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Scientists identify a new layer of complexity within colon cancer

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Cancer scientists led by Dr. John Dick at the Princess Margaret Cancer Centre have found a way to follow single tumour cells and observe their growth over time. By using special immune-deficient mice to propagate human colorectal cancer, they found that genetic mutations, regarded by many as the chief suspect driving cancer growth, are only one piece of the puzzle. The team discovered that biological factors and cell behaviour – not only genes – drive tumour growth, contributing to therapy failure and relapse.

The findings, published today online ahead of print in *Science*, are "a major conceptual advance in understanding tumour growth and treatment response," says Dr. Dick, who holds a Canada Research Chair in Stem Cell Biology and is a Senior Scientist at University Health Network's McEwen Centre for Regenerative Medicine and Ontario Cancer Institute, the research arm of the Princess Margaret Cancer Centre. He is also a Professor in the Department of Molecular Genetics, University of Toronto. The research work was primarily carried out in Toronto by Antonija Kreso, Catherine O'Brien, and other members of the Dick lab with support from clinician-scientists at Mount Sinai Hospital and at the Ontario Institute for Cancer Research, and from genome scientists at St Jude Research Hospital, Memphis, and the University of Southern California, Los Angeles.

By tracking individual tumour cells, they found that not all cancer cells are equal: only some cancer cells are responsible for keeping the cancer growing. Within this small subset of propagating cancer cells, some kept

the cancer growing for long time periods (up to 500 days of repeated tumour transplantation), while others were transient and stopped within 100 days. They also discovered a class of propagating cancer cells that could lie dormant before being activated. Importantly, the mutated cancer genes were identical for all of these different cell behaviours.

When chemotherapy was given to mice in which the human tumours were growing, the team made the unexpected finding that the long-term propagating cells were generally sensitive to treatment. Instead, the dormant cells were not killed by drug treatment and became activated, causing the tumour to grow again. The cancer cells that survived therapy had the same mutations as the sensitive cancer cells proving that cellular factors not linked to genetic mutation can be responsible for therapy failure.

The research challenges conventional wisdom in the cancer research field that the variable growth properties and resistance to therapy of cancer cells are solely based on the spectrum of genetic mutations within a tumour, says Dr. Dick. Instead, the scientists have validated a developmental view of cancer growth where other biological factors and cell functions outside genetic mutations are very much at play in sustaining disease and contributing to therapy failure.

The research published today builds on decades of experience by Dr. Dick, who focuses on understanding the cellular processes that maintain tumour growth. In 2004, Dr. Dick published related findings in leukaemia, but in the present study his team was able to compare the importance of genetic events with cellular mechanisms for the first time. It is also the first study of its kind in a solid tumour system.

Dr. Dick says the findings convinced him that the conventional view that only explores gene mutations is no longer enough in the quest to accelerate delivery of personalized cancer medicine to patients –

targeted, effective treatments customized for individuals.

"The data show that gene sequencing of tumours to find the spectrum of their mutations is definitely not the whole story when it comes to determining which therapies will be most effective," says Dr. Dick.

"This is a paradigm shift that shows research also needs to focus on the biological properties of cells. For example, finding a way to put dormant cells into growth cycles could make them more sensitive to chemotherapy treatment. Targeting the biology and growth properties of cancer cells could expand the repertoire of usable therapeutic agents and provide better outcomes for patients."

Dr. Dick is renowned for pioneering the cancer stem cell field by identifying leukemia stem cells in 1994 and colon cancer stem cells in 2007. Also in 2011, Dr. Dick isolated the normal human blood stem cell in its purest form – as a single stem cell capable of regenerating the entire blood system. Collectively, Dr. Dick's research is paving the way for better clinical cancer therapy.

More information: "Variable Clonal Repopulation Dynamics Influence Chemotherapy Response in Colorectal Cancer," by A. Kreso; *Science*, 2012

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