New therapeutic target identified for rare virus-associated lymphomas

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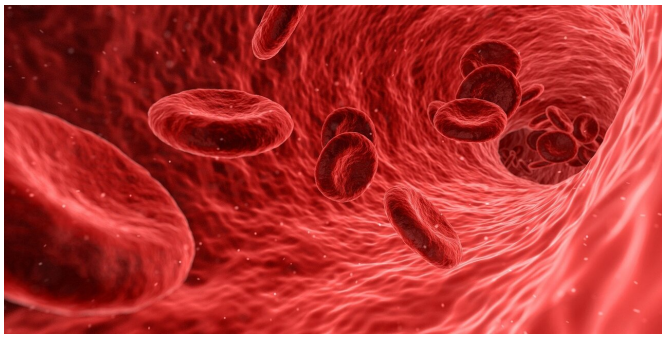

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Targeting a "cell survival" protein could be a valuable new approach to treating certain blood cancers associated with Epstein-Barr virus (EBV), according to research resulting from a collaboration between scientists at the Walter and Eliza Hall Institute, Australia and the University of Birmingham, UK.

The research team discovered that the protein BCL-XL was required for survival of cells from EBV-associated T/NK cell lymphomas, which are rare but aggressive blood cancers, mainly found in East Asia and South America.

The discovery, published in *Blood Advances*, suggested that blocking the function of BCL-XL could be an effective approach to treating these lymphomas, and that similar treatments might be effective for other cancers associated with EBV.

The research was led by Dr. Nenad Sejic and Dr. Gemma Kelly from the Walter and Eliza Hall Institute, with Dr. Claire Shannon-Lowe from the University of Birmingham.

Tackling a rare cancer

EBV is one of the most common viruses worldwide, infecting most people at some point in their lives—often without any symptoms. EBV causes "glandular fever" in some people, particularly in young adults, and also increases a person's risk of developing certain cancers.

Some EBV-associated blood cell-derived cancers arise from immune cells called NK and T cells, said Dr. Sejic. "While these EBV-associated T/NK cell lymphomas are very rare, they are also very aggressive and respond poorly to chemotherapy and radiotherapy. New, effective treatments would be of great benefit to people with these lymphomas—most of whom live in East Asia or South America," he said.

The research team focused on the proteins that keep EBV-associated T/NK cell lymphoma cells alive.

"In the last decade there has been great success in targeting 'cell survival' proteins in a range of blood cell-derived cancers, so we looked to see whether this approach might be effective in EBV-associated T/NK cell lymphomas," Dr. Sejic said.

"Using T/NK lymphoma cell lines in the laboratory, derived from patients, we showed that the protein BCL-XL was essential for keeping these cells alive. When we blocked BCL-XL, the cells rapidly died, suggesting that targeting this protein might be an effective treatment for EBV-associated T/NK cell lymphomas," he said.

"The research also identified that blocking both BCL-XL plus another related survival protein, MCL-1, could further enhance the killing of these T/NK lymphoma cells."

New approaches to targeting cell survival

Dr. Kelly said using medicines to target BCL-XL as a cancer treatment had proved challenging because this protein is also important for the

survival of platelets, a vital cell type in the body.

"There is intense interest in developing new approaches to target BCL-XL given many cancers rely on this survival protein. We are hopeful there will soon be new and safe approaches to blocking BCL-XL function, or even lowering the levels of BCL-XL selectively in cancer cells," she said.

"Our research has identified EBV-associated T/NK cell lymphomas as one type of cancer that could respond well to these approaches, if they are shown to be safe. The ultimate goal would be to find approaches to safely combine BCL-XL inhibitors with existing MCL-1 inhibitory drugs that are already in clinical trials, given we have seen a role for MCL-1 in these cancers."

The research also highlighted the potential for BCL-XL to be a therapeutic target in other EBV-associated cancers.

"While some more-common EBV-associated cancers have already been well-studied, we hope our research might inspire further investigations of other rare cancers, for which new treatments are urgently needed," Dr. Kelly said.

More information: BCL-XL inhibition by BH3-mimetic drugs induces apoptosis in models of Epstein-Barr virus–associated T/NK-cell lymphoma. *Blood Advances* (2020). DOI: 10.1182/bloodadvances.2020002446

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