Using personalized medicine to avoid resistance to leukemia treatment

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By using mass spectrometry, the researchers can analyze the entire protein set (the proteome) of a cell at once. Credit: University of Copenhagen

T-cell acute lymphoblastic leukemia (T-ALL) is a very aggressive type of blood cancer. It is relatively rare but still draws a lot of attention as it mostly develops in children under the age of 20. The standard treatment for T-ALL involves heavy chemotherapy procedures, which result in favorable outcomes with an overall survival of 75% after 5 years.

However, some patients do not respond to this treatment, or they only respond for a short period, after which the disease grows back. These patients therefore need alternative therapies.

Researchers from the Faculty of Health and Medical Sciences, University of Copenhagen, have now identified a combination treatment, which could potentially benefit patients that do not respond to standard chemotherapy.

"Our study suggests that we could use personalized medicine to target the cancer cells in the subgroup of T-ALL patients that do not initially respond to or stop responding to the standard chemotherapy. By combining two specific protein inhibitors, we have shown that we can obtain a strong and durable effect on leukemia cell growth. This might improve the overall survival of T-ALL patients," says Giulia Franciosa, Assistant Professor at the Novo Nordisk Foundation Center for Protein Research.

Targeting two proteins to avoid resistance

The majority of T-ALL patients have mutations in the so-called Notch1 gene. This mutation causes a cell surface receptor to induce cancer cell growth. By using a drug that inhibits this receptor, it is possible to stop the cancer cells from dividing and growing. Unfortunately, the cancer cells are good at adapting and in many cases develop resistance towards the Notch-inhibitor.

"The challenge we are facing with drug resistance is very hard to overcome as long as we are only targeting one protein, in this case the Notch1 receptor, at a time. That is why we have been looking for a therapy option that targets two proteins at the same time, making it much more difficult for the cancer cells to develop resistance. And we found one," says Giulia Franciosa.

Mass spectrometry proteomics gives unbiased answers

By comparing cells that are sensitive to Notch-inhibition with cells that are resistant—either from the beginning or develop resistance over time—the researchers identified a specific signaling protein responsible for the drug resistance: Kinase C. By targeting both proteins at the same time, they were able to eliminate the resistance.

"We used high-resolution mass spectrometry based proteomics to study the underlying molecular mechanisms that cause the resistance. The proteomics technology allows us to analyze the entire set of proteins, the proteome, present in a cell at the same time. By using this technique, we

can map out differences and similarities between the responsive and non-responsive cells in an unbiased way. And that is how we found that Protein Kinase C activity is upregulated in resistant cells," says Jesper Velgaard Olsen, Professor at the Novo Nordisk Foundation Center for Protein Research.

The researchers hope that their findings in time can be used in the treatment of T-ALL patients who do not tolerate or respond to standard chemotherapy.

More information: Giulia Franciosa et al, Proteomics of resistance to Notch1 inhibition in acute lymphoblastic leukemia reveals targetable kinase signatures, *Nature Communications* (2021). DOI: 10.1038/s41467-021-22787-9

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