Stem cells core of more cancers

New discoveries that pinpoint bad seeds leading to a major redirection of research

CAROLYN ABRAHAM
FROM MONDAY'S GLOBE AND MAIL
NOVEMBER 20, 2006 AT 3:47 AM EDT

A spate of new discoveries about the basic biology of cancer is pushing researchers toward an astonishing conclusion: For decades, efforts to cure the disease may have targeted the wrong cells.

Current therapies treat all cancer cells the same. They're aimed at shrinking tumours on the basis that the various cells within them all have similar powers to spawn new cancers and spread destruction.

But mounting evidence suggests that cancer's real culprits -- the roots of perhaps every tumour -- are actually a small subset of bad seeds known best to the world as stem cells.

"It is not unreasonable to say that all this time, the 30 or 40 years that chemotherapy and radiation [have] been around, we've been going after the wrong cells," said Alan Bernstein, president of the Canadian Institutes of Health Research, the country's main medical research funding agency. If the theory bears out, he said, "All of our therapies have been targeting and killing the pawns.

Related Articles

From the archives

- Our national shame: The killing cost of drug treatment
- Province-by-province: One family, 10 outcomes
- Live discussion, 12:30 p.m. EST: Erin Anderssen

Interactives

- How cancer stem cells become tumours

Internet Links

- Globe special report: Confronting cancer

"But like chess, you have to kill the king to win the game."

Abnormal stem cells have now been identified as the engines driving certain cancers of the blood, breast, brain, bone and prostate. And today, two research groups -- one in Canada and another in Italy -- report in an advance online publication of the journal Nature that they have pinpointed aberrant stem cells as the source of colon cancer, the second leading cause of cancer deaths.

"A lot is known about the genetics of colon cancer, but despite all our knowledge, too many people keep relapsing and dying," said John Dick, the senior scientist at the University of Toronto and Princess Margaret Hospital who led the work.

Dr. Dick, who discovered the first cancer stem cell in 1994 in leukemia, said the new work shows that while current therapies treat colon cancer as a "homogeneous entity, not every colon cancer cell has the ability to keep that tumour going; only one in 60,000."

New research has repeatedly shown that contrary to conventional wisdom, only abnormal stem cells can sprout and sustain tumours by renewing themselves indefinitely. Without signals from cancer stem cells, ordinary tumour cells seem to stop growing.

What's more, some experiments have found these bad seeds to be highly resistant to standard cancer therapies, including radiation, medicine's nuclear weapon.

The findings may explain why cancers come back even after treatments seem to make tumours disappear. Just a small number of mutant stem cells left behind -- invisible to the naked eye or any scan -- may be enough to spark cancer's regrowth.

"Killing 98 per cent of tumour cells on a scan may look good, but that 2 per cent could be enough to grow the cancer back," said Jeremy Rich, a neuro-oncologist and cancer researcher at Duke University in North Carolina. "Maybe one of the reasons we haven't been as good as we thought we could be is because we've been looking at the wrong cells."

Normal stem cells are usually cast as stars in science. Plucked from a developing embryo, they're prized as immortal chameleons with the power to multiply indefinitely and give rise to myriad tissues that make up the human body. They've become lightening rods for moral and political debate as researchers rush to explore their potential as the keys to regenerative medicine.

But only in recent years have scientists developed the means to detect them and the methods to test their function. In the process, an old theory about their more sinister side as the source of cancer has moved from fringe to forefront.

"This is the most promising advance in thinking about cancer in a very long time. This opens up brand new targets," said the CIHR's Dr. Bernstein, even if, he acknowledged, "All of our thinking about how to treat cancer needs to be rethought."

Indeed, some scientists suspect that heaps of cancer research will have to be reinterpreted -- if not redone -- in light of what has been dubbed "the cancer stem cell hypothesis."

"The whole cancer stem cell hypothesis suggests that a lot of cancer research that's been done might be a waste," said Peter Dirks, a neurosurgeon and cancer researcher at Toronto's Hospital for Sick Children.

Dr. Dirks, who discovered cancer stem cells as the root of brain tumours in 2003, said numerous studies, for example, have looked at the mutant genes expressed in cancer cells. "If it's only the gene expression of 1 per cent of the cells in the bulk that's driving the growth of that tumour . . . you are not going to be able to see what's going on in the key cells."

The cancer stem cell hypothesis is not universally accepted. One of the key unanswered questions, for example, is whether stem cells actually do make up only about 1 per cent of solid tumours. If their proportion is much larger, it suggests current therapies can sometimes kill them. But few doubt that the idea warrants urgent and further study.

