MedicalXpress

Researchers discover new therapeutic agents that may benefit leukemia patients

October 4 2013

An Indiana University cancer researcher and his colleagues have discovered new therapeutic targets and drugs that may someday benefit people with certain types of leukemia or blood cancer.

Reuben Kapur, Ph.D., the Frieda and Albrecht Kipp Professor of Pediatrics at the IU School of Medicine and a researcher at the Indiana University Melvin and Bren Simon Cancer Center, and colleagues discovered in pre-clinical and pharmacological models that cancer cells with a mutation in the KIT receptor—an oncogenic/cancerous form of the receptor—in mast cell leukemia and acute myeloid leukemia can be stopped.

Their findings were published online Sept. 16 in the *Journal of Clinical Investigation* and appeared in print Oct. 1.

According to Dr. Kapur, activating mutations of KIT receptors are almost always associated with a type of leukemia called mast cell leukemia. The mutations in the KIT receptor are found in about 90 percent of patients with this type of leukemia. In addition, activating mutations of KIT are also exclusively associated with a subtype of acute myeloid leukemia known as core binding factor leukemia. When KIT is associated with these two types of leukemia, the survival rate for patients is profoundly reduced in comparison to patients who do not have this mutation.

Dr. Kapur and colleagues investigated whether they could shut down the

growth response that is induced by this mutation.

"We identified two new targets in leukemic cells bearing this mutation, which when targeted or inhibited, cause leukemia cells to die," Dr. Kapur said.

The researchers discovered that the two targets are Rac GTPase and Pak (p21-activated kinase). In return, they designed a novel Rac inhibitor—EHop-016—that is considerably more potent than previously described inhibitors of Rac. They also demonstrated a novel role for Pak inhibition in leukemia using an existing Pak inhibitor.

Both are being tested in pre-clinical models to further examine their growth inhibitory properties as well as long-term treatment-associated toxicity.

Dr. Kapur said treatments for leukemia have remained mostly unchanged in the past 30 years. Thus, researchers continue to search for better and more effective ways to treat this debilitating disease.

"We've been looking for new targets and new ways of treating leukemia and special types of leukemias," Dr. Kapur said.

"Leukemia is an extremely complex disease. It's a combination of multiple alterations in the patient's DNA, which eventually results in leukemia. Therefore, it will be very difficult to cure leukemia with just one drug. It will have to be a combination of multiple drugs, if we're to cure this disease."

Dr. Kapur is also professor of biochemistry and molecular biology, of medical and molecular genetics, and of microbiology and immunology at the IU School of Medicine.

Principal authors of the study were Suranganie Dharmawardhane and Cornelis P. Vlaar of the Department of Pharmaceutical Sciences at the University of Puerto Rico; Ramon V. Tiu and Valeria Visconte of the Taussig Cancer Institute, Cleveland Clinic; Ray R. Mattingly of Wayne State University; Joydeep Gosh, Emily Sims, Baskar Ramdas, Anindya Chatterjee, Raghuveer Singh Mali and Holly Martin of the IU Department of Pediatrics, Herman B Wells Center for Pediatric Research; and Veerendra Munugalavadla of the Department of Cancer Immunotherapy and Hematology, Genentech Inc.

Provided by Indiana University