MDs create human cancer in mouse

Seeded leukemia allows researchers to study progression

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Canadian scientists have grown a human cancer from scratch in a lab mouse -- a feat that, for the first time, allows researchers to see how the disease unfolds from start to finish.

The animal model, which researchers have chased for years, could represent a crucial new tool to learn more about cancer in its earliest stages and potential ways to stop it.

By inserting just one cancerous gene into human stem cells, scientists at Toronto's Princess Margaret Hospital have been able to seed leukemia in specially bred lab mice.

Currently, researchers can engineer mice to develop cancer, but it is the animal form of the disease. They can also implant human cancers into immune-deficient mice, but miss how the disease originates.


Enlarge Image

Scientist John Dick, pictured, is one of the authors of a new report in the journal Science in which researchers detailed the use of stem cells harvested from umbilical cords to grow a blood cancer. *(Fernando Morales/The Globe and Mail)*

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But in the new work, by implanting cancer-tainted human stem cells into mice, the animals developed leukemia in the same way that the disease evolves in people, allowing scientists "to watch" its realistic and deadly progression.

"This isn't a mouse approximation of a human disease, but the actual human disease that we're generating," said John Dick, a senior scientist at Princess Margaret and senior author of the report published today in the journal Science.

"With the method we have developed, we have duplicated the natural process every step of the way."

Scientists expect the stem-cell implant method could lead to growing other human cancers from scratch in lab

animals. And the finding adds another way to test the theory that cancer is the result of normal human stem cells gone awry.

The theory, known as the cancer stem cell hypothesis, holds that not all cancer cells have the same power to sprout and sustain tumours. A growing body of work suggests that only a tiny subset of abnormal stem cells have the ability to keep renewing themselves and grow into the various tissues that make up tumours.

If the evidence bears up, the hypothesis helps to explain why traditional cancer treatments can fail, since abnormal stem cells are naturally resistant to the standard therapies, including radiation.

Scientists prize normal stem cells as the potential keys to regenerative medicine, because they can grow infinitely and become the various tissues that make up the human body. But to date, stem cells in abnormal form have also been identified as the source of several cancers, including brain, breast, bone, colon and blood.

"We know cancer is a multiphase disease; what we don't know is in which cell type did the cancer originate and this gives us a way to test [various theories]," said Dr. Dick.

Donna Hogge, a senior scientist at the B.C. Cancer Agency in Vancouver, noted that Dr. Dick has "succeeded where many others have failed."

"It's the first time that I'm aware of [that anyone has grown a human cancer model]," said Dr. Hogge, who is also a clinician involved in bone marrow transplants and treating leukemia patients. "It has been done with mouse cells many times ... but human cells tend to be resistant to making a malignant transformation."

It may be because Dr. Dick's team used primitive cells from an umbilical cord that it was successful, she suggested.

The model "opens up a number of different areas of research," Dr. Hogge said, and could be used not only to test new drugs, but to find new targets to halt cancer.

Dr. Dick, a leader in blood cancer stem cell research, and co-authors Frédéric Barabé, James Kennedy and Kristin Hope, set out to improve the animal model for leukemia to better understand how cancer grows. But not even Dr. Dick expected that the addition of a single gene to a stem cell could have such an effect.

Six years ago, an experiment by U.S. researchers concluded that at least three cancer-causing genes had to be added to epithelial cells (cells involved in body linings, such as the skin and intestines) to grow a solid-tumour cancer.

"It's pretty remarkable that, with just one gene added, we essentially get cancer in 100 per cent of the mice," Dr. Dick said, adding that they have since tested roughly 80 animals. "This isn't a fluke ... this gene is very potent."

The leukemia gene in question is known as the "MLL-ENL fusion gene" because it's actually two genes that fuse together after chromosomes 11 and 19 break and rearrange themselves. Other research has suggested this defect can occur in DNA while a fetus is developing or in response to environmental toxins. The fusion gene, for example, is known to be involved in more than 50 per cent of infant leukemias, 2 per cent of childhood cases and 7 per cent of adult leukemias.

To test the gene's effects, the researchers used a retrovirus to deliver the gene into the DNA of cells collected from human umbilical cord blood. The virus was also tagged with a green fluorescent marker, allowing researchers to follow the modified cells.

The cells were then implanted into immune-deficient mice that would not reject the human tissue. Within 135 days of the transplant, 75 per cent of the mice were pale, lethargic and dying.

"What we think is happening here is that these genes lie at the heart of the stem cell regulatory machinery," Dr. Dick said. "It acts at a higher order in organizing DNA ... it regulates whole sets of genes.

By tracking the cancerous cells as they spread to the animals' livers, kidneys and lungs, researchers found further evidence that their model mimics the human disease pattern.

Dr. Dick noted that advances in chemotherapy mean that 80 to 90 per cent of children survive childhood leukemia. But in about 10 or 20 per cent of cases, he said, children relapse because cancerous cells remain in "sanctuary sites" of the brain and testes. In their mouse models, researchers found their implanted cells had also found sanctuary in the brains and testes.

Milestones

Key developments in the cancer stem cell hypothesis and those in which Canadians have been involved: **1961**

Canadians Ernest McCulloch and James Till prove in mice the existence of the first normal stem cell.

1994

Canadian John Dick and colleagues isolate the first cancer stem cell, in acute myeloid leukemia.

1997

Dr. Dick's team isolates cancer stem cells in three other forms of leukemia.

2003

Peter Dirks and colleagues at the Hospital for Sick Children in Toronto isolate the first cancer stem cell in a human brain tumour.

2004

Dr. Dirks's group proves the function of a brain cancer stem cell in a mouse model.

2005

University of Florida researchers report finding stem cells in bone cancer.

2006

In October, a Duke University scientist demonstrates brain cancer stem cells are resistant to radiation. In November, Dr. Dick and colleagues identify abnormal stem cells as the source of colon cancer.

Compiled by Carolyn Abraham