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An “Achilles heel” of acute myeloid leukemia

Heidelberg cancer researchers have found a new target in the treatment of acute myeloid leukemia (AML). A team of scientists headed by Prof. Dr. Stefan Fröhling from the National Center for Tumor Diseases (NCT) Heidelberg and the German Cancer Research Center (DKFZ) has discovered that a specific subtype of this disease, which is particularly aggressive and difficult to treat, is strongly dependent on the activity of an enzyme that controls the cell cycle. Drugs that inhibit this enzyme are already being tested on patients with other types of cancer, so it might be possible to swiftly translate these findings into clinical applications.

Acute myeloid leukemia (AML) is an aggressive type of blood cancer that cannot be controlled in a majority of patients. AML is characterized by an out-of-control multiplication of cells in the bone marrow that have undergone a transformation and no longer mature into functioning blood cells. This is caused by genetic defects that have accumulated over a person's lifetime in bone marrow cells. Until now, it has proven extremely difficult to find specific targets in the treatment of AML, because in most cases it is not possible to use drugs to directly inhibit the genetic changes responsible for the disease.

Stefan Fröhling and his team at the Department of Translational Oncology of the NCT/DKFZ investigated a particularly persistent subtype of AML that is characterized by mutations in a gene called MLL. The scientists systematically searched for "weak points" in these leukemia cells. To accomplish this, they switched off over 1000 genes using a technique called RNA interference, with the aim of discovering genes that play a particularly important role in the blood cancer cells.

The effects were especially dramatic when scientists used this method to block CDK6. This gene encodes an enzyme that controls the cell cycle. When the researchers inhibited CDK6 in experiments in the test tube and in mice, both exhibited a slower growth and maturation of AML cells with MLL mutations. Other types of AML, on the other hand, did not show a significant dependence on CDK6.

The researchers are hopeful that this finding can be translated into a new method of treatment more quickly than is usually the case. They observed that applying a drug called palbociclib, which is a CDK6 inhibitor, affects the leukemia cells in a way that resembles using RNA interference to block the CDK6 gene. Moreover, palbociclib is already effectively being used to treat other types of cancer and has proven to be well tolerated, for example, by patients with advanced breast cancer. Fröhling and his colleagues are now planning a clinical trial to study the effectiveness of using drugs to block CDK6 in patients with MLL-driven AML.

"Patients suffering from this type of AML have an extremely poor prognosis, because the disease does not respond to conventional chemotherapy," says Fröhling. "We urgently need to develop new treatment strategies for these leukemias, and their strong dependence on CDK6 is an ‘Achilles heel.’ We hope to take advantage of this to improve the prognosis of the patients."

The study was carried out in collaboration with Dr. Claudia Scholl (DKFZ and Ulm University Hospital. Further collaboration partners were Dr. Michael Milsom (DKFZ and HI-STEM) and Prof. Alwin Krämer (DKFZ and Heidelberg University Hospital) as well as scientists from

Tübingen and Magdeburg (Germany), Cambridge (UK), Boston, Cambridge, New York and Philadelphia (all USA). The German Research Foundation (DFG) provided substantial funding for this research.

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