Protein activity reveals new childhood ALL combination treatment strategy

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Blocking a protein chain reaction makes childhood leukemia cells more sensitive to an existing targeted treatment, a new study shows. The research is still at an early stage, but the drugs used in the study already exist, which could speed up the translation to the clinic. Ph.D. student Valentina Cordo' explains: "We've shown that looking at protein activity gives a more complete picture of the weaknesses in leukemia. In future, our research could help discover new treatment strategies for children with the disease who don't respond to standard treatment."

For 1 in 5 children with T-cell acute lymphoblastic leukemia (T-ALL), their disease comes back after treatment. In many of these cases, the current standard treatment of high-dose chemotherapy has stopped working. New ways of tackling the disease are urgently needed.

Faulty proteins

Targeted drugs are designed to kill cancer cells while leaving healthy cells alone. These types of drugs can tell cancer cells apart from healthy cells by specific weaknesses—usually a faulty protein. Such faulty proteins are often caused by mistakes in the tumor's DNA.

In a new study, scientists at the Princess Máxima Center for pediatric oncology in Utrecht, the Netherlands, worked with colleagues at Amsterdam UMC to explore all the active proteins in T-ALL cells in the lab. Proteins are the workhorses of the body, and carry out the jobs that our cells and organs need to do in order to function properly. They can be switched on and off, and these switches are often derailed in cancer.

The new study was published in *Nature Communications* today, and was funded by the Dutch Cancer Society (KWF Kankerbestrijding).

Unusual activity

Valentina Cordo' is a Ph.D. student in the Meijerink group at the Princess Máxima Center, and worked on the study. She explains: "Often, scientists tell cancer cells apart from healthy ones by looking at faults in the DNA. In our new study, we looked at proteins instead. We looked for proteins with unusually high activity, which likely point to ways for cancer cells to evade treatment. These could be potential targets for therapy." This approach has been used in different forms of (childhood) cancer before, but it's the first time scientists applied it to T-ALL cells.

Overactive chain reaction

Analyzing all the protein switches in 11 different kinds of T-ALL cells, the team found a number of proteins already known to be linked to the disease, including two proteins called LCK and SRC. They also found an overactive chain reaction of proteins called INSR/IGF-1R.

"Excitingly, we found that blocking LCK or SRC at the same time as INSR/IGF-1R killed the cancer cells very effectively. Even at low concentrations of the drugs we used, the combination was more effective than either treatment on its own," says Cordo'.

To further study the drug combination, the researchers looked at the effect in leukemia cells from children with T-ALL grown in mice. In those cells with high activity for both the SRC protein and the INSR/IGR-1R chain reaction, the drug combination was again very effective. Cordo' says, "There were no faults in the genes that coded for these proteins, which shows us that protein activity is a valuable clue in looking for drug targets in ALL"

Early stage

The research is still at an early stage. The promising drug combinations found in this study need to be tested further in the lab and in animal studies before they could go on to clinical trials. But the drugs used in the study already exist, which could speed up the translation to the clinic.

"When exploring potential new ways of attacking leukemia, it's important to have the full picture of weaknesses in these cells. We've shown that looking at protein activity gives a more complete picture of those weaknesses. This could in future help discover other new treatment strategies for children with ALL who don't respond to standard

treatment," says Cordo'.

More information: Phosphoproteomic profiling of T cell acute lymphoblastic leukemia reveals targetable kinases and combination treatment strategies, *Nature Communications*, DOI: 10.1038/s41467-022-28682-1

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