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Central signaling pathway in lymphoma can be blocked successfully

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Diffuse large B-cell lymphoma (DLBCL) is a blood cancer and the most common malignant condition of the lymphatic system. Although DLBCL is always fatal if left untreated, the cure rate after chemotherapy combined with antibodies approaches 60 to 70 percent. Certain types of DLBCL, however, do not respond well to this standard treatment, which results in a very poor prognosis for the patients. As the biology of this type of lymphoma remains poorly understood, there is a lack of targeted therapeutic approaches.

A research group headed by Corina Schmid and Anne Müller from the Institute of Molecular Cancer Research at the University of Zurich has now identified a new signaling pathway that is active in and crucial for DLBCL cells – and can be attacked efficiently using substances that are already in clinical development for other diseases.

Prognosis factor for long-term survival

The UZH researchers based their experimental approach on the hypothesis that not only genetic, but also epigenetic changes might play a crucial role in the development of lymphoma. Consequently, they analyzed the so-called methylation of DNA, an epigenetic change that controls the activity of many human genes across the genome. Altered DNA methylation is a common feature of a wide variety of tumor types, which is why it seemed likely that lymphoma cells might also use this regulatory mechanism to their advantage.

And sure enough: The bioinformatical analysis of the methylation profilesof around 70 patient samples revealed eight regions on the DNA, so-called gene loci, that were all abnormally hypermethylated and turned out to be important for the cells' survival. "Follow up experiments revealed one locus in particular that is blocked in almost all the lymphoma patients examined due to DNA methylation and therefore cannot be translated into protein," sums up principal investigator Müller.

Moreover, the cancer researchers made an astonishing discovery: In several large patient cohorts, the epigenetic silencing of this gene locus proved to be an extremely significant, negative prognostic factor for the long-term survival of DLBCL patients. "This factor could thus be important for the diagnosis and prognosis of the disease, as well as therapeutic decisions in the future," says Müller.

Inhibitors effective

The newly identified gene locus contains the genetic information for an enzyme, a phosphatase, which regulates an important signaling pathway in the lymphoma cells and is evidently essential for the tumor cells to survive. Inhibitors are under clinical development for this signaling pathway. First author Schmid and principal investigator Müller were now able to demonstrate that these are also effective against lymphoma cells in cell cultures and in an animal model: Lymphomas in mice treated with the compound grew considerably more slowly than those in untreated mice. "Interestingly, combination therapies with other established substances proved especially effective," explains Schmid, "which makes the newly described signaling pathway a promising target for future cancer treatments."

The study was conducted in collaboration with the Institute of Molecular Life Sciences at the University of Zurich, the University Hospital Basel and the Cantonal Hospital of St. Gallen.

More information: "DUSP4 deficiency due to promoter hypermethylation drives JNK sig-naling and tumor cell survival in diffuse large B-cell lymphoma." *Journal of Experimental Medicine*, DOI: 10.1084/jem.20141957

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