI-high patients also had a mutation in a gene associated with Lynch syndrome. This condition runs in some families and has been shown to increase the risk of developing certain types of cancer. In 2018, an MSK-led study estimated that people with high MSI had a one in six chance of carrying Lynch syndrome mutations. Our study suggests that this rate could be even higher in people with MSI-H prostate cancer — about one in four or one in five. So testing for Lynch syndrome mutations should be considered for people with MSI-H prostate cancer and can have implications for their family members as well.

We also found that the MSI characteristic occasionally did not appear until the disease spread. It was not present in samples from the prostate but was found in a later metastasis in two people with MSI-H prostate cancer. This means that MSI can be acquired during the course of the disease, and it suggests that, if possible, it is preferable to test a new biopsy rather than an older tumor.

This study was supported by Challenge and Young Investigator awards from the Prostate Cancer Foundation; Cancer Center Support grant P30 CA008748 from the National Cancer Institute (NCI), National Institutes of Health; Prostate Specialized Program of Research Excellence grant P50CA092629-16 from the NCI; Prostate Cancer Research Program awards W81XWH-17-1-0124, and PC071610 and PC121111 from the Department of Defense; the David H. Koch Fund for Prostate Cancer Research; the Marie-Josée and Henry R. Kravis Center for Molecular Oncology; and the Robertson Foundation.

Dr. Abida reported consulting for Clovis Oncology, Janssen Pharmaceutica, and More Health, Inc; receiving honoraria from Caret Healthcare; receiving research funding from Clovis Oncology, Zenith Epigenetics, Ltd, and AstraZeneca; and receiving travel funding from Clovis Oncology, Sanofi, and GlaxoSmithKline.

By Jim Stallard Friday, January 11, 2019

https://www.mskcc.org/blog/genetic-finding-can-guide-immunotherapy-prostate

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Statins Plus ADT May Up Survival in Advanced Prostate Cancer

Statin use by men receiving androgen deprivation therapy (ADT) for prostate cancer (PCa) is associated with improved overall and cancer-specific survival, new data suggest.

The data are from an observational study that included 87,346 men on ADT for advanced PCa identified using the national Veterans Affairs database. Of these patients, 53,360 used statins and 33,986 did not. Statin users had a significantly longer median overall survival (6.5 vs 4.0 years) and a significantly greater 5-year cancer-specific survival rate (94% vs 87.3%), a team at the University of Wisconsin-Madison led by Kyle A. Richards, MD, reported online ahead of print in Urologic Oncology.

Statin use independently predicted a significant 34% decreased risk of death from any cause, 44% decreased risk of death from PCa, and 36% decreased risk of skeletal-related events, after adjusting for multiple potential confounders, including age, race, Charlson comorbidity index (CCI), Gleason score, and PSA.

"Statins are inexpensive, well-tolerated medications that offer a promising adjunct to ADT, but require further prospective studies," Dr Richards and his colleagues concluded.

The authors noted that statins are thought to have antineoplastic properties related to their effect on cell proliferation and steroidogenesis. Progression to castration-resistant PCa, they explained, includes de-regulation of androgen synthesis, suggesting a role for statins in this setting.

Statin users were significantly younger than nonusers (median 73 vs 76 years) and significantly more likely to have a CCI greater than 3 (3.1% vs 2.5%) and a Gleason score of 8–10 (12.3% vs 10.9%).

Reference

Anderson-Carter I, Posielski N, Liou JI, et al. The impact of statins in combination with androgen deprivation therapy in patients with advanced prostate cancer: A large observational study. Urol Oncol. 2018; published online ahead of print.

Jody A. Charnow December 27, 2018

https://www.renalandurologynews.com/statin-adt-combo-linked-to-better-survival-in-advanced-prostate-cancer/article/821494/

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Guideline Supports Shorter Radiation Therapy Option In Prostate Cancer

The American Society for Radiation Oncology, ASCO and the American Urological Association have published a guideline supporting moderately hypofractionated external beam radiation therapy as an alternative to longer, conventional radiation courses for men with localized prostate cancer. The motivation for the guideline — developed by a panel of clinicians and researchers — was twofold, according to co-author Howard Sandler, MD, MS, Ronald H. Bloom chair in cancer therapeutics and chair of the department of radiation oncology at Cedars-Sinai Medical Center,

"One, there is biological rationale to suspect that, for slow-growing tumors like prostate cancer, they might be safely and effectively treated with fewer radiation treatments," he said. "Second, a number of important papers were published on the topic recently that rose the supporting data to a high enough level of evidence that we felt it was worth putting together a guideline document."

The panel defined hypofractionation as 20 to 28 radiation treatments, as opposed to the standard 40 to 44 treatments. Ultrahypofractionated radiation therapy, which received a conditional recommendation from the task force, could bring the total down to as few as five treatments.

Eric M. Horwitz, MD, chair of the department of radiation oncology at Fox Chase Cancer Center, offered perspective on the more convenient approach to radiation therapy for these patients.

"The standard of care for generations has been 5 days a week for 2 months," said Horwitz, who was not involved with the guideline development. "If there's no other option, then men will do it. But if we can tell them they don't have to come in here for 9 weeks, of course they're going to say yes. Now we have the option to tell them that, yes, they can come in for a shorter period of time without losing anything in terms of safety and efficacy."

Guideline overview

Moderate hypofractionation is defined as a fraction size of 240 cGy to 340 cGy, according to the authors. This approach may be offered as an alternative to standard fractionation — defined as 180 cGy to 200 cGy — for patients in any cancer risk group, anatomy or baseline urinary function category, and regardless of age or comorbidities.