This fall, the U.S. National Cancer Institute has vowed to accelerate studies on cancer stem cells, issuing a request for research proposals. Dr. Bernstein confirmed the CIHR may make it a priority for funding in Canada, where researchers have long led the field.

Across North America and Europe, meetings are being held to discuss the cancer stem cell hypothesis and its implications. Several academic centres, including McMaster University in Hamilton and Stanford University in California, have launched new institutes devoted to cancer and stem cells.

"The exciting thing is that the cancer stem cell model explains so much about how cancers develop," said

oncologist Max Wicha, director of cancer research at the University of Michigan. "What it also explains is why we're not doing better at treating cancer."

The connection between cancer and stem cells is actually a concept that stretches back to the 19th century and scientists have long noticed the striking similarities between them.

Stem cells, present in an embryo from the earliest stirrings of life, have the infinite ability to renew themselves and produce the many different cell types that make up a human. Cancer's hallmark is its ability to grow infinitely, multiplying into the various cells that make up a tumour.

Normal stem cells remain in the body through adulthood to regenerate the tissues of a healthy human, our blood supply, say, or the skin we slough off every few weeks.

But no one yet knows if cancer is the result of a normal stem cell turned bad, or an ordinary cell that somehow acquires a stem cell's immortality and versatility.

"Tumour cells are genetically unstable," said Richard Hill, a senior scientist at the Ontario Cancer Institute at Toronto's Princess Margaret Hospital. "What we don't know is whether tumour cells that don't have stem cell properties can become stem cells at a later point in time."

Still, some researchers in the field feel strong clues support the theory that cancer is the result of a normal stem cell gone awry.

Areas of the body susceptible to cancer, such as the blood, colon and skin, are all considered busy regions for stem cells since there is regular demand for regeneration, to replace, for instance, the skin we shed.

Normal cells in those body regions seem to live too short a life to rack up all the genetic mutations needed to become cancerous. Dr. Dick suspects that only a stem cell lives long enough to accumulate the many genetic mutations needed to seed cancer. Another clue that cancer springs from the stem cells we carry with us from birth comes from cases in which the disease strikes children. Dr. Dirks at Sick Kids, for example, notes that brain cancers, while rare in adults where brain stem cells are hard to find, are the second most common cancer in children after cancers of the blood.

The telltale markers of normal stem cells have also been the best guides to detecting malignant stem cells.

Those markers are proteins on the cell surface known as receptors. In colon cancer, Dr. Dick found the most powerful tumour-producing cancer stem cells carry a high number of CD133 receptors on their surface. This is the same marker found on cancer stem cells at the root of both brain and prostate tumours.

Yet the receptor itself was first identified as a marker of normal brain stem cells in 1992. Research shows that a normal stem cell will divide to become two cells. One will be a stem cell, an exact copy of the original. The other will be a progenitor cell that will mature and, depending on its location, become a new blood cell, or a skin cell, and eventually die.

"But a cancer stem cell is unpredictable," said Dr. Dick, who holds the Canada Research Chair in Stem Cell Biology. The cancer stem cell might produce one stem cell or two, and those produce progenitor cells that proliferate wildly and form a tumour. Those cells might bear some resemblance to the breast or colon tissue where they're found, but instead of maturing, they just keep growing.

"They're caricatures of normal development," Dr. Dick said.

Yet, like the normal stem cell, the cancer stem cell divides far more slowly than the fast-growing, deadly system it spawns. And researchers suspect this is where cancer drugs fall short.

"The cancer stem cell hypothesis suggests that we don't cure cancer because our current drugs know how to

kill rapidly proliferating tissue," said Dr. Dirks at Sick Kids. "But our limited understanding of the cancer stem cell is that it does not proliferate rapidly."

Evidence from Dr. Dick's research on blood cancers suggests a stem cell may divide only once a year. Aberrant stem cells behind leukemia, he said, "can be swimming in a sea of chemotherapy agents and still survive."

This fall, Dr. Rich at Duke University published an experiment in Nature that showed cancer stem cells at the root of one of the deadliest forms of brain cancer, glioblastoma, can survive blasts of radiation.

No one suggests abandoning current treatments; only that the stem cell model casts serious doubt on the long-term ability of standard therapies to eliminate the disease.

"I don't believe that killing the cancer stem cell is the only way we should target cancer," Dr. Dirks explained. "In my field, in brain, for example, people present with a large mass and they are suffering because of that mass and they need that tumour out to relieve symptoms and to save life due to symptoms. It's important to deal with the bulk."

