Genetic changes in tumours could help predict if patients will respond to immunotherapy

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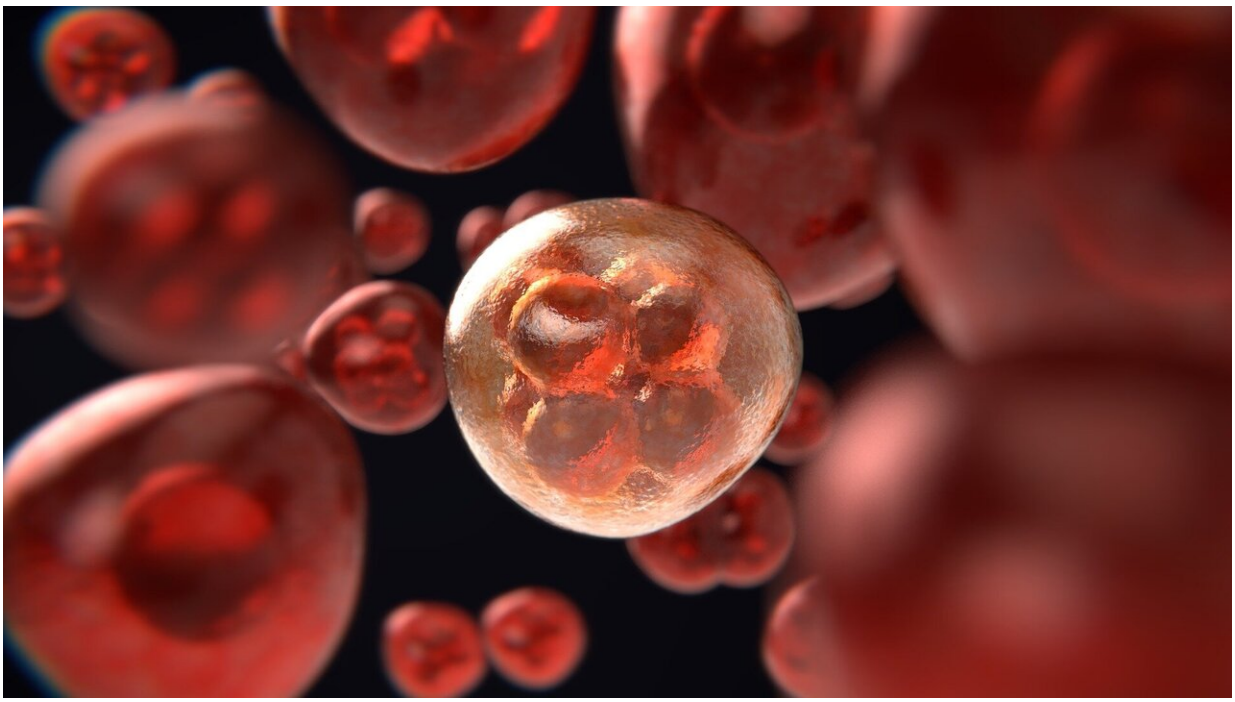

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Researchers at the Francis Crick Institute, the UCL Cancer Institute, and the Cancer Research UK Lung Cancer Centre of Excellence have identified genetic changes in tumors which could be used to predict if immunotherapy drugs would be effective in individual patients.

Immunotherapies have led to huge progress treating certain types of cancer, but only a subset of patients respond, and hence a challenge for doctors and researchers is understanding why they work in some people and not others, and predicting who will respond well to treatment.

In their paper, published in *Cell* today (27 January), the scientists looked for genetic and gene expression changes in tumors in over 1,000 patients being treated with checkpoint inhibitors, a type of immunotherapy which stops cancer cells from switching off the body's immune response.

They found that the total number of genetic mutations which are present in every cancer cell in a patient was the best predictor for tumor response to immunotherapy. The more mutations present in every tumor cell, the more likely they were to work. In addition, expression of gene CXCL9 was found to be a critical driver of an effective anti-tumor immune response.

The researchers also looked at the cases where checkpoint inhibitors had not been effective. For example, having more copies of a gene called CCND1 was linked to tumors being resistant to checkpoint inhibitors. More research is needed, but the scientists suggest that patients with this mutation in their tumors may benefit more from alternative drug treatment options.

Kevin Litchfield, co-lead author, visiting scientist at the Crick and group leader of the Tumor Immunogenomics and Immunosurveillance lab at UCL says: "This is the largest study of its kind, analyzing genetic and gene expression data from across seven types of cancer and over a thousand people.

"It has enabled us to pinpoint the specific genetic factors which determine tumor response to immunotherapy, and combine them into a predictive test to identify which patients are most likely to benefit from

therapy. Furthermore, it has improved our biological understanding of how immunotherapy works, which is vital for the design and development of new improved immunotherapeutic drugs."

The researchers are now working with clinical partners in Denmark to see if their test correctly identifies the patients who will or will not respond to checkpoint inhibitors and if this is more accurate than tests currently available.

Charles Swanton, chief clinician at Cancer Research UK and group leader at the Crick and UCL says and a lead author of the study: "Checkpoint inhibitors are really valuable in treating a number of cancers, including skin and lung cancers. But sadly, they do not always work and they can also sometimes cause severe side effects.

"If doctors have an accurate test, that tells them whether these drugs are likely to be effective in each individual patient, they will be able to make more informed treatment decisions. Crucially, they will be able to more quickly look for other options for patients who these drugs are unlikely to help."

Michelle Mitchell, chief executive of Cancer Research UK, says: "One of the main roadblocks preventing us from unleashing the full potential of immunotherapies is that we don't fully understand how these drugs work, or why this type of treatment doesn't benefit everyone. And we still can't fully predict who will respond to these expensive treatments.

"This new research has furthered our understanding around these issues, revealing new drug development tactics and approaches to treatment. It's fantastic to think of a future where we give patients a simple test before they start their immunotherapy to find out if this is the right course of treatment for them. This not only will spare patients from taking needless treatment and enduring serious side effects that might come

with it, but it could also save the NHS treatment costs."

The work was partly funded by Cancer Research UK, the Royal Society, the Wellcome Trust, the Medical Research Council and Rosetrees Trust, among others.

More information: Kevin Litchfield et al, Meta-analysis of tumor- and T cell-intrinsic mechanisms of sensitization to checkpoint inhibition, *Cell* (2021). DOI: 10.1016/j.cell.2021.01.002

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