Advanced bowel cancers have very few molecular flags, hindering immune recognition

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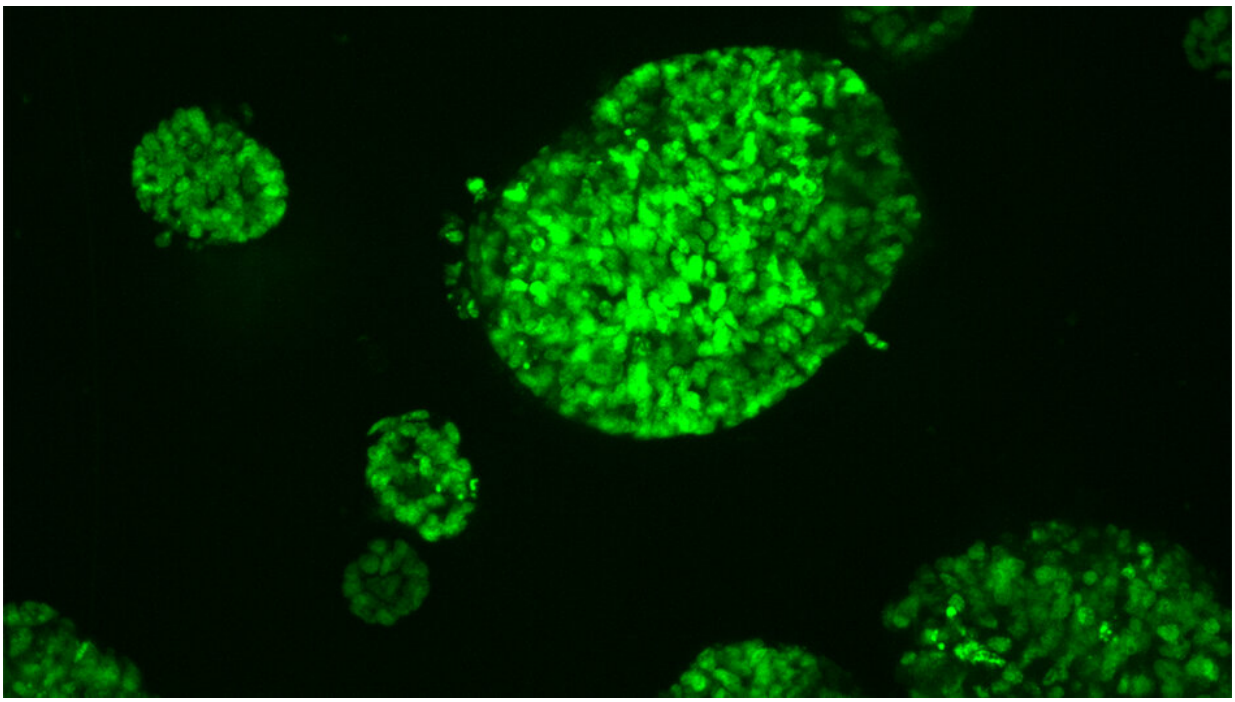

Mini tumours grown from a bowel cancer. Credit: Maria Semiannikova/ICR

Advanced bowel cancer cells have very few "molecular flags" on their surface, helping to explain why they may be hard for the immune system to detect, a new study has shown.

Molecules on the surface of tumor cells, arising from faults in their DNA, help the immune system pick them out as cancerous—enabling immune cells to selectively kill tumor cells, but to leave the body's own cells alone.

The number of different kinds of these molecular flags in a cancer has typically been estimated using computer predictions based on the number of gene faults in cancer cells.

The range of different molecular flags on cancer cells, known as neoantigens, is used to predict how well a patient might respond to immunotherapy, or to design personalised immunotherapy "vaccines."

Far fewer neoantigens than expected

But the new study found that bowel cancer cells have far fewer neoantigens than suggested by computer predictions, offering a possible explanation as to why immunotherapies have so far not worked well in the majority of advanced bowel cancers.

The new insights could help to predict response to immunotherapy which takes the brakes off the body's own immune system. They could also enable the design of more effective personalized vaccines against a person's tumor.

Scientists at The Institute of Cancer Research, London, working with colleagues at the Ludwig Institute for Cancer Research in Lausanne, Switzerland, developed a new way to analyze neoantigens on cancer cells using mini-tumors.

They looked at five mini-tumors grown from patient samples, which together contained 612 faults in genes that could potentially result in a neoantigen.

They only detected three different neoantigens across all the gene faults in the five mini-tumors, a fraction of the number expected from the computer predictions.

New way of growing 3-D mini-tumors

The study, published in the *Journal for ImmunoTherapy for Cancer* today (Monday), was supported by funders including Cancer Research UK, the Wellcome Trust and the European Research Council.

The new study is the first to have managed to directly measure the number of neoantigens on the surface of cancer cells in mini-tumors grown from patients, using a technique called mass spectrometry.

The team developed a new way of growing large numbers of mini-tumors from patient tumor samples, so that they could analyze more than 100 million cancer cells.

The large number of cancer cells in the mini-tumors, without contamination from other cell types—which is an issue when looking at samples taken directly from patients—allowed the researchers to better analyze the number of neoantigens in detail.

They also tested if the number of neoantigens on the surface of cancer cells could be boosted by treating the mini-tumors with an immune signaling molecule, interferon gamma, and the targeted drug, trametinib.

Earlier studies had suggested interferon gamma and trametinib could increase the diversity of presented neoantigens, but the researchers found no such effect.

Challenges in improving immunotherapy response

This shows that the new technique enables the researchers to directly measure the neoantigens rather than having to rely on computer predictions, offering a closer look at the landscape of the molecular flags on tumor cells.

After further validating their technique, the researchers plan to study new ways of boosting the diversity of neoantigens on cancer cell surfaces, and to explore the design of personalized vaccines tailored to a tumor's specific neoantigens.

Dr. Marco Gerlinger, Team Leader in Translational Oncogenomics at the ICR, and Consultant Medical Oncologist at The Royal Marsden NHS Foundation Trust, said:

"Immunotherapies are starting to show promise for some people with advanced bowel cancer—but there is still a majority of patients for whom these exciting new treatments don't work.

"We found that some patients only have very small numbers of molecular flags on the surface of their cancer cells, which help the body's own immune system spot and kill them.

"Our findings shed new light on the challenges we face in improving the response to immunotherapy, so more people with advanced bowel cancer could benefit. In future, our work could pave the way for personalized vaccines tailored to the specific molecular flags on the surface of each person's tumor cells."

More information: Alice Newey et al. Immunopeptidomics of colorectal cancer organoids reveals a sparse HLA class I neoantigen landscape and no increase in neoantigens with interferon or MEK-inhibitor treatment, *Journal for ImmunoTherapy of Cancer* (2019). DOI: 10.1186/s40425-019-0769-8

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