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Researchers Target Cancer Stem Cells' Unique Vulnerability

New research into the unique properties of stem cells indicates there is a useful difference between cells that keep the blood system healthy and the stem cells that make leukemia lethal, scientists report.

Discovery of the difference is important, because experiments in mice now show that the stem cells promoting leukemia can be killed by rapamycin, a drug that has already received Food and Drug Administration (FDA) approval, said Sean J. Morrison, a Howard Hughes Medical Institute investigator at the University of Michigan Life Sciences Institute who led the research.

"This is proof-of-principle that it's possible to identify differences between cancer stem cells and normal stem cells, and then therapeutically exploit these differences to eliminate cancer stem cells without harming the normal stem cells."

— Sean J. Morrison

Our study demonstrates that it's possible to identify mechanistic differences between normal stem cells and cancer stem cells, and that the differences can be exploited therapeutically, Morrison explained. A full report on the work is published in the April 6, 2006, issue of the journal *Nature*. Omer H. Yilmaz, a graduate student in Morrison's lab, is the lead author of the report. Colleagues Riccardo Valdez, Brian K. Theisen, David O. Ferguson, are co-authors, as well as collaborators Wei Guo and Hong Wu from the University of California - Los Angeles.

Worldwide there is a huge amount of research underway on stem cell biology, and researchers are hoping to learn how stem cells can be manipulated to treat diseases, including cancer, or used to replace failing organs. The new work begins to answer how those stem cells involved in cancer resemble and differ from the normal stem cells that keep bone marrow and other tissues healthy.

Finding exploitable differences between cancer cells and normal cells has ranked among the most important goals of cancer research. According to Morrison, the idea is to find some vulnerability, some chink in the cancer cell's armor, that will enable scientists to kill cancer cells while sparing cells needed for normal functioning, such as bone marrow cells. This would allow the development of anti-cancer therapies that are more effective and that have less toxic side-effects to normal tissues.

According to Morrison, Cancer stem cells — cells thought to initiate and maintain tumors — share many properties with normal stem cells, making it difficult to design cancer treatments that target cancer stem cells without killing normal stem cells. The problem is that damaging normal blood-forming stem cells during treatment for leukemia would severely compromise the immune system, rendering patients extra-vulnerable to infections, he said.

But now, evidence from mouse studies in Morrison's lab shows that rapamycin can reduce the number of existing leukemic stem cells, and prevent the growth of those that remain, while restoring the function of normal stem cells needed to maintain a healthy supply of blood. The treatment also restores the animals' ability to replenish the supply of immune system cells after the bone marrow has been depleted.

The new work is founded on the observation that there are inherent distinctions among different types of stem cells. In leukemia, Morrison said, it was discovered that not all cancer cells have an equal ability to proliferate. Some cancer cells have only limited ability to grow, while a smaller subset of cells has tremendous ability to proliferate, to transfer disease in transplantation, and kill. This malignant subset is called cancer stem cells because they are similar in function and appearance to normal stem cells.

So the problem, Morrison said, is to find some exploitable difference between the two. To cure leukemia it is necessary and sufficient to kill the cancer stem cells, but if they are so similar to normal stem cells, how do we kill them without also killing normal stem cells in the same tissue? Morrison asked.

The answer is to seek small, rare differences in the mechanisms that maintain the leukemic stem cells compared to normal blood-forming stem cells. And cancer researchers have found one such difference: a gene called *Pten*, which has opposite effects on the two types of stem cells: When scientists remove or inactivate the *Pten* gene, the supply of normal stem cells declines, while the growth of cancer stem cells increases dramatically.

That offered a golden opportunity.

We were able to target this Pten pathway with the drug rapamycin, which killed leukemic stem cells without harming normal stem cells, Morrison said. So this is proof-of-principle that it's possible to identify differences between cancer stem cells and normal stem cells, and then therapeutically exploit these differences to eliminate cancer stem cells without harming the normal stem cells.

Although it is still early in the research process, and experiments have not yet moved beyond those conducted in mice, it seems likely that there will soon be progress in the clinic, since rapamycin is already in use as an FDA-approved anti-cancer drug.

I believe these results will have an impact on current clinical trials which are being performed with rapamycin, Morrison added. They offer hope that it will be possible to develop more effective and less toxic chemotherapy drugs based on a better understanding of stem cell self-renewal.