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Inactivating a single enzyme could effectively eradicate an aggressive form of leukemia

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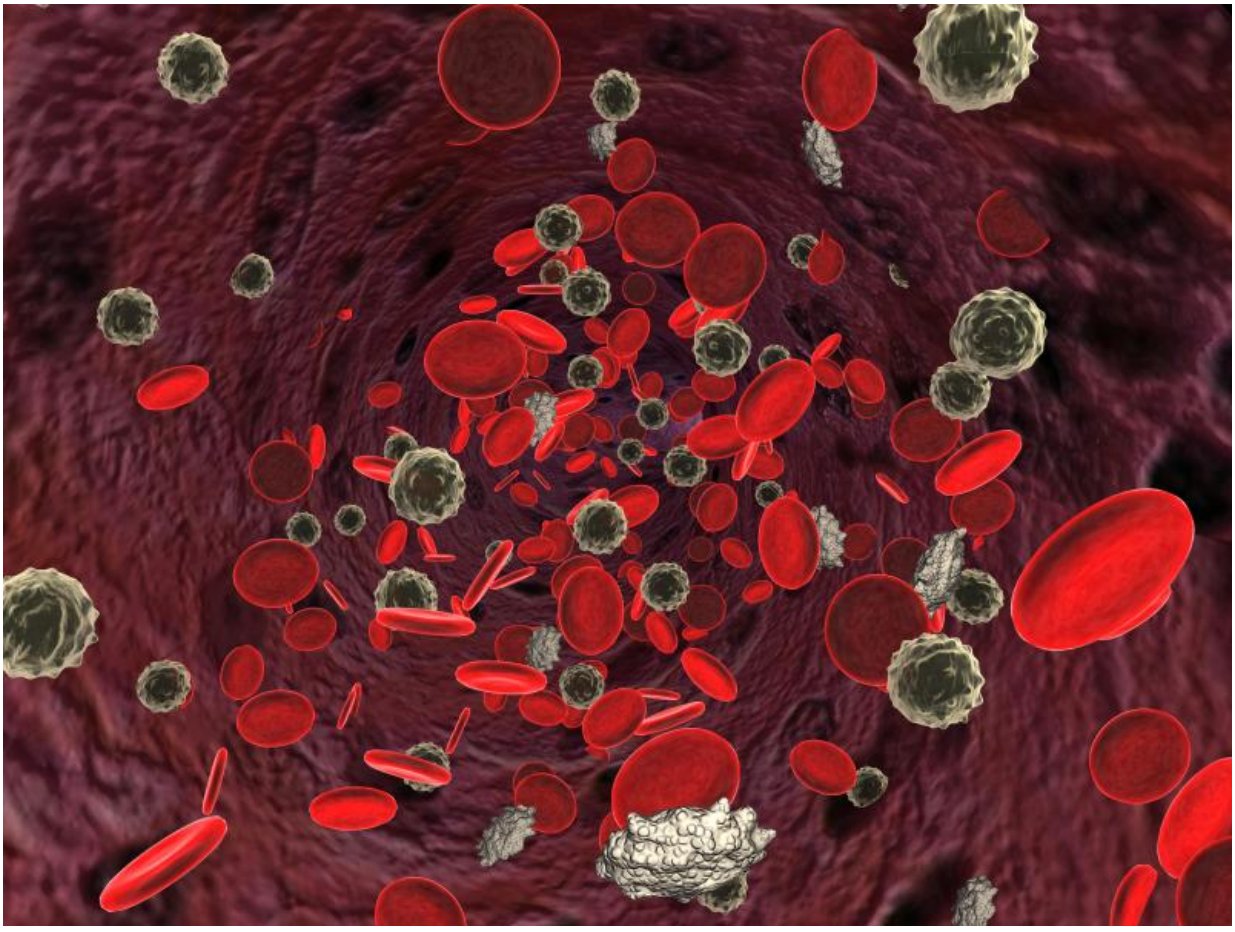

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EPFL scientists show how inactivating a single enzyme could effectively

eradicate an aggressive form of leukemia. The principles could apply to other cancers as well.

T-cell acute lymphoblastic leukemia (T-ALL) is a rare type of leukemia that is more common in older children and teenagers. It affects white blood cells, which are an essential component of our immune system that fights infection. T-ALL onset is linked to microRNAs, small non-coding RNA molecules that silence RNA and regulate gene expression. Most MicroRNAs are generated with the help of the enzyme Dicer1, which has been the focus of research for treating T-ALL. EPFL scientists now show that Dicer1 is crucial for the development of T-ALL, and inhibiting it can actually prevent the disease altogether. The work is published in the journal *Blood*.

MicroRNAs begin life as hairpin-like structures in the cell's nucleus. An enzyme called Dicer1 then cuts the hairpins into two strands of microRNA. One strand is discarded, while the other will form a complex with a group of proteins, which will then bind to and block the RNA carrying the genetic information of interest. The cell's machinery can no longer read the information, and the gene stops producing its protein.

The lab of Freddy Radtke at EPFL has now shown that Dicer1 is a central factor in T-ALL, and that blocking it can prevent the disease altogether. The scientists tracked the development of T-ALL in genetically engineered mice where Dicer1 could be abrogated in a mouse model where a mutated cancer gene induces T-ALL. This type of leukemia evolves from a relatively benign stage to an aggressive form that eventually kills the patient. In this study, Fabian Junker, a recent PhD graduate from Radtke's team, "switched off" Dicer1 in the mice at different stages of T-ALL. The aim was to see what role the enzyme plays in the evolution of this cancer.

Switching Dicer1 off at an early stage of T-ALL completely prevented

the development of the disease despite the mutated gene. But even more fascinating was the fact that, in mice where Dicer1 was completely abrogated, T-ALL cells were entirely eliminated, allowing all the mice to survive. This survival effect was further confirmed by monitoring the few residual "leukemic" cells taken from these animals. "You can actually see the cancer cells dying off after Dicer1 has been abrogated," says Freddy Radtke.

The key to this cell death is the production of microRNAs by Dicer1. The researchers observed that a previously unrecognized microRNA molecule (miR-21) was deregulated in both mouse and human T-ALL. The team also discovered why: when a person suffers from T-ALL, this particular microRNA blocks a gene that normally suppresses the blood tumor cells. But without Dicer1, there is no miR-21 to do this, thereby allowing the tumor-suppressing gene to fight back the disease.

The study is the first to conclusively demonstrate that Dicer1 plays a role in T-ALL, and paves the way for a new set of treatment for in this, and possibly other types of cancer. However, when dealing with molecules that are so fundamental to the cell's life, the challenge is to specifically target the cells of interest. "We can't just go shutting down Dicer1 across the board," explains Freddy Radtke. "Otherwise we'll end up killing healthy cells as well." His lab is now focused, among other projects, to tackling this obstacle.

More information: "Dicer1 imparts essential survival cues in Notch driven T-ALL via miR-21 mediated tumor suppressor Pdcd4 repression." *Blood* 21 May 2015. DOI: 10.1182/blood-2014-12-618892

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