Scientists find that the way tumours grow impacts their genetics

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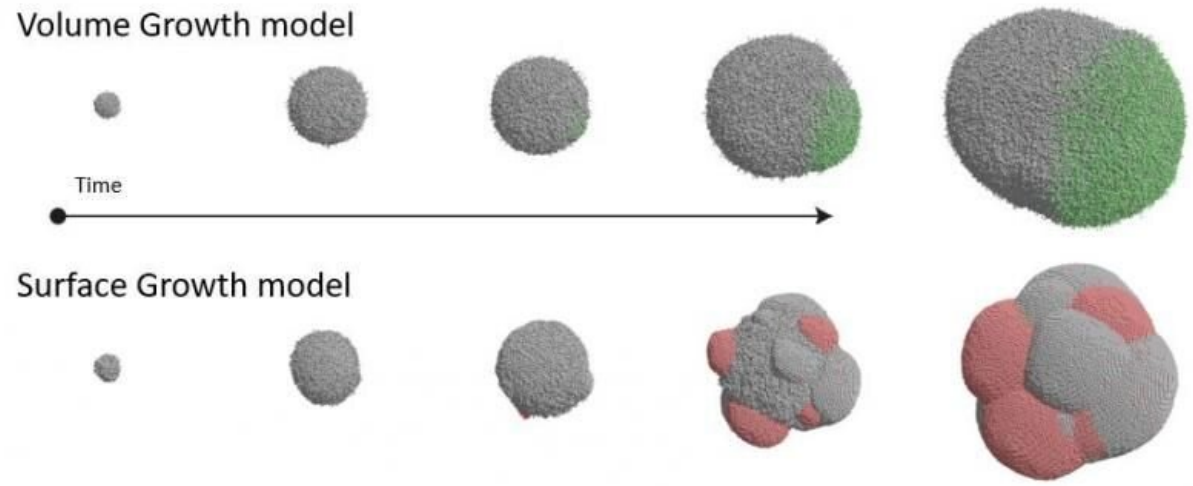

Representative in-silico tumours under Volume Growth model (top) and Surface Growth model (bottom). Credit: The Francis Crick Institute

Researchers at the Francis Crick Institute, UCL, The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London have developed a computer model to analyze how the way in which tumors grow affects their genetic makeup.

Using this new model, they have identified links between tumor growth and shape, and how quickly a patient's cancer might progress.

As cancer cells mutate, some gain an advantage through mutations which make them more likely to survive, divide and create a group of 'fitter' cells. This group may outcompete others to become dominant, for example, if they have evolved to survive in conditions where there is a low supply of nutrients or oxygen.

This process of tumor evolution is highly complex and is impacted by many factors, including how the tumor is growing. But it is not fully understood.

In their study, published in *Nature Ecology and Evolution*, the scientists used their computer model to study two types of tumor growth in kidney cancers: one where growth is consistent throughout the tumor, the 'volume growth model' and one where growth is restricted to the surface, the 'surface growth model'.

Two scenarios occurred in the volume growth model. In some cases, a single 'fit' group of genetically related cancer cells arose in the tumor at an early stage. In others, the tumors did not develop a new 'fit' group but rather the original group of parental cancer cells remained dominant.

In the surface growth model, there was extensive genetic diversity with different groups of 'fit' cells forming on the surface. The team suggest that this creates a competitive environment where different groups of cells are pushed to evolve more rapidly.

Xiao Fu, first author and postdoctoral training fellow in the Biomolecular Modelling lab at the Crick says that they've "taken two distinct growth models and identified stark differences in how tumors evolve over time and in space. This is difficult to do with real tissue as it requires repeatedly taking multiple biopsies from various parts of a tumor. These findings are just the start of what we hope to uncover with this model."

The researchers validated their model using data from 66 tumors analyzed through the TRACERx Renal study. By cross-referencing the model and this tumor data, they found that different rates of real-world tumor progression corresponded with different growth models. For example, tumors which rapidly progressed fitted with the volume growth model where one 'fit' group of cells was present from early on. While cases which did not progress fitted with the volume growth model where the parental group of cells remained dominant.

The model also provided insights into how different types of growth impact the shape of tumors. Volume growth tumors grew outwards in a more consistent shape, while surface growth tumors showed bulges on the surface, where the 'fitter' groups were growing.

Xiao adds that "what's exciting is how this structural information could be used as a window into the evolution of a tumor. More research is needed but it could be used to help determine what sort of growth a tumor is undergoing, for example, if radiological imaging of an early tumor shows bulges this means it's more likely to be undergoing surface growth. This information could help inform medical teams and treatment decisions."

The researchers also used their model to analyze the impact of necrosis, the death of tissue within the tumor, on its evolution. When necrosis was present under the surface growth model, the tumors quickly developed more 'fit' groups of genetically distinct cells.

Paul Bates, paper author and group leader of the Biomolecular Modelling lab at the Crick says that "computer simulations are extremely valuable in further our understanding of how tumors evolve over time. By developing these models and using them to analyze how cancers change, we hope to find periods in their evolution and growth where the cancer may be most vulnerable to treatments."

Samra Turajlic, author and group leader of the Crick's Cancer Dynamics Laboratory and consultant oncologist at The Royal Marsden NHS Foundation Trust, said that "the most important observations regarding cancer behavior are gleaned through analyses of patients' tumors because they reflect the time-scales and complexities of actual cancer evolution. However, every instance of cancer evolution in a patient is unique, cannot be rewound, and repeated, making it hard to predict how likely tumors are to go down certain paths.

"This is where mathematical modeling can be a powerful tool to help us understand how the patterns we observe in real tumors come about. Informed mathematical models combined with detailed clinical, molecular, histological and radiological data from real-life tumors can bring about critical insights that will translate into patient benefit."

Erik Sahai, author and group leader of the Tumor Cell Biology Laboratory at the Crick says that "technological advances mean that we now have more information than ever before about individual cancers, the challenge is to decode this for patient benefit. This requires highly talented people who can work across disciplines, engaging with both clinicians and 'basic' researchers. The set-up of the Crick enables and encourages these interactions, and it is gratifying to see the dividends in work like this."

The researchers will continue developing their model and using it to better understand tumor evolution.

More information: Xiao Fu et al, Spatial patterns of tumour growth impact clonal diversification in a computational model and the TRACERx Renal study, *Nature Ecology & Evolution* (2021). DOI: 10.1038/s41559-021-01586-x

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