Researchers who have been seeking a handle on what makes cancer stem cells different from normal stem cells have gotten a welcome grip on the process. A series of recently published research studies implicate the tumor suppressor PTEN as a key player in maintaining normal stem cell function.

Three published studies all point to PTEN (phosphatase and tensin homologue) as a major developmental switch that both maintains normal blood cell-forming stem cells and, when mutated or missing, leads to stem cell loss, deregulation, and sometimes cancer. The research may have surprisingly near-term clinical impact because at least one study indicates that the FDA-approved drug rapamycin may be effective in fixing damage to blood cell-forming stem cell populations caused by a loss of PTEN function.

Two of the studies used mouse models in which PTEN can be turned off in bone marrow stem cells. In those studies, both published in the journal Nature in April, researchers observed that without functional PTEN, blood stem cells begin multiplying rapidly, show diminished self-renewal capacity, and begin to move out of the bone marrow, colonizing distant organs.

In a study led by Linheng Li, Ph.D., of the Stowers Institute for Medical Research at the University of Kansas Medical Cancer in Kansas City, scientists observed that several days after PTEN depletion, stem cell numbers decreased in the bone marrow and increased in organs such as the spleen and peripheral blood. They all developed into myeloproliferative disease—a precancerous condition in which immature blood cells of the myeloid and T cells multiply rapidly—and the cells died within about 40 days. The researchers also showed that the cells with PTEN deleted can transfer leukemia to mice whose normal bone marrow had been irradiated, demonstrating their ability to function as cancer stem cells.

Sean Morrison, Ph.D., a Howard Hughes Medical Institute investigator, and his colleagues at the University of Michigan in Ann Arbor treated animals with the drug rapamycin, which inhibits an enzyme, mTOR, that is activated by loss of PTEN. Rapamycin is currently approved to help prevent organ rejection after transplants, and it has shown promise in treating several forms of cancer, including skin cancer.

“If we administered rapamycin within days of deleting PTEN, and if they stayed on rapamycin, [the animals] stayed completely healthy with no signs of leukemia,” said Morrison. “But if we waited until after the mice had frank leukemias before we treated them with rapamycin, then rapamycin really reduced the frequency of leukemic stem cells in these mice, made the mice much healthier, and prolonged their lifespan substantially, but was not completely effective in curing the leukemias.”

Rapamycin restored the animals’ ability to replenish the supply of blood cells simultaneously after their immune systems had been depleted of blood stem cells.

In a study published in the April issue of Current Biology, postdoctoral student Masamitsu Fukuyama, Ph.D., now at the University of Tokyo, and Joel Rothman, Ph.D., of the University of California in Santa Barbara, examined the ability of the developing nematode worm Caenorhabditis elegans to remain in a quiescent state, which it often does while waiting for an environmental cue that signals the availability of food to complete its development. The researchers wanted to understand the braking mechanisms that keep organisms inactive. They discovered that PTEN is the trigger that breaks this quiescent state, and when the PTEN gene is mutated, cells start growing and dividing inappropriately.

“What we did find is that a mutation in (the PTEN gene) causes a dysregulation, which I think is certainly analogous to the regulation of these (blood cell forming) stem cells,” said Rothman. “You can think if it as the hints of a beginning of a cancer-like state. I think it is probably true for all animals that [PTEN] serves as a fundamental function for keeping cells quiescent.”

The studies have created a buzz among cancer stem cell researchers because it suggests a clear difference between normal stem cells and cancer stem cells, which are generally defined as cells capable of self-renewing and populating the body with cancer cells. Recent studies have shown that cancer stem cells don’t respond to treatments that kill most cancer cells and, at least in leukemias and lymphomas, may cause the recurrence of cancer after remission. Many researchers had been concerned that it would be difficult to kill cancer stem cells without harming normal stem cells. But the PTEN studies suggest a way to attack cancer stem cells without harming normal stem cells. Also, the animal models may allow researchers to search for other differences that serve to differentiate between the two.

