Immunotherapy could offer hope for some men with aggressive prostate cancers

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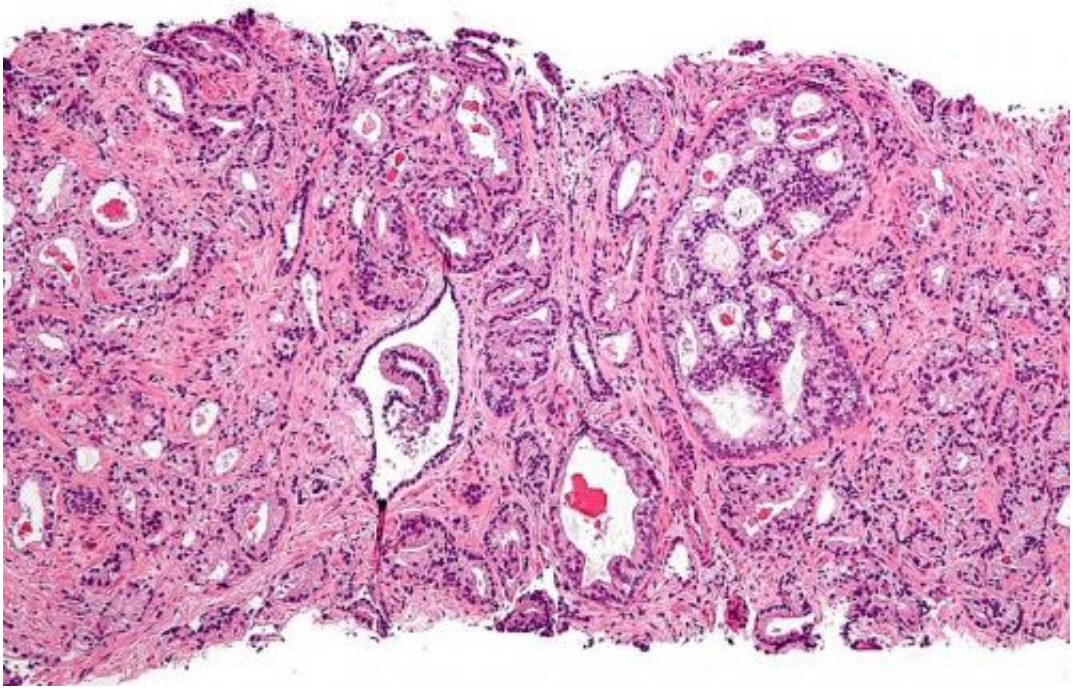

Micrograph showing prostatic acinar adenocarcinoma (the most common form of prostate cancer) Credit: Wikipedia, CC BY-SA 3.0

A group of men with especially aggressive prostate cancer may respond unusually well to immunotherapy, a major new study reports.

The research offers the possibility of effective treatment for men with prostate cancer who currently die from their disease much more rapidly than other patients – with clinical trials already starting.

An international team led by scientists at The Institute of Cancer Research, London, and the Dana-Farber Cancer Institute in the US showed why some men with advanced prostate cancer have much worse survival than others.

Their research found that men with prostate cancer who have specific faults in their tumours that make their DNA error-prone and unstable survive only half as long as other men with advanced disease.

And the findings have exciting implications for treatment – with the researchers showing that these unstable tumours are more likely to stimulate an immune response than other cancers. That should make patients with these aggressive prostate cancers particularly good candidates for immunotherapy.

The new study, published in the *Journal of Clinical Investigation*, looked at 127 tumour biopsies from 124 patients and genomic information from a further 254 patients acquired by the Prostate Cancer Foundation/Stand Up to Cancer International Prostate Cancer Dream Team.

The research was funded by the Prostate Cancer Foundation, Movember Foundation, Prostate Cancer UK, Stand Up to Cancer, V Foundation, the Stewart J. Rahr Foundation, Cancer Research UK, the Experimental Cancer Medicine Centre and NIHR Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research (ICR).

The team found that 8.1 per cent of men with advanced prostate cancer had evidence of mismatch repair mutations in their tumours.

These men survived only 3.8 years after beginning prostate cancer treatment, compared with 7.0 years for men with advanced disease with no detectable mismatch repair defects.

Cancers with 'mismatch repair' gene mutations can't correct single-letter mistakes in their DNA code properly and so are genetically unstable.

They acquire more and more mutations as they grow and rapidly evolve drug resistance – which is why new treatment approaches are so badly needed.

But the researchers suspected these ultra-mutant cancer cells might be particularly easy for the immune system to recognise, since they will look different from healthy cells.

They looked at the levels of a protein called PD-L1 on the surface of cancer cells as a way of indicating the likely response to checkpoint inhibitor immunotherapy.

Targeting PDL-1 activity with an immune checkpoint inhibitor takes the 'brakes' off the immune system, setting it free to attack cancer cells.

The researchers found that half of tumours with mismatch repair mutations had high levels of PD-L1, compared with only 9.8 per cent without these mutations – making men with these tumours much more likely to benefit from a checkpoint inhibitor drug.

They also found that over half of tumours with mismatch repair mutations had been invaded by T cells from the patient's immune system – another indicator that immunotherapy may well be effective.

The researchers are now developing tests to identify men with mismatch repair mutations in their tumours.

Based on these results, new clinical trials led by The Institute of Cancer Research (ICR) and The Royal Marsden are testing the effectiveness of checkpoint inhibitor immunotherapies in this group of patients.

Study leader Professor Johann de Bono, Regius Professor of Cancer Research at The Institute of Cancer Research, London, and Consultant Oncologist at The Royal Marsden NHS Foundation Trust, said, "Our study found that some men with advanced prostate cancers have genomic mutations in their tumours that make the disease unstable, aggressive and resistant to standard therapies. These men with 'mismatch' repair mutations only live about half as long as others who also have advanced prostate cancer but whose tumours don't carry such mutations.

"We made an exciting step forward in working out how to treat men with such aggressive, unstable tumours. We discovered that tumours with mismatch repair mutations have key hallmarks which make them particularly likely to respond to checkpoint inhibitor immunotherapy. We are now developing tests that could pick out patients with these mutations, and we're running new clinical trials to see if immunotherapy can offer new hope for these men."

Professor Paul Workman, Chief Executive of The Institute of Cancer Research, London, said, "We are seeing a revolution in cancer treatment as immunotherapy becomes an important option for many types of the disease.

"Immunotherapy is an unusual treatment in working best in cancers that have a lot of mutations. Prostate cancers normally tend to have fewer mutations than other cancer types, which may be why immunotherapy has so far only been successful in a small minority of patients.

"This new study is exciting in providing a way to pick out those men with prostate cancer who have the most aggressive, unstable disease and the worst survival – but who conversely might be the best responders to immunotherapy. It will be fascinating to see whether we can translate the theory into practice in the new clinical trials to test out immunotherapy

in men with genetically unstable tumours."

Howard Soule, Ph.D., executive vice president and chief science officer of the Prostate Cancer Foundation, said, "This important study informs identification of prostate cancer patients whose disease is likely to respond to treatment with immune checkpoint inhibitors. We applaud the achievement of this international research team which has been funded by the Prostate Cancer Foundation, the V Foundation, and the Stewart J. Rahr Foundation."

More information: More information about one of the clinical trials can be found here: clinicaltrials.gov/ct2/show/NC … cond=prostate&rank=1

Daniel Nava Rodrigues et al. Immunogenomic analyses associate immunological alterations with mismatch repair defects in prostate cancer, *Journal of Clinical Investigation* (2018). DOI: 10.1172/JCI121924

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