Suspect eliminated as a therapeutic target in B cell lymphoma

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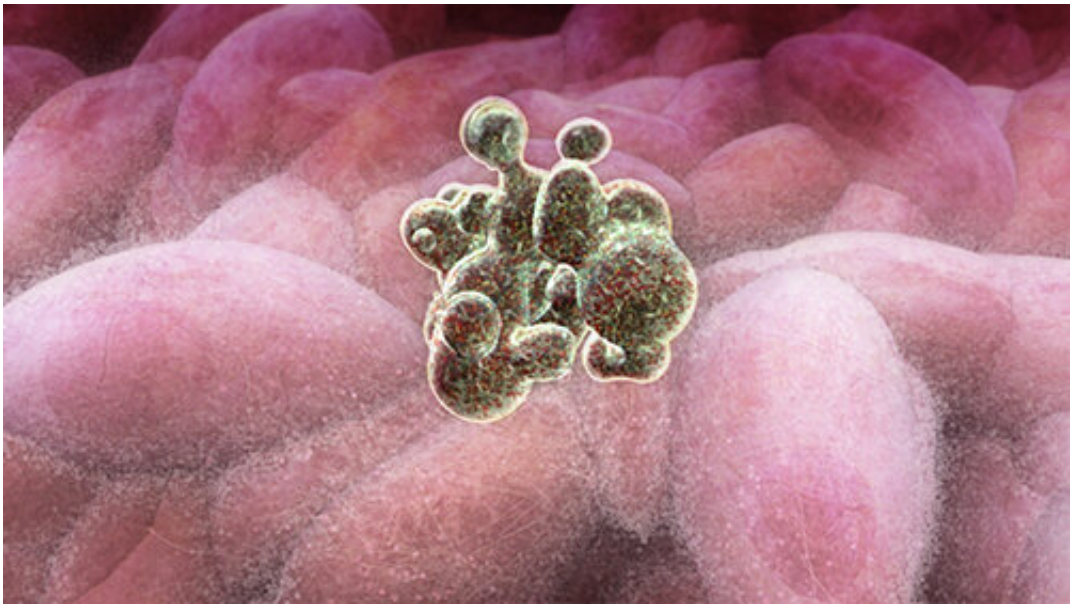

Credit: Walter and Eliza Hall Institute of Medical Research (WEHI)

Walter and Eliza Hall Institute researchers have narrowed the focus on which survival proteins are important for the survival of B cell lymphomas, eliminating the protein BCL-W from the "suspect list."

Using gene editing technology, the research team showed that human B cell lymphoma cell lines can survive without BCL-W—dismissing this protein as a potential therapeutic target for these particular B cell lymphomas. The discovery upends earlier speculation that BCL-W could

be an important survival factor for B cell lymphomas, and will focus future research efforts on more important targets.

The research, led by Dr. Gemma Kelly and Dr. Sarah Diepstraten, was published in the journal *Blood Advances*.

Lymphoma survival factors

BCL-W is a member of the BCL-2 protein family, and promotes cancer cell survival by inhibiting apoptotic cell death. Other pro-survival members of the BCL-2 family, including the proteins BCL-2 and MCL-1, have shown promise as targets for anti-cancer drugs, particularly for certain leukemias and lymphomas.

Dr. Kelly said that recent research from other groups showed that many B cell lymphomas had increased levels of BCL-W, suggesting that this protein may promote cancer cell survival.

"This led to speculation that drugs targeting BCL-W could be useful for treating B cell lymphomas," she said.

Eliminating a suspect

To investigate whether inhibiting BCL-W could be effective in treating B cell lymphomas, the team reduced the amount of BCL-W protein within B cell lymphoma cell lines.

Dr. Diepstraten said that in the B cell lymphoma cell lines tested, losing BCL-W did not impact cell survival. "We showed BCL-W was not required by these lymphoma cells, suggesting that drugs targeting BCL-W would not be effective treatments for all B cell lymphomas," Dr. Diepstraten said.

"We also investigated the possibility that high levels of BCL-W in lymphomas might cooperate with other related survival proteins, such as BCL-2 or MCL-1, to promote survival," she said. "However, this was not the case: loss of BCL-W did not sensitize lymphoma cells to drugs that inhibit BCL-2 or MCL-1."

Shifting focus

Dr. Kelly said the results showed that, at least for certain B cell lymphomas, targeting BCL-W should not be a priority for future research and drug development. "It is likely that other pro-survival proteins are much more important in these diseases," she said.

"BCL-W is considered to be a particularly appealing therapeutic target because it is not required for the function of most normal (non-cancerous) cells in the body, so we would not expect drugs targeting BCL-W to have significant side-effects.

"While BCL-W may not be a critical survival factor for B cell lymphomas, it is possible that BCL-W may contribute to the survival or drug resistance of other types of cancer—meaning that BCL-W inhibitors could be relevant in these cases," Dr. Kelly said.

More information: Sarah T. Diepstraten et al. BCL-W is dispensable for the sustained survival of select Burkitt lymphoma and diffuse large B-cell lymphoma cell lines, *Blood Advances* (2020). DOI: 10.1182/bloodadvances.2019000541

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