MedicalXpress

Gene test picks out prostate cancers that could respond to 'search-and-destroy' medicine

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Testing for genetic weaknesses in repairing DNA could pick out men who may benefit from a new type of targeted nuclear medicine, a new study reports.

An emerging class of drugs are made up of a radioactive particle that can kill cells attached to a 'homing device' to seek out cancers by detecting the presence of a target molecule on their surface.

These new 'search-and-destroy' treatments are starting to show promise even in men with prostate cancer for whom targeted treatments and chemotherapies have stopped working—but not all patients respond.

In the new study, scientists at The Institute of Cancer Research, London, found that testing men for faults in DNA repair genes in their tumours could identify those most likely to respond to the new type of treatment.

The study is published in the journal *European Urology* today (Tuesday), and was funded by the Movember Foundation, Prostate Cancer UK, Cancer Research UK and the Prostate Cancer Foundation.

The researchers analysed tumour samples from men with advanced prostate cancer who had been treated at The Royal Marsden NHS Foundation Trust, in order to try to understand why the response to search-and-destroy treatment varied.

They found that the target for these new treatments—a protein molecule called prostate-specific membrane antigen, or PSMA—was present at higher levels on the surface of cancer cells in some patients than others. PSMA levels even varied substantially between different cancer sites in the same patient.

But crucially, the amount of PSMA on the surface of cancer cells was more than four times higher in tumours where there were also faults in DNA repair genes.

That means that testing for genetic faults in DNA repair genes could be used as a first-stage screen to select patients for PSMA-targeted treatment—followed by having tumours scanned using PSMA imaging technology.

The researchers believe that PSMA plays a key role in keeping the genome in cells stable—and could be produced by tumours as a survival mechanism where they are defective in repairing their DNA. This could explain the link between DNA repair faults and high levels of PSMA.

These findings also suggest that combination therapy with other drugs that increase genetic instability could make prostate tumours more likely to respond to PSMA-targeting treatments.

Next, the researchers aim to assess whether testing for DNA repair faults can effectively target search-and-destroy treatment as part of clinical trials, and to explore combination strategies to see if the response to these treatments could be heightened.

Precise targeting of cancer cells and use of drug combinations are among a range of strategies being pursued at The Institute of Cancer Research (ICR) through its new Centre for Cancer Drug Discovery.

The ICR—a charity and research institute—is raising the final £15 million of a £75 million investment in the Centre for Cancer Drug Discovery, to create new 'anti-evolution' treatments that can overcome drug resistance.

Professor Johann de Bono, Regius Professor of Cancer Research at The Institute of Cancer Research, London, and Consultant Medical Oncologist at The Royal Marsden NHS Foundation Trust, said:

"Our new study helps to explain why some patients respond to search-and-destroy treatments and others don't. Understanding the biology of response to these new treatments is critical to getting them into use in the clinic as soon as possible.

"We found that testing for DNA repair defects was a good indication of which tumours had high levels of PSMA—and so would be expected to respond to these PSMA-targeted therapies. We will need to further assess the use of DNA tests to target these treatments effectively in routine care, but we can already now start to take into account DNA repair faults in our design of clinical trials."

Professor Paul Workman, Chief Executive of The Institute of Cancer Research, London, said:

"PSMA-targeting drugs are an exciting new wave of treatments coming through for prostate cancer. They combine a potent nuclear medicine with a 'homing signal' that searches out prostate cancer cells.

"To get these new drugs into the clinic, we need a good understanding of the biology of the treatment response and how to spot those patients who will most benefit. This new study gives us an important handle on how to select men for treatment.

"Innovative new treatment strategies such as PSMA-targeting drugs are one of the ways in which we can start to overcome the challenge of cancer evolution and drug resistance—which will be the focus of the pioneering work in our new Centre for Cancer Drug Discovery."

More information: Alec Paschalis et al, Prostate-specific Membrane Antigen Heterogeneity and DNA Repair Defects in Prostate Cancer, *European Urology* (2019). DOI: 10.1016/j.eururo.2019.06.030

Provided by Institute of Cancer Research