Protein that predicts prognosis of leukemia patients may also be a therapeutic target

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Researchers at Whitehead Institute and Children's Hospital Boston have identified a protein, called Musashi 2, that is predictive of prognosis in acute myeloid leukemia (AML) and chronic myeloid leukemia (CML) patients.

High levels of Musashi 2 protein is associated with increased cell proliferation, decreased cell maturation, and multiple cancer-related cellular pathways in human leukemias.

The protein and the cellular functions it affects could potentially represent therapeutic targets in certain types of leukemia, according to the researchers' article in *Nature Medicine*.

Leukemia, blood cancer characterized by an overgrowth of certain blood cells, is diagnosed in an estimated 48,000 new patients annually. In AML and CML, a cell type in the bone marrow becomes defective, dividing repeatedly and eventually crowding out normal red and white blood cells, leading to anemia and an inability to fight infections.

AML progresses very quickly, and, if untreated by chemotherapy or bone marrow transplant, results in death. CML's beginning phase is much milder until the number of immature blood cells, called blast cells, suddenly increases—an occurrence known as blast crisis. Some drug therapies, such as Gleevec, may help treat patients in the early phase and even the blast phase of CML, but only a bone marrow transplant is considered curative.

Like other cancer cells, AML and CML cells proliferate more rapidly and are more resistant to routine programmed cell death than normal cells. Although each type of cancer has a different genetic or biochemical method for reproducing and staying alive, sometimes there are common threads that bind some cancer types together.

For AML and CML, one of those threads is Musashi 2, a protein that regulates other proteins' production by binding to their RNA templates.

Scientists Michael Kharas and, Christopher Lengner both first authors on the Nature Medicine article, examined Musashi 2's function in established cell lines from AML and CML patients, mouse models of AML and CML, and gene expression data from 600 AML and CML patients.

All of the data pointed to Musashi 2 playing an integral role in AML and during the blast crisis stage of CML.

"It seems like Musashi 2 on its own is not sufficient to cause the cancer—there is another genetic hit that must first occur to initiate the cancer," says Lengner, who is a postdoctoral researcher in the lab of Whitehead Institute Founding Member and MIT biology professor Rudolf Jaenisch. "And if you then add Musashi 2, it makes the cancer more stem cell-like, and as a consequence of that, much more aggressive."

Kharas's and Lengner's experiments showed a direct correlation between increased Musashi 2 levels and increased aggressiveness of the cancer. When the researchers reduced the amount of Musashi 2 in AML and CML cell lines, the cancers were less aggressive, and in some cases, matured and even underwent programmed cell death. When they examined patient data, Kharas and Lengner found that patients with high levels of Musashi 2 had poorer outcomes than did patients with lower

Musashi 2 levels.

"It's actually very amazing," says Kharas, who is is an instructor at Brigham and Women's Hospital and a researcher in the Children's Hospital Boston lab of George Daley. "Everyone says that human cell lines have nothing to do with human patients. But, we could go from a mouse, to an in vitro cell culture model, to patient data. And when we saw that you could reduce Musashi 2 in these cell lines and use that information to predict the survival of patients, we were really impressed."

Although Musashi 2 has been the subject of little research, it is known to regulate a self-renewing pathway in stem cells as well as a cell-proliferation pathway. To see what cellular pathways Mushasi 2 is affecting in human leukemia cells, Kharas and Lengner analyzed the genes expressed in those cells compared with the genes expressed in leukemia cells whose Musashi 2 expression had been turned down. The top targets turned on by Musashi 2 reads like a who's who of cellular pathways associated with cancer: Wnt, Ras-Mapk, and Myc, among others.

In the future, Kharas and Lengner say that controlling Musashi 2 expression or its targets may lead to new therapies for leukemia patients. Daley agrees.

"We've made great strides against certain forms of leukemia, but AML remains highly fatal," says Daley, Director of the Stem Cell Transplantation Program at Children's Hospital Boston and a former Whitehead Institute Fellow. "We've linked a new gene to the most aggressive leukemias, which is immediately helpful in identifying patients with good and bad prognoses. We are hopeful our new insights into leukemia will help us identify new drug targets."

More information: "Musashi-2 regulates normal hematopoiesis and promotes aggressive myeloid leukemia", *Nature Medicine*, online July 8, 2010

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