MedicalXpress

'Vicious circle' offers new acute leukemia treatment target

April 13 2010

Researchers have identified a self-feeding "vicious circle" of molecules that keeps acute leukemia cells alive and growing and that drives the disease forward.

The findings suggest a new strategy for treating acute myeloid leukemia (AML), one that targets this molecular network and lowers the amount of a protein called KIT, say researchers at the Ohio State University Comprehensive Cancer Center-Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC-James) who conducted the study.

Published in the April 13 issue of the journal *Cancer Cell,* the study described a new network of protein and microRNA molecules that, when imbalanced, contributes to abnormal KIT protein abundance and favors leukemia development. The researchers were also able to target this network with therapeutic drugs.

"We now understand the mechanism responsible for making so much KIT protein in AML cells, and we believe that targeting that mechanism and reducing the amount of that protein will prove to be a more effective therapy for this disease than the current standard of care," says study leader Dr. Guido Marcucci, professor of internal medicine and an AML specialist at the OSUCCC-James.

AML strikes 12,800 Americans, killing 9,000 of them each year. More than 80 percent of those cases have elevated levels of KIT protein.

Currently, doctors treat AML using standard chemotherapy. Drugs that target and block the activity of the KIT protein are being tested in clinical trials. These agents, called tyrosine kinase inhibitors, bind to the protein and stop disease progression, but they can lose their effectiveness when new mutations that arise during the course of the disease alter the protein.

"Our study suggests that the amount of KIT protein in cancer cells is as important as its activity, and we discovered that the amount of the protein is controlled by a circular network of molecules that has many points of entry," says senior co-leader Dr. Ramiro Garzon, assistant professor of internal medicine and an AML specialist at the OSUCCC-James.

"These findings provide a strong rationale for the use and development of drugs that target the components of this network rather than focusing on the activity of KIT alone."

Marcucci, Garzon, first author Shujun Liu, assistant professor of internal medicine, and their colleagues began this study by showing that patients with mutations in the KIT gene in their leukemic cells had the highest levels of the KIT protein in those cells, and that these patients also had the poorest survival.

"This told us that the amount of the protein in cancer cells is important to the disease process," Liu says.

Using laboratory-grown AML cells, the researchers identified the series of molecules that control the amount of KIT protein, showing for the first time that a microRNA called miR-29b, along with several well-known cancer-related genes, regulate KIT production.

Normally, these elements work in a balanced fashion to produce the

correct amount of KIT protein for healthy cell survival and proliferation. That normal balance is derailed when gene mutations or other genetic damage occurs in the network and promotes the overproduction of the KIT protein.

"It becomes a vicious circle because no matter where genetic damage occurs, the result is the same - overactivation of the circle, overexpression of the KIT protein, and proliferation of leukemic cells," Liu says.

Using a mouse model, the researchers showed that raising the amount of mutated KIT protein causes leukemia, and drugs that target the network lower the amount of that protein and drive the leukemia into remission. These drugs included proteasome inhibitors, histone deacetylase inhibitors, along with inhibitors of molecules called NFκB and Sp1.

Provided by Ohio State University Medical Center