New classification of leukemia subtypes reveals potential of existing drugs

16 February 2021

Dr. Benjamin Haibe-Kains is the joint corresponding author for the study "Biological and therapeutic implications of a unique subtype of NPM1 mutated AML", published in *Nature Communications*. Credit: The Princess Margaret Cancer Foundation

Using advanced RNA sequencing, scientists have identified two unique subtypes of a prominent mutation present in many patients with Acute Myeloid Leukemia (AML)—called NPM1—that could help predict survival and improve treatment response for patients whose leukemic cells bear the mutation.

In research published Feb. 16, in *Nature Communications*, a team led by Princess Margaret Cancer Centre Senior Scientists, Drs. Benjamin Haibe-Kains, Aaron Schimmer and Mark Minden, have discovered that within the NPM1 mutation of AML there exists two unique subtypes, one of which can be effectively treated with drugs already in use.

It is the first study to classify within the common NPM1 mutant form of AML two subtypes, one being 'primitive' and the other 'committed.' Furthermore, the research shows that each subtype has a different response to treatment and long-term survival, cracking open opportunities to personalize treatment plans and introduce new targeted therapies in the future.

"Patients with NPM1 mutated AML face a relapse rate of around 40 percent," says Dr. Schimmer, Research Director and acute leukemia physician at the Princess Margaret, which is part of University Health Network. "While we're getting better at incorporating new monitoring techniques, we're still not at a point where we can adequately predict what side of the curve a patient might fall.

By going deeper with our sequencing, we can better predict outcomes and adjust treatment accordingly for each patient."

NPM1 mutated AML makes up around 30 percent of all AML cases, but therapeutic discoveries for these patients have been limited.

"While the NPM1 mutation is relatively common, AML is a rare disease to begin with," says Dr. Haibe-Kains, who is also an Associate Professor of Medical Biophysics at the University of Toronto. "Generating enough data to be able to sequence and understand the biology of this mutation is very challenging."

This was made possible in large part thanks to a team led by Dr. Minden, Senior Scientist and medical oncologist, and Andrea Arruda, staff scientist at the Princess Margaret Cancer, who have been collecting samples to enable deeper learning since the mid-1980s thanks to the willingness, generosity and foresight of patients.

"Recognizing those 'needles in a haystack' - the small groups of patients that don't benefit from certain treatments is critically important for improving personalized medicine," says Dr. Minden. "Now we can start to improve outcomes for this more discreet patient population."

An advanced computational model was custom-built to analyze RNA from patient leukemic cells obtained from the Leukemia Live Cell Tissue Bank, along with other data published from NPM1 mutant leukemia studies.

"We developed a unique machine-learning model that was able to clearly discriminate two subtypes of NPM1 mutant AML in datasets collected from patients," says Dr. Haibe-Kains.

These two subtypes both contain mutant AML but they express different genes that can now separate them into two clear subtypes based on their RNA.

The study also suggests that certain drugs already used to treat other types of cancer could be effective in the primitive subtype.

"Once we were able to identify the pattern of each subtype, we analyzed existing pharmacogenomics data to narrow a list of drugs that might be able to target one subtype or the other," explained Dr. Haibe-Kains. "We found two drugs that seemed to effectively target the primitive subtype in the lab, with potential to move to clinical trials in the future."

"This finding could change the way we treat patients," says Dr. Schimmer. "It opens up the opportunity to better refine and time treatments—whether it's the decision for a stem cell transplant early on, or choosing more effective and less toxic therapies throughout the course of treatment.

Our goal with all of our patients is to get better and better outcomes. This is one step towards doing better."

This research was supported by funds from the Canadian Institutes for Health Research, the Orsino Chair in Leukemia Research and the Princess Margaret Cancer Foundation.

ADS has received research funding from Takeda Pharmaceuticals and Medivir AB, and consulting fees/honorarium from Takeda, Novartis, Jazz, and Otsuka Pharmaceuticals. ADS holds stock in Abbvie. ADS, is an inventor on patent applications claiming the use of DNTs for the treatment of AML.

More information: Mer, A.S., Heath, E.M., Madani Tonekaboni, S.A. et al. Biological and therapeutic implications of a unique subtype of NPM1 mutated AML. *Nat Commun* 12, 1054 (2021). doi.org/10.1038/s41467-021-21233-0

Provided by University Health Network