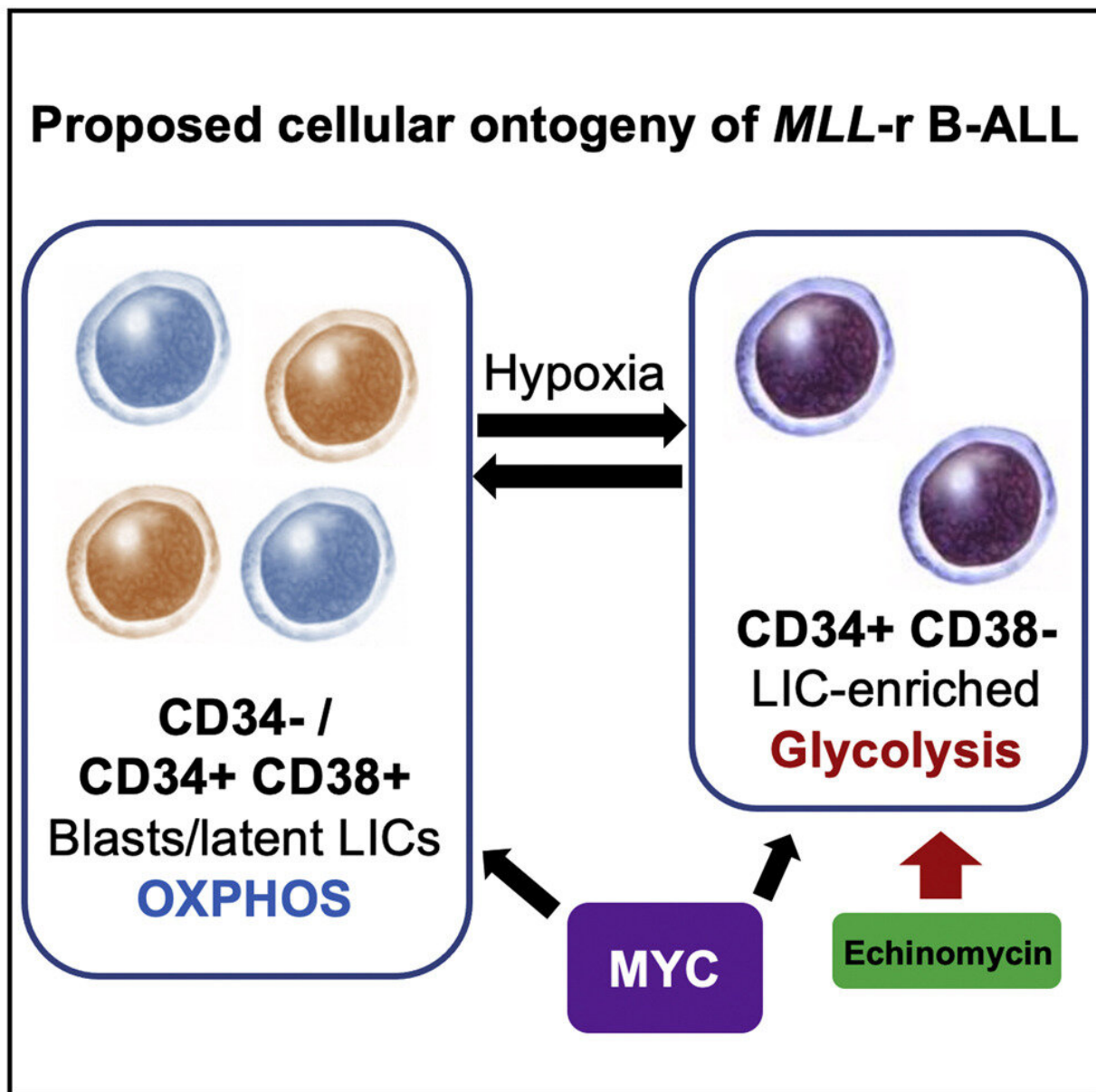


Exploiting a vulnerability in an aggressive leukemia affecting babies

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Graphical abstract. Credit: *Cell Reports* (2022). DOI: 10.1016/j.celrep.2022.110752

Survival has improved greatly in children with acute lymphocytic leukemia (ALL). But a certain form of ALL that occurs mostly in babies is still very lethal, with a survival rate below 50 percent: B-cell acute lymphoblastic leukemia with rearrangements of the mixed lineage leukemia gene, or MLL B-ALL.

