Zebrafish models identify high-risk genetic features in leukemia patients

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Leukemia is the most common childhood cancer; it also occurs in adults. Now researchers working with zebrafish at Huntsman Cancer Institute (HCI) at the University of Utah have identified previously undiscovered high-risk genetic features in T-cell acute lymphocytic leukemia (T-ALL), according to an article published online May 9, 2011, in the cancer research journal *Oncogene*. When compared to samples from human patients with T-ALL, these genetic characteristics allowed scientists to predict which patients may have more aggressive forms of the disease that either recur after remission or do not respond to treatment.

While there are several subtypes, in all leukemias the body overproduces certain blood cells that have not matured properly. In this study, the researchers investigated a particular type of leukemia that results from genetic mutations in T-cells, a type of white blood cell found in both humans and zebrafish.

Using a technique called serial transplantation, the research team studied T-ALL in zebrafish and selected cancer cells from those in which the disease advanced more rapidly for further testing. This method allowed the research team to zero in on genes associated with T-ALL's most aggressive forms. They then compared these genetic features to samples from human patients whose clinical outcomes with T-ALL are known.

"We can cure 80% of the children who come to us with leukemia, but there are 20 percent we cannot cure. Sometime the cures come at a high

cost to patients in immediate and delayed side effects from chemotherapy," said Nikolaus Trede, M.D., Ph.D., associate professor in the Department of Pediatrics at the University of Utah (U of U) School of Medicine, HCI investigator, and a senior author of the article. "These results may lead to tests that can show which children with the disease need the strongest chemotherapy to overcome their cancer. Children with less aggressive forms of leukemia can be cured with milder chemotherapy that produces fewer side effects, both during treatment and long after treatment is complete."

Kimble Frazer, M.D., Ph.D., assistant professor of pediatrics at the U of U and a member of the Trede Lab, is co-senior author of the article. "One of the genes identified in the study had not previously been recognized as important in T-ALL," said Frazer. "Another gene, associated with patients whose outcomes were least favorable, has not received enough research attention to even have an official name. It only has an 'address' that tells its location on a specific chromosome."

The researchers stress that their results are still preliminary. They plan further laboratory studies to bolster the case that this unnamed gene with the address C7orf60 is important in the development of T-ALL. Additional zebrafish experiments that focus on this gene could be designed to amplify its effects and confirm its contribution to creating more, or hardier, leukemia. In the end, the research could lead to a test that would allow doctors to determine the best course of treatment for an individual leukemia patient by analyzing a blood sample.

Both Trede and Frazer credit the article's first-listed author, Lynnie Rudner, with much of the work leading to the published results. Rudner is the recipient of the American Medical Association (AMA) Foundation's Seed Grant, one of only 38 individuals nationwide who received a seed grant in 2010, and a student in the U of U's M.D./Ph.D. program, which produces graduates qualified in both clinical practice

and laboratory research.

Provided by University of Utah