Protein discovery sparks treatment hope for aggressive cancer

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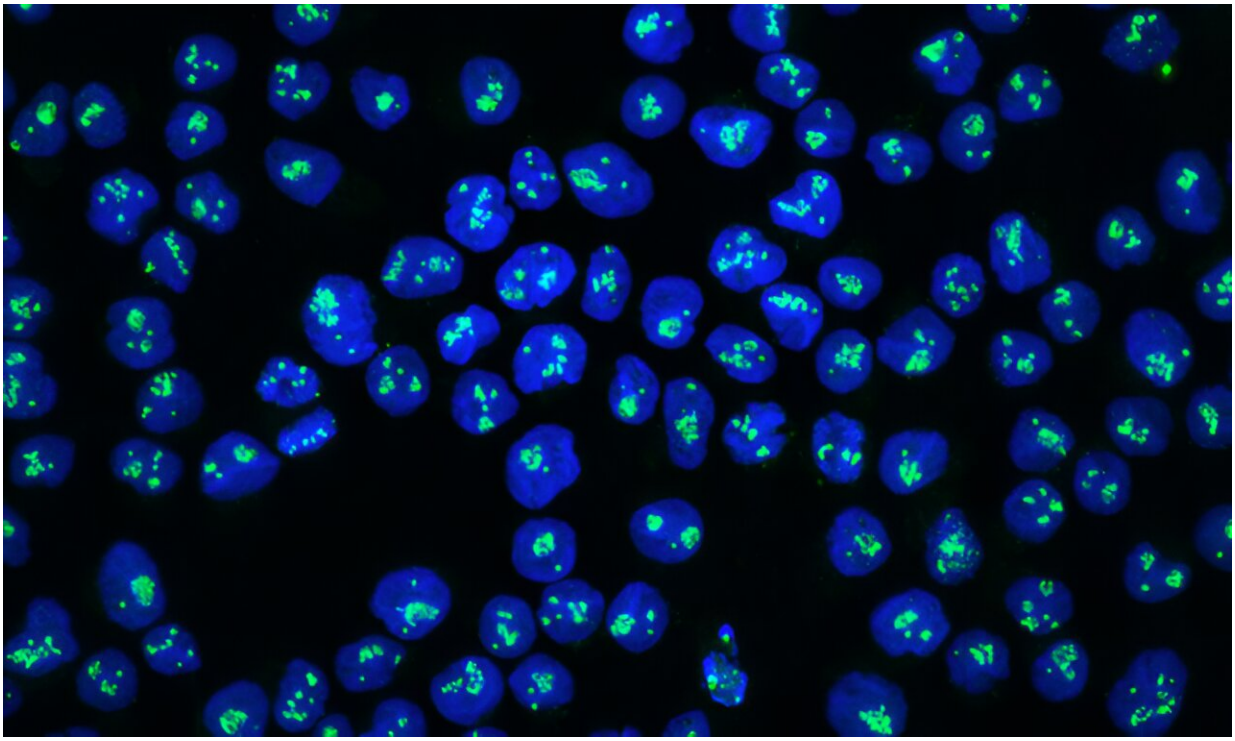

Treating acute lymphoblastic leukaemia cells with the drug CX-5461 disrupts the nucleolar ribosome machinery shown by the fibrillarin protein (green) in the nucleus (blue) that stimulates the nucleolar stress response and initiates leukaemia cell death. Credit: Peter Mac

Researchers have found a new way to potentially treat one of the most common forms of acute lymphoblastic leukemia.

The study, led by WEHI and the Peter MacCallum Cancer Center, was able to kill leukemia cells in the lab and stop cancer cells from growing after identifying two new proteins critical for the development of the aggressive disease. The findings could lead to enhanced treatment options in the future, and plans are underway to develop a clinical trial based on the research.

About 5,200 people are diagnosed with a form of leukemia in Australia each year. An estimated 1,500 of these cases are acute—meaning the blood cancer appears suddenly and grows quickly.