"Something about the biology of this type of [leukemia](#) is very peculiar," says Grant Rowe, MD, Ph.D., attending physician in the Dana-Farber/Boston Children's Cancer and Blood Disorders Center. "It can switch its cellular lineage from lymphoid to myeloid and it aggressively infiltrates the nervous system."

New work by Rowe, together with members of the Stem Cell Program and the Hematopoietic Stem Cell Transplant Program, may open a window to treating this aggressive, chemotherapy-resistant form of B-ALL.

Probing leukemia-initiating cells

Knowing that self-renewing leukemia-initiating cells spark relapse of high-risk B-ALL, Rowe and his colleagues wanted to better understand their properties. They used single-cell RNA sequencing to see what genes these cells were turning on at different points, coupled with transplant experiments to study the cells' proliferation. This brought several key insights, published recently in *Cell Reports*.

First, leukemia-initiating cells were more abundant in MLL B-ALL than expected. Second, they could emerge not only from immature,

undifferentiated B-ALL cells, but also from more mature cell populations. And third, they were of two types. "We found an enriched population of apparent leukemia-initiating cells," says Rowe. "But these cells would change state. It turns out that they can adjust their metabolic profile to go from a stem-cell state to a non-stem-cell state, and vice versa."

RNA profiling revealed two distinct metabolic states:

- an active, proliferation and growth state, marked by energy production through oxidative phosphorylation
- a quieter, stem cell state, marked by low-oxygen conditions and [energy production](#) through glycolysis, likely reflecting an ability to remain latent, similar to normal blood stem cells.

The cells' ability to morph between these two states could explain why they are so hard to target, and why MLL-rearranged B-ALL is so dangerous, Rowe says.

Taming high-risk B-ALL aggression

The most surprising discovery was a paradox: When the researchers tried inhibiting leukemia cells in the active proliferation state, more of these cells emerged, contrary to results reported in other forms of leukemia.

"Many therapies in adult leukemia try to target the oxidative phosphorylation state to curb growth," says Rowe. "We thought this infant leukemia would follow that same paradigm, but we were surprised that the intervention had the opposite effect. It slowed overall proliferation, but by forcing the leukemia cells to assume a more resting state, more stem-like cells emerged and made the leukemia more aggressive."

Conversely, Rowe and colleagues found that targeting leukemia-initiating cells in their quiet state, by inhibiting glycolysis and hypoxic signaling, curbed the leukemia. It forced the cells back to the [oxidative phosphorylation](#) state, but they lost their leukemia-initiating properties in the process.

"They don't seem to act like stem cells any more, and don't have the leukemia-initiating properties that seem to be related to relapse," says Rowe. "We need to go after stem cells in this infant leukemia differently than we do in adults."

An agenda for the future

Eventually, these insights could lead to a new approach to taking down this tough cancer. The hypoxic, glycolytic state is a way for the cancer to lie low, but it's also a vulnerability that presents an opportunity.

A chemotherapy drug previously used for solid tumors, echinomycin, inhibits hypoxic signaling. Rowe and colleagues tried it in mice transplanted with human MLL-rearranged B-ALL. Two weeks of echinomycin treatment slowed the growth the leukemia and depleted leukemia-initiating cells.

"We know how to dose this drug in children and its safety profiles," says Rowe. "But our next step is to try to better understand the properties of leukemia-initiating cells, see if they're shared in other aggressive leukemias, and better understand how to target them."

His lab is also interested in doing similar profiling of other forms of ALL across the age spectrum.

"Hopefully we can better understand the initiating cell properties using this type of approach, and identify new vulnerabilities that could be

predicted by genetics or other factors read out from the tumor."

"Studies like these from Dr. Rowe's lab provide deep insight into the biology of this aggressive type of childhood leukemia and may help us develop desperately needed novel therapeutic approaches," says Scott Armstrong, MD, Ph.D., associate chief of hematology/oncology at Boston Children's and president of Dana-Farber/Boston Children's.

More information: Vivian Morris et al, Hypoxic, glycolytic metabolism is a vulnerability of B-acute lymphoblastic leukemia-initiating cells, *Cell Reports* (2022). [DOI: 10.1016/j.celrep.2022.110752](https://doi.org/10.1016/j.celrep.2022.110752)

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