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STING agonists developed to induce cellular death in B cell malignancies

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In almost every mammalian cell, you will find the endoplasmic reticulum, a network of continuous membranes responsible for controlling metabolism as well as the folding, assembly and secretion of proteins. Since the endoplasmic reticulum is critical in manufacturing important proteins that facilitate communication between cells, researchers are exploring new ways to find important targets within these membranes that could help stimulate immune responses against cancer cells.

Now, new research from The Wistar Institute shows how one protein found on the endoplasmic reticulum can serve as a target for stimulating the immune system and a more direct target for cellular death in B cell malignancies. The findings of the study were published in the journal Cancer Research.

A protein called Stimulator of interferon genes (STING) is found on the endoplasmic reticulum and plays a critical role in producing type I interferons that help regulate the immune system. A new class of drugs called STING agonists were developed to induce powerful immune responses by boosting the production of interferons as an adjuvant therapy, meaning they were applied to enhance response to therapy. Improved immune responses were observed when STING agonists were used in cancer immunotherapy or as vaccine adjuvants.

As an adjuvant therapy, STING agonists play an accessory role in eliciting a response. However, additional studies confirmed that these drugs also induce apoptosis in normal and malignant B cells, suggesting that they could be used as a primary therapy in certain types of leukemia, lymphoma and multiple myeloma. The responses that have been observed thus far are transient, meaning that longer responses could lead to better direct treatment in B cell malignancies like chronic lymphocytic leukemia and multiple myeloma.

"In non-B cells, STING agonists stimulate the production of interferons, but since they induce apoptosis in B cells, these B cells do not live long enough to help boost the immune response," said Chih-Chi Andrew Hu, Ph.D., associate professor in the Translational Tumor Immunology program at The Wistar Institute and senior author of the study. "We wanted to determine why STING agonists behave differently in normal and malignant B cells and how to extend this cytotoxic activity in malignant B cell leukemia, lymphoma and multiple myeloma."

Hu and his colleagues focused their attention on the IRE-1/XBP-1 stress response pathway found in the endoplasmic reticulum. This pathway must be activated for STING to function properly in non-B cells. If cells are deficient in either IRE-1 or XBP-1, the cells cannot produce interferons as a response to STING agonists. Additionally, B-cell leukemia, lymphoma, and myeloma require the IRE-1/XBP-1 pathway to be activated for survival. Results showed the activation of this pathway reduces the level of apoptosis, suggesting that lowering activity of this pathway is important in promoting death of malignant B cells. Interestingly, stimulation by STING agonists also suppresses the IRE-1/XBP-1 pathway, which increases the level of apoptosis in malignant B cells. The team further confirmed these results in animal models, as treatment with STING agonists led to regression of chronic lymphocytic leukemia and multiple myeloma in mice.

"This specific cytotoxicity toward B cells strongly supports the use of STING agonists in the treatment of B cell hematologic malignancies," said Chih-Hang Anthony Tang, M.D., Ph.D., a postdoctoral fellow in the laboratory of Dr. Hu and first author of the study. "We also believe that cytotoxicity in normal B cells can be managed with the administration of intravenous immunoglobulin that can help maintain normal levels of antibodies while treatment is being administered. This is something we plan on studying further."

The Wistar Institute's business development team is looking for a co-development partner for the advancement of novel STING agonists in treating B-cell hematologic malignancies.

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