Cells from the centre of tumours most likely to spread around the body

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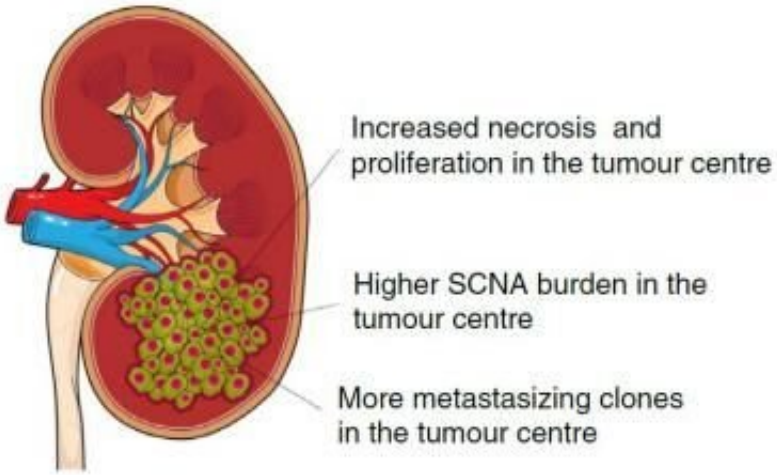

Cartoon summarizing the differences observed between tumor center and tumor margin, which might be explained by differences in blood supply to different parts of the tumor.

Researchers from the Francis Crick Institute, Royal Marsden, UCL and Cruces University Hospital have found that cells from different parts of kidney tumors behave differently, and surprisingly, cells within the center of a tumor are the most aggressive and have the highest chance of spreading around the body.

Cancers can spread to other parts of the body, with cells taking hold as secondary tumors which make the disease much harder to treat. Understanding the mechanics of this spread, a process called metastasis,

could lead to new treatments that block this migration.

In their multidisciplinary study published today (17 May) in *Nature Ecology and Evolution*, scientists led by the Litchfield lab at UCL and the Turajlic, Swanton, and Bates labs at the Crick, analyzed 756 cancer biopsy samples from different regions within tumors from the TRACERx Renal study.

They found that cells at the center of tumors have a less stable genome and a higher potential to spread to secondary sites around the body. By contrast cells at the tumor edge had lower rates of metastasis, as well as lower rates of growth and genetic damage.

"Cancer cells in the central zone of the tumor face harsh environmental conditions, as there's a lack of blood supply and oxygen. They have to adapt to survive, which makes them stronger and more aggressive. This also means they are more likely to successfully evolve into cells that can disseminate and take hold in distant organs," says Kevin Litchfield, paper author and group leader at the UCL Cancer Institute.

The results highlight a need to pay close attention to the tumor center to understand how cancer spreads and to find the cancer cells of greatest threat to the patient. It also shows the importance of developing treatments that target the unique environmental conditions found within the tumor core, in order to successfully eliminate the most aggressive tumor cells.

The scientists also looked at how genetically different populations of cancer cells grow within a tumor. Using a unique map building tool to reconstruct the growth of tumor cells, they found that, while most tumors follow a pattern where populations of cells grow in the local area —like a plant growing up and outwards—two cases demonstrated a "jumping" pattern where cells took hold in a new region of the tumor by

seemingly 'jumping' over other populations of tumor cells.

The researchers are now planning to reconstruct 3D tumor maps, which will provide an even clearer visualization of the spatial patterns within tumors.

Samra Turajlic, head of the Crick's Cancer Dynamics Laboratory, Consultant Medical Oncologist at the Royal Marsden NHS Foundation Trust and the Chief Investigator of TRACERx Renal, said: "Cancer spread is one of the biggest barriers to improving survival rates. In the context of the TRACERx Renal study we previously resolved the genetic make up of different tumor areas, but until now, there has been no understanding of how these differences relate spatially. The most critical question is the part of the tumor from which cancer cells break away and migrate making cancer incurable.

"Using this unique clinical cohort and a multidisciplinary approach, including mathematical modeling, we identified with precision the place in the tumor where genetic chaos emerges to give rise to metastases. Our observations shed light on the sort of environmental conditions that would foster emergence of aggressive behavior. These findings are a critical foundation for considering how we target or even prevent distinct populations of cells that pose the biggest threat."

More information: Zhao, Y., Fu, X., Lopez, J.I. et al. Selection of metastasis competent subclones in the tumour interior. *Nature Ecology and Evolution* (2021). DOI: 10.1038/s41559-021-01456-6

Provided by The Francis Crick Institute

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