

DECEMBER 21, 2004

Researchers Discover a Stem-Cell Switch Lurking Within Leukemias

Researchers have discovered that specific cancer-causing genes associated with leukemias can transform mature white blood cells into leukemic cells that have all the properties of stem cells. The findings are noteworthy because they show that certain leukemia oncogenes can commandeer and switch on genetic programs that govern self-renewal, one of the unique characteristics of stem cells.

The findings may also help explain why the cancer drug Gleevec, which targets the BCR-ABL enzyme, does not cure the disease, but only puts it into remission. The researchers propose that targeting the additional aberrant growth pathway—outlined in their new studies—will be necessary to cure chronic myeloid leukemia.

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— D. Gary Gilliland

The researchers, led by Gary Gilliland, a Howard Hughes Medical Institute investigator at Brigham and Women's Hospital and Harvard Medical School, published their findings in the December 2004 issue of the journal *Cancer Cell*. Other co-authors were from the Dana-Farber Cancer Center and Emory University.

Mature white blood cells follow a developmental program that leads to what is called a terminally differentiated state. At that point in development, mature white blood cells have irrevocably lost one of the key properties of stem cells - the ability to self-renew indefinitely. "The results of our study are quite surprising, because it had been thought that once a cell was committed to differentiation, it had forever lost the ability to self-renew," said Gilliland. "Our data show that certain leukemia oncogenes can commandeer programs that govern self-renewal and turn the switch back on again."

One of the implications of the study is that it provides new information for researchers to target the cancer stem cell therapeutically. “The cancer stem cell is likely the most important target of therapy,” said Gilliland. “It’s thought to be the main reason why cancer patients relapse after initial response to therapy.”

Researchers believe that leukemia is fueled by a small population of blood cells that divide continually, or self-renew, when they harbor certain genetic abnormalities. Continuous self-renewal prevents these cells from developing into the specialized blood cells that the body needs to function normally. According to Gilliland, previous research had established that leukemia and some other cancers were not made up of a homogeneous population of cells.

“Rather,” he said, “they were similar to normal hematopoietic cells involved in development - in which there is a very rare population of leukemia stem cells that sustains the tumor, just as there’s a very rare population of normal stem cells that sustains normal blood growth.

“These sustaining cells are like the queen bee in a colony—they are the one type of cell required to propagate the entire tumor and probably the most important target for therapies,” said Gilliland. “It’s an attractive theory, because it fits so nicely with what we have known about leukemias—which we can treat patients into complete remission, and yet they ultimately relapse in most cases. And that has to be from some small population of cells that has this self-renewing capacity.”

In their studies, Brian Huntly, the first author of the report, Gilliland, and their colleagues explored the difference between two abnormal chromosomal rearrangements they thought might confer the ability to self-renew. These cancer genes cause leukemia in white blood cell progenitors that have already committed to become a particular type of blood cell, and are therefore no longer self-renewing stem cells. The team studied *BCR-ABL*, the most common genetic mix-up in chronic myeloid leukemia, and, *MOZ-TIF2*, an abnormal genetic rearrangement that causes acute myeloid leukemia (AML). AML is the most common type of leukemia, and an estimated 12,000 new cases of AML are diagnosed in the United States each year. In their experiments, Gilliland’s team introduced these abnormal genes into normal progenitor cells and tested the ability of the resulting cells to self-renew.

The researchers found that only *MOZ-TIF2* could cause normal progenitor cells to assume the properties of “leukemic stem cells” - most importantly, the ability to self-renew. *MOZ-TIF2* could cause AML in any progenitor cell type, both in cell cultures and in mice. In contrast, *BCR-ABL* by itself was unable to trigger such proliferation.

“In the case of *MOZ-TIF2* and *BCR-ABL*, it was known that both of these oncogenes are associated with a self-renewing phenotype in humans, in which the disease is continually propagated,” said Gilliland. “But we found that only *MOZ-TIF2* could confer the property of self-renewal on any type of progenitor cell. *BCR-ABL* could not turn on those self-renewal programs by itself.

“This finding goes against the dogma that once these cells make a decision to differentiate, there is no going back, and the cell is ultimately destined for death. In contrast, we found that *MOZ-TIF2* could engage the self-renewal program and change a cell that has absolutely no capacity for self-renewal back into a stem cell,” Gilliland said. Irving Weissman and colleagues at Stanford University have also shown that other leukemia-associated genes have the same property, he said.

According to Gilliland, the finding has implications for both understanding and treating cancers. “We are excited because we think with this knowledge we now have the tools we need to understand how a leukemic change turns a normal cell into a cell that looks like a stem cell. Such studies will yield two benefits: First, we will be able to therapeutically target these genetic programs that enable a leukemia gene to confer self-renewal. And, we should be able to learn to switch on these same programs in normal cells to trigger tissue regeneration - and, although it's something of a pipe dream, perhaps even organ regeneration.”

Specifically, said Gilliland, the finding that *BCR-ABL* is unable to confer self-renewal by itself indicates that other drugs are needed to target the cancer stem cells in CML. Most cases of CML are seen in adults, and an estimated 4,600 new cases of CML are diagnosed in the United States each year. “Treatment with targeted therapies such as Gleevec has been a great leap forward in treating CML,” he said. “But the experience with that treatment has shown that it simply puts the disease into abeyance, and it doesn't seem to eradicate that critical stem cell. It suggests that either that other pathway should be targeted with drugs, or perhaps both the *BCR-ABL* and the self-renewing pathway should be targeted.”

In further studies, Gilliland and his colleagues will analyze the genes that are switched on by *MOZ-TIF2* and other such cancer genes. By comparing their gene activity with that of *BCR-ABL*, the researchers hope to identify drug targets that can specifically eliminate the self-renewal capability of such cancers.