Why the presence of healthy cells enables cancer to resist treatment

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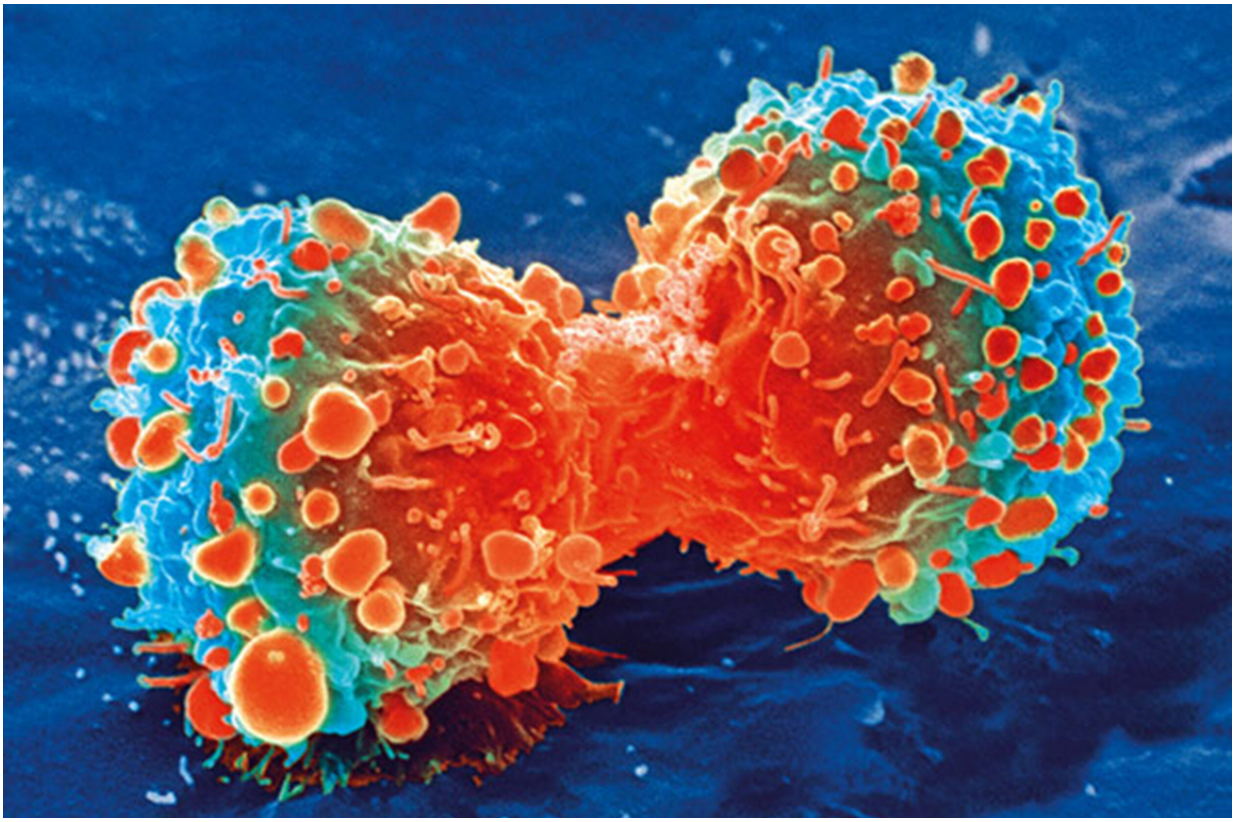

Cancer cell during cell division. Credit: National Institutes of Health

Chemotherapy becomes less effective because healthy cells push cancer cells to grow more slowly, according to two studies from researchers at UCL and Yale.

In the two studies published in *Cell*, researchers used 'mini-tumors' and the latest single-cell analysis technologies to begin to solve the puzzle of why healthy cells in a patient's bowel cancer tumor might lead to poor outcomes.

Bowel cancer kills over 900,000 people a year and is the second highest cause of cancer mortality worldwide. In the UK, it accounts for 10% of all cancer deaths.

In the first study, UCL researchers used the latest single-cell analysis technologies to measure how 1,107 mini-tumors derived from mice responded to changes in both their genes and their environment.

Analysis revealed that bowel cancer cells can exist in two major states, fast-growing or slow-growing, and that healthy cells can push bowel cancer cells towards the slow-growing state. Because chemotherapies target fast-growing cells, these slow-growing cancer cells are more likely to be resistant to treatment.

Dr. Chris Tape, a senior author of the studies from UCL Cancer Institute, said, "Recent research has shown that bowel cancer patients with more healthy cells in their tumor, including cells called fibroblasts that are involved in wound healing, often have a poor prognosis. But what we didn't know until now was why this is the case. Our research suggests that because chemotherapies target fast-growing cells, cancer cells that have their growth slowed down by healthy cells are no longer sensitive to chemotherapy."

In the second study, the team sought to confirm their findings in human cells, using over 2,500 mini-tumors grown from donated tissue from bowel cancer patients who had undergone surgery.

Results showed that factors such as patient age and the specific

mutations a tumor carried did not affect how the cancer responded to chemotherapy. The key factor was how fast-growing the cancer was. Crucially, healthy fibroblast cells could slow down cancer growth in some patients, completely protecting the cancer from chemotherapy.

Dr. Maria Ramos Zapatero, a first author on one of the studies from UCL Cancer Institute, said, "The slow-growing state that we observed in these bowel cancers is very unusual and normally only found during fetal development or following intestinal tissue damage. The presence of fibroblasts in healthy tissue seems to stimulate the cancer cells to enter a defensive state, which protects them from chemotherapy."

"This happens really quickly, often within a couple of hours, so it's easy to see why treatment fails to work. The cancer cells suffer damage, but they don't die."

Professor Smita Krishnaswamy, a senior author of one of the studies from Yale University, said, "There has been a lot of research in recent years to understand what is happening in cancer cells and in the surrounding environment at the single-cell level. But previously technical limitations meant we could only analyze a handful of different scenarios at a time. This is a problem when you're dealing with thousands of variables, including cancer cells with different mutations, different therapies and the complex interaction between tumors and the cells around them."

"The mass cytometry workflow and our new computational method, called TRELLIS, creates a way of embedding samples from cytometry in such a way that distances between entire samples can be computed, allowing us to map the landscape of different cancers under various treatment and culture conditions. These technical advances have allowed us to see the big picture and help to explain why some cancers are less sensitive to treatment."

The authors say that finding ways to force cancer cells into a fast-growing state prior to a patient beginning a course of chemotherapy may be able to make the treatment more effective.

Dr. Tape concluded saying, "By understanding the molecular processes driving this change, we may be able to develop ways to block communication between cancer cells and healthy cells in order to return the tumor to the fast-growing state, making the cancer sensitive to chemotherapies even in the presence of healthy cells. I think we now have a huge opportunity to improve outcomes for those whose bowel cancer is not or would not be easy to treat."

More information: Xiao Qin and Ferran Cardoso Rodriguez et al, An Oncogenic Phenoscape of Colonic Stem Cell Polarisation, *Cell* (2023). DOI: 10.1016/j.cell.2023.11.004. www.cell.com/cell/fulltext/S0092-8674(23)01221-7

María Ramos Zapatero et al, Trellis tree-based analysis reveals stromal regulation of patient-derived organoid drug responses, *Cell* (2023). DOI: 10.1016/j.cell.2023.11.005

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