Colon cancer researchers target stem cells, discover viable new therapeutic path

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Dr. John Dick, Senior Scientist, Princess Margaret Cancer Centre, and a team of researchers at the Princess Margaret have discovered a new approach to treating colorectal cancer. Credit: UHN

Scientists and surgeons at Princess Margaret Cancer Centre have discovered a promising new approach to treating colorectal cancer by disarming the gene that drives self-renewal in stem cells that are the root cause of disease, resistance to treatment and relapse. Colorectal cancer is the third leading cause of cancer-related death in the Western world.

"This is the first step toward clinically applying the principles of cancer

stem cell biology to control cancer growth and advance the development of durable cures," says principal investigator Dr. John Dick about the findings published online today in *Nature Medicine*.

Dr. Dick pioneered the cancer stem cell field by first identifying leukemia stem cells (1994) and colon cancer stem cells (2007). He is also renowned for isolating a human blood stem cell in its purest form – as a single stem cell capable of regenerating the entire blood system – paving the way for clinical use (2011). Dr. Dick holds a Canada Research Chair in Stem Cell Biology and is a Senior Scientist at University Health Network's Princess Margaret Cancer Centre and McEwen Centre for Regenerative Medicine. He is also a Professor in the Department of Molecular Genetics, University of Toronto, and Director of the Cancer Stem Cell Program at the Ontario Institute for Cancer Research.

In pre-clinical experiments, the research team replicated human colon cancer in mice to determine if specifically targeting the stem cells was clinically relevant. First, the researchers identified that the gene BMI-1, already implicated in maintaining stem cells in other cancers, is the pivotal regulator of colon cancer stem cells and drives the cycle of self-renewal, proliferation and cell survival. Next, the team used an existing small-molecule inhibitor to successfully block BMI-1, thus demonstrating the clinical relevance of this approach.

Lead author Dr. Antonija Kreso writes: "Inhibiting a recognized regulator of self-renewal is an effective approach to control tumor growth, providing strong evidence for the clinical relevance of self-renewal as a biological process for therapeutic targeting."

Dr. Dick explains: "When we blocked the BMI-1 pathway, the stem cells were unable to self-renew, which resulted in long-term and irreversible impairment of tumour growth. In other words, the cancer was

permanently shut down."

Surgeon-scientist Dr. Catherine O'Brien, senior co-author of the study says: "The clinical potential of this research is exciting because it maps a viable way to develop targeted treatment for colon cancer patients. It is already known that about 65% have the BMI-1 biomarker. With the target identified, and a proven way to tackle it, this knowledge could readily translate into first-in-human trials to provide more personalized cancer medicine."

More information: Paper: dx.doi.org/10.1038/nm.3418

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