New mechanism of cell survival in chronic lymphocytic leukemia

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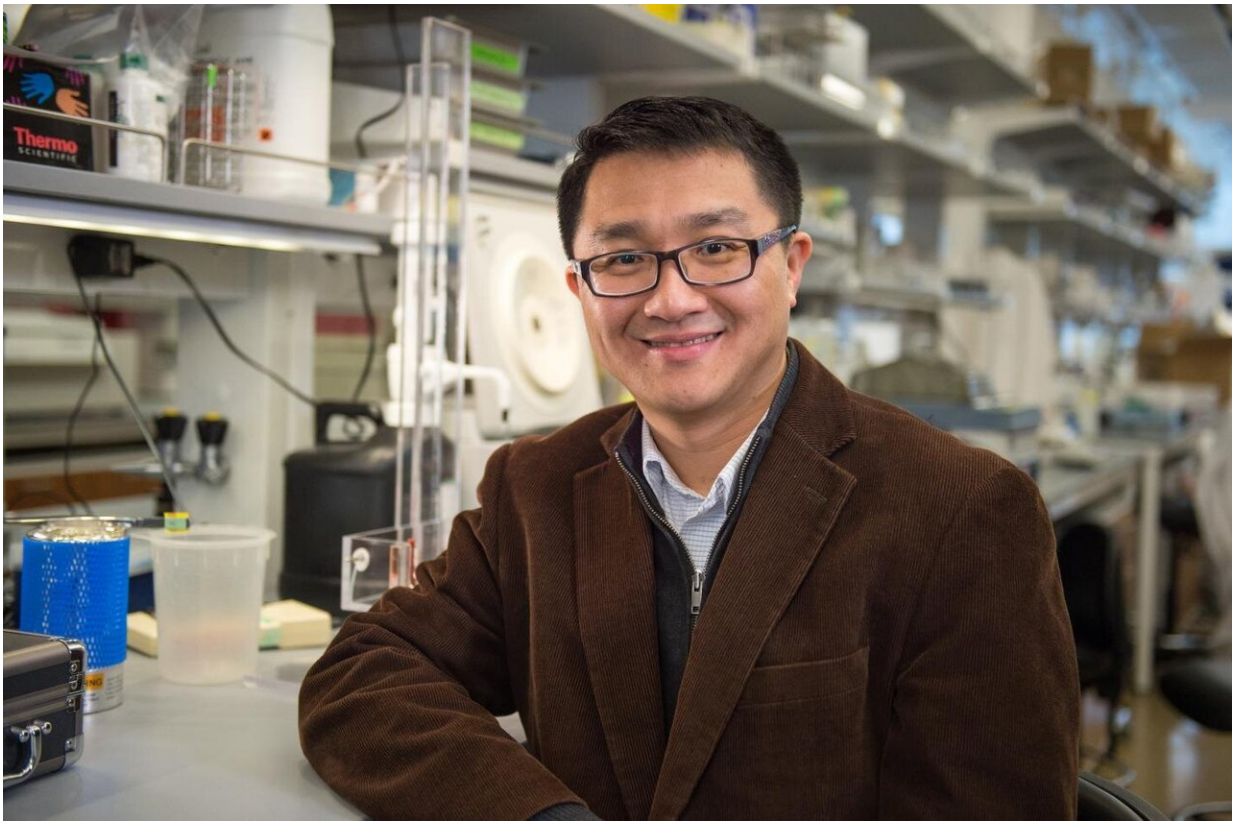

Dr. Andrew Hu Credit: The Wistar Institute

Researchers at The Wistar Institute unraveled a mechanism employed by chronic lymphocytic leukemia (CLL) cells for their survival. According to the study, published online in *Cellular & Molecular Immunology*,

malignant B cells turn down expression of the STING protein to allow for increased expression of B cell receptor on their surface.

STING is located on the membrane of the endoplasmic reticulum (ER), the cell's protein manufacturing and packaging factory, and is critical for sensing the presence of DNA in the cytoplasm, which can be associated with cell anomalies or infection by viruses and intracellular bacteria. In response to these conditions, STING promotes production of type I interferons and other pro-inflammatory molecules to enhance immunity. Because of this function, STING activation has been proposed as a strategy for cancer and infectious disease immunotherapy.

The lab of Chih-Chi Andrew Hu, Ph.D., professor in Wistar's Immunology, Microenvironment & Metastasis Program, studies the role of STING in the context of B cell differentiation and CLL. They previously discovered that STING activation by agonists induce cell death in normal and malignant B cells.

"Malignant CLL cells typically have low STING levels and strong B cell receptor (BCR) signaling that supports their survival," said Hu, who is senior author on the study. "We explored the role of STING in BCR and B cell differentiation and discovered that reduction in STING expression could contribute to the robust BCR signaling phenotype in CLL cells."

To investigate STING function in B cells, Hu and colleagues generated two genetic mouse models harboring a permanently activated STING mutant (STING V154M) and lacking STING in B cells (B cell-specific STING knockout), respectively. B cells purified from STING V154M mice had reduced BCR expression and signaling upon stimulation, due to activated STING that could efficiently cause destruction of the BCR through a mechanism called ER-associated degradation (ERAD). As a result, activated STING in B cells suppressed formation of plasma cells and antibody production. Conversely, B cells purified from B cell-

specific STING knockout mice showed higher levels of BCR and more robust BCR signaling in response to stimulation, and STING deficiency in B cells promoted formation of plasma cells and antibody production in mice.

"Our studies point to a novel B cell-intrinsic role of STING in regulating BCR signaling and plasma cell differentiation," said Chih-Hang Anthony Tang, M.D., Ph.D., a staff scientist in the Hu lab and co-corresponding author of the study. "Our findings also suggest that CLL cells may downregulate STING to promote a stronger BCR signaling to support their survival."

While STING downregulation is also present in other cancer types, it serves the tumor through a different, extrinsic function, reducing the production of type I interferons and preventing activation of antitumor immunity.

More information: Chih-Hang Anthony Tang et al, STING regulates BCR signaling in normal and malignant B cells, *Cellular & Molecular Immunology* (2020). DOI: 10.1038/s41423-020-00552-0

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