As well, it is not yet understood how, or whether, cancer stem cells are themselves responsible for spreading the disease to other body parts, which often leads to death.

Harvard University oncologist William Hahn recently described himself as a "skeptical observer who likes the idea of cancer stem cells" in a recent Nature news story. But he said he believes the field still lacks details about the workings of cancer stem cells, and he noted that previous strategies billed as breakthroughs have failed to become a panacea for patients.

Still, proponents feel enough evidence already exists to show that preventing cancer's return will require one therapy to shrink a tumour and another to kill the abnormal seeds that sprouted it.

Dr. Wicha in Michigan, who has treated breast cancer patients for 25 years and co-discovered the breast cancer stem cell with Michael Clarke in 2003, put it this way: "We are getting good successes at shrinking tumours, but the ability to shrink tumours has little or no correlation to survival times."

For any new treatments, he said, "We have to ask, 'Is this decreasing the number of cancer stem cells?' "

But currently, there is no way of routinely identifying cancer stem cells in a patient and no proven way to safely wipe them out. Doing so also represents a risky proposition.

Normal stem cells, Dr. Dick noted, actually protect us from cancer because they replace old, mature cells before they rack up too many cancer-causing mutations.

Normal stem cells are also essential to a healthy human.

"If we devise a drug that kills a neural stem cell," said Dr. Dirks, "maybe that will mean you won't be able to form new memories. . . . It will inhibit stem cells and they are thought to have a role in memory formation."

At the University of Michigan, Dr. Wicha has found the cancer stem cell seems to orchestrate the growth of a tumour like a general directing troops. "There is a communication between the stem cell and its progeny," he said. "It sends out the signals that make . . . the different cells of the tumour and the cancer cells then [send chemical messages] that cycle back to the cancer stem cell."

Invariably, that message seems to be: Send more troops, and the more troops that are sent, the more resources are rallied to enable the tumour to survive.

In the new work on colon cancer, Dr. Dick and lead author Catherine O'Brien, a surgeon with Toronto's

University Health Network, studied cells from the freshly removed colon tumours of 17 patients. Six tumours came directly from the colon, 10 came from colon cancers that had spread to the liver, and one from the rear lining of the abdominal cavity.

From these, the researchers sorted two batches of cell samples. One contained the cancer stem cells found in the tumours, the other was ordinary cancer cells.

Even at doses as high as 250,000 cells, the ordinary cells failed to grow tumours in 46 of 47 mice (which were immune-deficient models to prevent rejection). Dr. Dick suspects that the one high-dose transplant that led to a tumour had been contaminated with stem cells.

In contrast, just a thousand cancer stem cells implanted into the mouse model could generate and regenerate a replica of the tumour from which it had originally come, complete with the varied cells it had contained -- the gold standard for proving the seed role of cancer stem cells.

But Dr. Hill of the Ontario Cancer Institute cautioned that while evidence on blood, brain and now colon cancers is convincing, the results from other solid tumour experiments could still be coloured.

"My major concern," said Dr. Hill, also a professor of medical biophysics at the University of Toronto, "is that people have not been successful in identifying pure populations of stem cells."

Dr. Rich acknowledged that a great deal of research remains to be done to clarify the role of cancer stem cells in all stages of the disease. "We are remarkably ignorant about the biology of cancer," he said.

But the growing evidence that cancer stem cells grow tumours, he added, "is like finding the Grand Canyon in your backyard."

Editor's Note: This article is part of a month-long Globe special series on cancer.

Series schedule

Saturday, Nov. 18 A day in the life of cancer:

How 60 Canadians coped

Those who died

Letter from the Editor

Today Drugs and dollars:

The pressure of high costs on care

Tomorrow So tired of waiting:

Treatment is still taking too long

Wednesday Canada's research chasm: A nation falls behind

Thursday PET scan scandal: High tech sits idle

Friday Screen test: Beating the

colorectal killer

Next weekend in Focus

English lessons: The quest for

a national strategy

Next weekend in News The science of stem cells: A new way of looking

at cancer

Tuesday, Nov. 28 The end of chemo: There must be a better way

Thursday, Nov. 30 Can a shot of the flu cure cancer?

Saturday, Dec. 2 In his shoes:

Eight-year-old Spencer fights to live

Wednesday, Dec. 6 It's everywhere: Is the environment killing people?

Saturday, Dec. 9 "C-type" mentality:

The psychology of survival