Cooperation between cancer cells makes therapies ineffective, suggests new treatment

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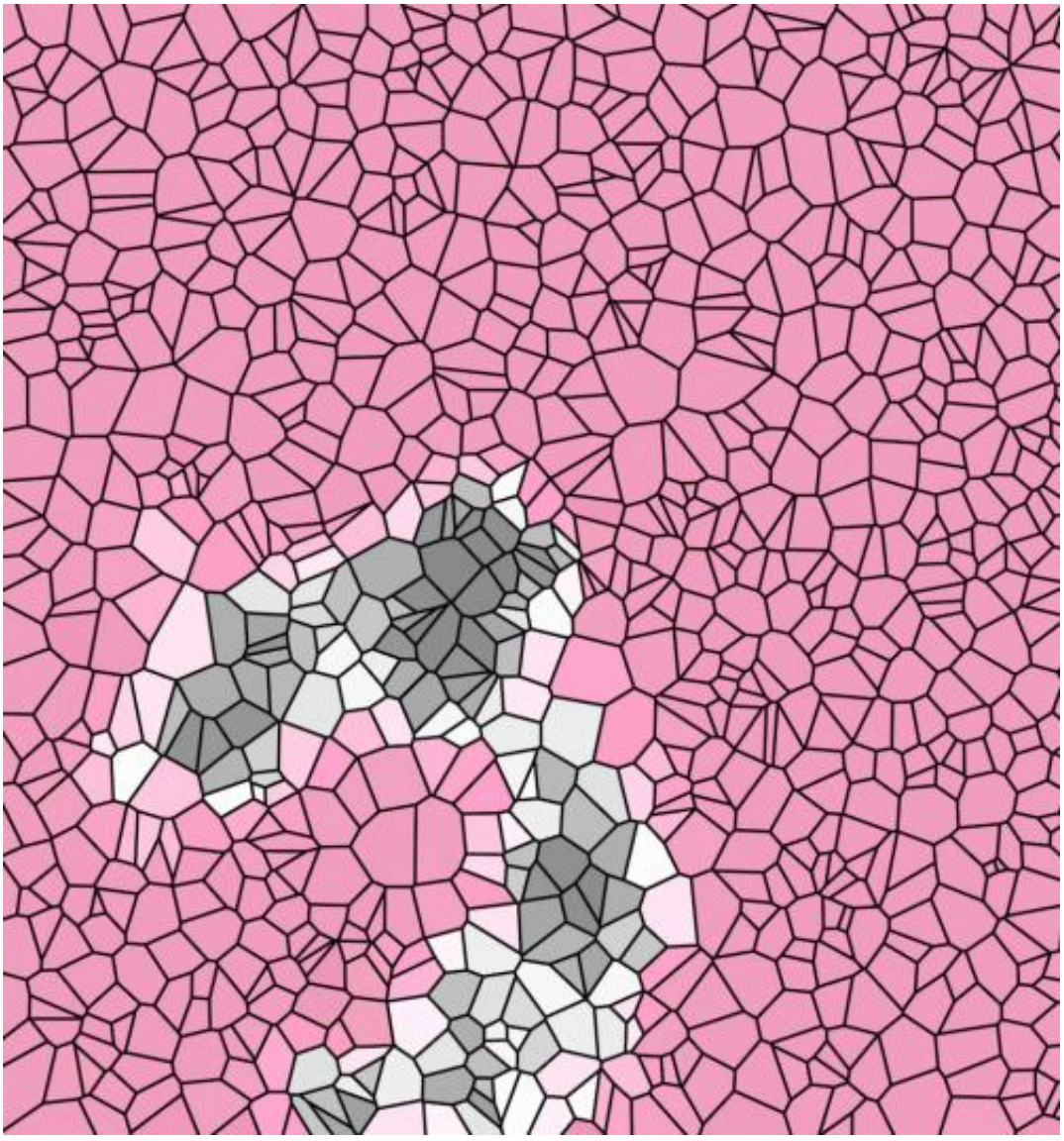

Cancer cells in vitro form networks like the one pictured here, in which cells not only compete for space and resources, but also cooperate by sharing diffusible

growth factors. Cells that do not produce growth factors, however, can free-ride on the factors produced by their neighbours, forming clusters of non-cooperative cells (dark areas) that can lead to stable intra-tumor heterogeneity. This research shows how the dynamics of growth factor production in monolayers of cells can be understood using evolutionary game theory. Credit: University of East Anglia

Cooperation between cancer cells makes current therapies ineffective but also suggests new treatment

Researchers at the University of East Anglia have made an important step in understanding why many cancers are difficult to treat and come back following treatment.

They have shown that cancer cells cooperate with each other in the production of growth factors, diffusible molecules produced by the cancer cells that are essential for tumour progression.

The findings, published today in the journal *PNAS*, help to explain why therapies that target growth factors are prone to the evolution of resistance and why relapses happen after treatment.

It is hoped that the findings will lead to a new type of treatment involving genetically modified cancer cells being reinserted into a tumour.

Lead researcher Dr Marco Archetti, from UEA's School of Biological Sciences said: "The cancerous cells that make up a tumour often show different profiles - for example in their shape and appearance, in the genes they express, or their potential to spread to other parts of the body. This is called tumour heterogeneity, and these differences make cancer diagnosis and treatment difficult.

"It is not clear why heterogeneity exists, but understanding its origin and dynamics is essential for treating cancer."

The research team studied pancreatic cancer cells in the lab and used mathematical models to show why heterogeneity persists within a tumour.

"We have shown that cancer cells cooperate with each other. A tumour is a group of cells that have an advantage against normal cells, due to the fact that cancer cells produce their own molecules that stimulate growth - known as growth factors. We have shown that cancer cells that do not produce growth factors can 'free-ride' on the growth factors produced by other cooperative cancer cells. The two types - co-operators and free-riders - can form a heterogeneous tumour under certain circumstances.

"Cancer is an evolutionary process of selection among cells on the timescale of an individual's lifetime, and when a drug modifies the amount of available growth factors it also make the tumour evolve. A heterogeneous tumour can easily adapt to changing amounts of growth factors, which is why current therapies against cancer are unstable and why relapses happen post treatment."

As well as studying pancreatic cancer cells, researchers repeated their experiments with other cancer types. They are currently screening a large number of cancer types and growth factors.

Dr Archetti's team is now working towards a new kind of cell therapy. They plan to genetically modify cancer cells by removing the genes which control the production of growth factors. They will then reinsert these modified cells into the tumour.

Laboratory experiments show that, under the right conditions, these modified cells spread like a tumour within the tumour, driving the

original, cooperative cells to extinction - instead of leading to heterogeneity. This would cause the tumour to collapse because of a lack of growth factors.

More information: 'Heterogeneity for IGF-II production maintained by public goods dynamics in neuroendocrine pancreatic cancer' *PNAS*, January 26, 2015. www.pnas.org/cgi/doi/10.1073/pnas.1414653112

Provided by University of East Anglia