Blood cancers like leukemia are notoriously difficult to treat in adults, with 50% of Australian patients relapsing after the first round of chemotherapy and subsequently becoming resistant to further treatments.

Associate Professor Ashley Ng, a corresponding author on the paper, said this presented a unique treatment challenge for these blood cancers and highlighted the urgent need for new therapeutics.

"About 135,000 people live with a blood cancer or blood disorder in Australia, with 16 people dying every day from the disease," Assoc Prof Ng, a WEHI researcher and clinical hematologist at the Peter MacCallum Cancer Center and Royal Melbourne Hospital, said.

"Despite the medical advancements made in the cancer field over the years, the incidence of blood cancer has grown by 47% in the past decade.

"The best way to enhance treatment options for patients is to continually improve our understanding of how leukemia cancers behave and what drives their growth.

"Our new research has identified two proteins that are critical for the development of B-cell acute lymphoblastic leukemia, expanding our knowledge into how these cancers can form.

"By uncovering this new vulnerability in leukemia formation, we hope to exploit the findings for therapeutic benefit and also apply them to other forms of the disease."

The research has been published in the journal *Science Advances*.

Master regulators

Assoc Prof Ng has spent over a decade researching a protein that regulates gene activity in the cell nucleus, known as ERG. Imbalances in this protein can lead to blood cancers, like acute lymphoblastic leukemia.

His previous research uncovered the protein's critical role in Down syndrome associated blood disease and normal blood cell function, including how B cells—which are essential for producing antibodies to fight against infections—develop.

First author Dr. Kira Behrens said the research team wanted to understand what other types of proteins ERG works with to fuel leukemia development.

"We looked at the proteins that control how specific genes switch 'on' or 'off' to analyze how normal B-cells—and critically, B-cell acute lymphoblastic leukemia—can develop," Dr. Behrens said.

"After analyzing the genes regulated by ERG and another protein, c-MYC, we discovered that these proteins were actually the master regulators of several important pathways and processes within the leukemia cell."

Researchers then narrowed the list down to focus on one pathway essential for making proteins, known as ribosome biogenesis.

This led the team to focus on targeting a key gene essential to this pathway, POL I, which is also controlled by these master regulator proteins.

The gene helps direct an important cell growth and division process that can lead to the development of cancer if it goes awry.

Dr. Behrens said, "By targeting POL I with inhibitors, we were able to kill leukemia cells and stop their growth in our pre-clinical and human tissue models."

"This was a surprising, yet remarkable discovery, as we were able to unravel a new pathway and potential drug target that can hopefully be used in the fight against leukemia in the future."

The study also involved a collaboration with Associate Professor Elaine Sanij (St. Vincent's Institute of Medical Research) whose work focuses on targeting POL I and ribosome biogenesis in cancer therapy.

"The findings show that a subset of aggressive acute lymphoblastic leukemia exhibit a form of addiction to producing of ribosomes, the protein making molecular machinery," Assoc Prof Sanij said.

"They render this aggressive leukemia sensitive to POL I inhibitors which target ribosome production.

"Altogether, our work highlights the importance of developing this new approach to cancer therapy to treat oncogene-driven cancers."

Collaborative power

One of the drugs used in the study to target POL I was an agent developed by the Peter MacCallum Cancer Center.

Professor Rick Pearson, former Associate Director of Laboratory Research at Peter Mac, said the team hopes to mimic the study in a future clinical trial to help patients with acute lymphoblastic leukemia.

"We worked with WEHI researchers to confirm our agent is effective in targeting POL I activity and demonstrated its potency in impeding the leukemia cell growth and division.

"These findings highlight the power of collaboration and the remarkable results that can be achieved when bringing together experts from across various areas.

"We hope this research will translate into successful clinical trials and potentially offer doctors a new treatment option for patients with acute lymphoblastic leukemia," Professor Pearson said.

More information: Kira Behrens et al, ERG and c-MYC regulate a critical gene network in BCR::ABL1-driven B cell acute lymphoblastic leukemia, *Science Advances* (2024). DOI: 10.1126/sciadv.adj8803

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