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Activity of Certain Stem Cell Genes Linked With Worse Outcomes in Acute Myeloid Leukemia Patients

Leukemia patients, whose cancers express higher levels of genes associated with cancer stem cells have a significantly poorer prognosis than patients with lower levels of the genes, say researchers at the Stanford University School of Medicine. The finding is among the first to show that the cancer stem cell hypothesis -- which posits that some cancers spring from and are replenished by a small, hardy population of self-renewing cells -- can be used to predict outcomes in a large group of patients and one day to tailor treatments in the clinic.

"The clinical implications of this concept are huge," said Acting Assistant Professor of Oncology Ash Alizadeh, MD. "If we're not able to design therapies to target this self-renewing population of chemotherapy-resistant cells, the patients will continue to have a tendency to relapse." And yet, although much laboratory evidence exists to support the idea, clinical evidence to support the cancer stem cell hypothesis has until now been sparse.

Alizadeh is a co-senior author of the research, which will be published Dec. 22 in the Journal of the American Medical Association. Senior researcher Andrew Gentles, PhD, is the first author. Alizadeh and Gentles teamed up with assistant professor of hematology Ravindra Majeti, MD, PhD, and associate professor of radiology Sylvia Plevritis, PhD, to conduct a retrospective analysis of more than 1,000 patients with acute myeloid leukemia who were treated at centers in the Netherlands, Germany, Japan and the United States including Stanford Hospital & Clinics. Alizadeh, Majeti and Plevritis are members of the Stanford Cancer Center. Majeti is the other co-senior author.

The cancer stem cell hypothesis has gained increasing credence as researchers from around the world have identified subpopulations of cells in a variety of solid and blood cancers that resist treatment and contribute to relapse in animal models. Eradicating these stem cells is necessary, many believe, for a complete cure. But studies in animals are still several steps removed from proving the idea's worth in humans.

"What's been lacking is clinical evidence that these observations in mice impact actual outcomes in human patients independently of existing prognostic factors," said Majeti. "We wanted to know, 'Do genes associated with leukemia stem cells confer a bad prognosis for a patient?'"

In September, Majeti and Alizadeh showed that targeting a protein called CD47 found on the surface of cancer stem cells in combination with another antibody could eliminate human non-Hodgkin lymphoma in laboratory mice. CD47, which has been dubbed a "don't eat me" signal that protects the cells from elimination by the host's immune system, has also been found on stem cells in several other cancers, and investigations aimed at eventually testing a similar combination antibody therapy in humans are ongoing.

In this study, the researchers were interested in learning whether leukemia stem cells play a similarly important role in acute myeloid leukemia, which is one of the most aggressive blood cancers in adults.

"We've made very little progress in the treatment of AML over the past 40 years," said Alizadeh. "We're still using the same drugs and therapies we've always used, even though about 70 percent of patients with AML die within five years of diagnosis."

The team used two cell surface markers formerly shown to identify leukemia stem cells to isolate these cells from tumor samples from seven patients. They then compared the overall gene expression patterns of the stem cells to other cells in the tumors and identified a total of 52 genes whose expression varies between the tumor stem cells and non-stem cells.

Interestingly, the gene expression pattern is similar to that found on normal blood stem cells, which give rise to blood cells and the immune system. This similarity implies that the cancer stem cells not only can self-renew, but also that they, like normal stem cells, don't divide unless they're needed. Infrequent division may be one way the cancer stem cells escape many conventional treatments that target rapidly dividing cells.

"It's as if these cells are lurking in the background, waiting to pounce after chemotherapy has wiped out most of the other cells," said Alizadeh.

When the researchers compared the levels of expression of these new leukemia stem-cell-associated genes among tumor samples from four groups with a total of more than 1,000 people with acute myeloid leukemia, they found a strong correlation between high levels of expression and a poor outcome for the patients. In one group from Germany, patients with high levels of gene expression had an absolute risk of death within three years of 78 percent, versus 57 percent for patients with lower levels of expression. High-expressing patients fared similarly poorly in comparisons of "event-free survival," or likelihood of relapse within a certain time period, and in how strongly their disease resisted initial rounds of treatment.

"The stronger the leukemia stem cell signal, the worse the patients did," said Gentles, who is a member of the Stanford Center for Cancer Systems Biology. "Their lives were shorter, they relapsed sooner and they were less able to respond to therapy." The center was established with a $12 million grant from the National Institutes of Health to stimulate the application of computer modeling to cancer research. Plevritis is the director of the center and a co-author of the research.

Plevritis and Gentles plan to study the gene expression pattern in the leukemia stem cells to identify important regulatory pathways that might be driving the cellular hierarchy in the cancer. The researchers are also working to develop ways to make their findings more useful in the clinic.

"It's difficult to measure the expression of this many genes in the clinic," said Gentles. "We'd like to try to whittle that panel of genes down to a more manageable three or four that are still prognostically important."

Finally, the team will continue to study the data to determine which treatments are most effective for patients with the high-expressing gene signature. "We'd like to know whether a group of patients with a high leukemic stem cell burden would respond well to certain types of therapy," said Gentles, "and which should be avoided. For example, bone marrow transplant can sometimes be an effective way to treat AML. But transplant itself carries significant risks for the patient. If it is not likely to help someone with high levels of expression of these genes, then we can try other approaches."

"This finding adds to our clinical confidence that the cancer stem cell hypothesis is important to human disease," said Majeti. "It may also define features of the disease that will help us to determine whether individual patients should participate in clinical trials or if their initial treatment should be more aggressive than the standard approach."

The research was supported by the National Institutes of Health, the Burroughs Wellcome Fund and the Leukemia & Lymphoma Society. Gentles, Majeti and Alizadeh have submitted a patent application for the use of the leukemia stem cell gene expression score as a diagnostic assay.

Andrew J. Gentles, Sylvia K. Plevritis, Ravindra Majeti, Ash A. Alizadeh. Association of a Leukemic Stem Cell Gene Expression Signature With Clinical Outcomes in Acute Myeloid Leukemia. Journal of the American Medical Association, Dec 22, 2010 DOI: 10.1001/jama.2010.1862