Compound that could prevent acute blood cancer relapse identified

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Researchers from the RIKEN Center for Integrative Medical Sciences in Japan report today that they have identified a compound that could be used as a new treatment to prevent relapse in acute myeloid leukemia patients.

In a study published in *Science Translational Medicine*, they show that this compound reduces the risk of relapse in a mouse model of the human disease. They report that this compound could be most active in patients that carry a mutation lowering their chances of recovery.

Acute myeloid leukemia (AML) is an acute type of blood cancer that starts in the blood-forming cells in the bone marrow. AML is the most common type of acute leukemia in adults.

While many patients are able to fight off the disease at first with conventional chemotherapy, long-term outcomes in the majority of patients are poor due to disease relapse.

"To improve patient outcomes, it is crucial to understand the mechanisms of AML relapse and to develop effective treatment strategies to reduce AML relapse," explains Dr. Ishikawa who led the study.

Over the last decade, bone marrow cells called leukemia stem cells (LSC) have been recognized as key players in human AML pathogenesis as well as chemotherapy resistance and relapse. Previous studies have

suggested that LSCs might cause relapse if they are not properly eliminated by conventional chemotherapy.

By transplanting LSCs obtained from AML patient samples into immune-deficient newborn mice, Ishikawa and his team developed a mouse model for AML, which they used to study AML and LSCs.

Using this model, they were able to identify a protein (HCK) present in higher quantities in human AML LSCs than in normal blood-forming stem cells, and that could be used as a target for therapeutic agents against human AML LSCs.

In the present study, the researchers screened a library of tens of thousands of small molecules that could act as therapeutic agents by specifically inhibiting HCK. They isolated one small molecule that was highly active against patient-derived AML LSCs grown in culture. To assess the potential of this molecule for therapeutic development, they administered it to their mouse model of AML. They find that administration of this molecule results in a significant reduction of human AML cells in the blood of the mice, as well as a reduction of human AML LSCs in the bone marrow of the mice.

In particular, in mice engrafted with human AML derived from patients with the FLT3-ITD mutation, one of the mutations associated with worse clinical outcomes, the administration of the small molecule led to nearly complete elimination of both AML LSCs and non-stem AML cells in the bone marrow of multiple bones (femur, tibia, sternum and spine) as well as the spleen and peripheral blood.

"These findings suggest that treatment with this small molecule may help reduce relapse in AML patients," conclude the authors.

"However, more work is needed before this small molecule can be

delivered to patients as a therapeutic agent. We now plan to proceed with a more in-depth biochemical and pharmacologic characterization of this compound in the lab, to find out whether it is safe and to determine which subset of AML patients could benefit from it. Ultimately, we hope to develop a drug that can be used in the clinic," adds Dr. Ishikawa.

More information: Yoriko Saito, et al. "A Pyrrolo-Pyrimidine Derivative Targets Human Primary AML Stem Cells in Vivo." *Science Translational Medicine*, 2013

Provided by RIKEN