“Here you have a wonderful circumstance that, if you can isolate the pure leukemia-initiating cell, you could look for all the changes that we’ve seen in leukemia. If they are all in that leukemia stem cell then you could ask, just as [the authors did in these studies], which of the steps can you block and block the leukemia,” said Irving Weissman, M.D., Director of the Institute of Stem Cell Biology and Regenerative Medicine at Stanford University in Palo Alto, Calif. “Therefore you could validate each step in the development of leukemia.”

Indeed, Fukuyama is using high-throughput genomic screens and the powerful genetic knowledge available...
about the C. elegans system to identify other players in the quiescence pathway that might also be targets for cancer.

“We hope to get many other components that act in a similar way in pathways for this quiescent arrest process that could be perturbed in cancer,” said Rothman.

The findings have also raised questions among those who study the mechanism of PTEN, which activates multiple enzyme pathways and induces protein cascades that lead to cell proliferation and gene transcription. For example, a key component of one of these inappropriately activated pathways is mTOR, the human target of rapamycin. But loss of PTEN also induces programmed cell death, and investigators are interested in what other genetic events switch cells from a cell death pathway to a survival pathway.

“Here is a situation whereby I may have a chance of studying the [transition] from a rapidly deregulated cell growth–induced cell death to a cell survival signal and into cancer,” said Tak Mak, Ph.D., director of the Advanced Medical Discovery Institute at Ontario Cancer Institute in Toronto.

Into the Clinic

Morrison and his colleagues at the University of Michigan are planning to take the results of their laboratory study to the clinic to examine the PTEN status of leukemia patients and gauge the response of cancer stem cells to rapamycin or a similar drug. The study will be led by Moshe Talpaz, M.D., associate chief of hematologic malignancies at the University of Michigan Comprehensive Cancer Center.

“We want to work from the specific angle of stem cells,” said Talpaz. “We need to confirm that [loss of PTEN activity] is a relevant driving mechanism in the real-life leukemia. We want to go specifically after the leukemic stem cells and try to create a differential between the behavior of the leukemic stem cell and the normal stem cell.”

Talpaz said the group would design a small translational study to examine how leukemia stem cells respond to treatment with an mTOR inhibitor (rapamycin or a rapamycin analog). The research team also plans to determine how often the PTEN gene is mutated in leukemia patients. He said the study should start relatively quickly because rapamycin is an approved drug and there are at least three rapamycin analogs currently in clinical trials for various types of cancer.

“We can’t predict based on this mouse model exactly what rapamycin will do in humans [in terms of its ability to kill cancer stem cells], but nonetheless what we’ve seen in the mouse model lends hope that rapamycin might be capable of killing some cancer stem cells,” Morrison said.

In the bigger picture, the researchers want to understand what governs cancer stem cells’ lack of response to certain drugs. They don’t know why cancer stem cells seem not to respond to treatments that kill almost all solid tumor or leukemia cells.

“The drug that works with the stem cells may be very, very different from the drug that works with the mature cells,” Talpaz said. “In the past the focus was that we needed more than one treatment because there are many mutations in the cancer cell. Here we argue that within the cancer cells there are different populations of cells that may require different treatments. That’s a major transition in our thinking process.”

He added that you won’t be able to cure cancer unless you kill the cells that cause a relapse because some cells—likely stem cells that aren’t killed by traditional treatments—are left behind. When they reemerge, they can have new mutations that are difficult to treat. Finding a way to kill these resistant stem cells should be a priority, he said.

Weissman agrees that researchers should be looking to multiple targets that would address both cancer stem cells and tumor stem cells.

“I think people will be using rapamycin in those subsets of patients that they can show have PTEN silenced,” he said. “I’m just warning them that they need to be thinking already of the next step. . . . If you can try combinations of chemotherapy you ought to try combinations of therapy.”

—Karyn Hede

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