"There was a particularly high level of evidence in favor of hypofractionation, with three strong and important randomized controlled trials," Sandler said. "It can be used for men with low, intermediate and high-risk prostate cancer, as long as the lymph nodes aren't being treated, and as long as there is active surveillance."

More than 4,000 patients were involved in these trials, Sandler said.

The suggested schedules for moderate hypofractionation are 6,000 cGy administered in 20 fractions of 300 cGy over 4 weeks, or 7,000 cGy administered in 28 fractions of 250 cGy over 5.5 weeks.

A slight increase in short-term gastrointestinal toxicity may accompany moderately hypofractionated external beam radiation therapy, but that risk is minimal. Sandler said.

"We want to stress that the guideline process used for ASTRO, ASCO and AUA is very strict," he said. "Studies were subject to very strict criteria."

Fox Chase has been using hypofractionation for nearly 2 decades with few safety issues, according to Horwitz.

"We did the first trial for hypofractionation from 2002 through 2006," he said. "We showed almost 20 years ago that this was a good way to treat men, and subsequent data have proven us out not only in terms of efficacy, but in how well the regimen is tolerated. The side-effect profile is basically the same as standard of care."

Ultrahypofractionation — defined as 500 cGy or greater — may be offered to patients with low-risk disease, according to the guideline. If patients with intermediate- or high-risk

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disease are offered this approach, the authors of the guideline strongly recommend treatment in the context of a clinical trial or multiinstitutional registry.

"For ultrahypofractionation, the recommendations were based on a number of smaller studies, so the level of evidence is a bit weaker," Sandler said. "We recommend this approach for low-risk patients, but there was less enthusiasm for intermediate- or high-risk patients."

Sandler suggested that the primary motivation for patients choosing this regimen is convenience. "Although convenience is important, the guideline committee felt that we should be careful to make sure it is also safe and effective," he said.

The authors suggest two schedules for ultrahypofractionation: 3,500 cGy in five fractions of 700 cGy, or 3,625 cGy in five fractions of 725 cGy. Patients should not receive 3,625 cGy in a fivefraction regimen outside of a trial or registry, according to the authors. When the five-fraction approach is used, patients should not receive consecutive daily treatments.

Other recommendations offer specifics about target and tissue volumes, dosing, margin definitions and methods for administering fractions. Imageguided radiation therapy is universally recommended.

Broader perspective

"As you know, this is a moving target," Sandler said of hypofractionated external beam radiation therapy for prostate cancer. "Studies are ongoing right now, testing these schedules in various patient populations, including intermediate- and high-risk patients. The results of those studies were not available when we put this document together, but I suspect we will need to revise them at some point."

Horwitz offered one more general caveat about hypofractionation.

"Men with big prostates who urinate a lot — and this has nothing to do with their cancer — are not good candidates for hypofractionation," he said. "They are technically candidates, but this symptom of frequent urination will get worse with this process."

The guidelines can be put into practice immediately, Sandler said.

"The pace of medical research is dynamic, and certainly subject to change," Sandler said. "What we have offered is a good signpost along the road, based on the best information at this time. We expect that as the word spreads of hypofractionation, it will become more widely used." — by Rob Volansky

For more information:

Eric M. Horwitz , MD, can be reached at Fox Chase Cancer Center, 333 Cottman Ave., Philadelphia, PA 19111; email: eric.horwitz@fccc.edu. Howard Sandler, MD, MS, can be reached at Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles, CA 90048; email: howard.sandler@cshs.org.

Disclosures: Sandler reports stock and other ownership interests in Advanced Bioinformatics, consultant or advisory roles with Blue Earth Diagnostics, Dendreon, Ferring and Janssen, and a relationship with Caribou Publishing. Horwitz reports no relevant financial disclosures.

https://jamanetwork.com/journals/jamaoncology/article-abstract/2705604

November 14, 2018

https://www.healio.com/hematology-oncology/prostate-cancer/news/in-the-journals/%7Bcb812c62-3506-4c37-a948-3dde59b6f297%7D/guideline-supports-shorter-radiation-therapy-option-in-prostate-cancer

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"You Can Help Spread The Word About Prostate Cancer"

Prostate cancer is one of the most common cancers in men. Discovered early, it can be successfully treated in the majority of cases. Such early discovery is dependent on men being aware of the facts about this disease and getting checked. *Early discovery saves lives.*

To help raise awareness and encourage "getting checked" the Manitoba Prostate Cancer Support Group is happy to provide speakers to make presentations to interested groups in the community. There is no charge for this service and the size of the group doesn't matter. If you are involved with a group that would like to learn more about prostate cancer, and perhaps save some lives in the process, please contact Pat Feschuk (tel: 204-654-3898; email: lizpat@shaw.ca). *Remember that if a man has prostate cancer the sooner he learns about it the better. Not knowing about it simply allows it to grow and spread.* **So do something about it** ….. help spread the word.

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FUTURE MEETINGS 2019

20 Feb. Speaker: **Jonathan Doherty** (Delta 9 Cannabis)
Title: *"Cannabis 101: An introduction to cannabis as medicine"*

20 Mar. Speaker: **Dr. Sabine Mai** (BSc, MSc, PhD**)**
Topic: Research progress towards improved therapy for prostate cancer

17 Apr. Speaker: **Jennifer McLaren** (Reh-Fit Centre)
Topic: Moving forward after prostate cancer

All meetings (except September) will be held at :
The First Unitarian Universalist Church of Winnipeg, 603 Wellington Crescent

All meetings are 7 – 9 pm.
(First hour for general discussion;
second hour for expert guest speaker)

Everyone Welcome Plenty of free parking

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