Discovery of relationship between proteins may impact development of cancer therapies

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By identifying a surprising association of two intracellular proteins, University of Iowa researchers have laid the groundwork for the development of new therapies to treat B cell lymphomas and autoimmune disease.

The researchers studied mouse B cells expressing the viral protein Latent Membrane Protein 1 (LMP1), which has been implicated in several types of cancer because of its role in the proliferation and survival of Epstein-Barr virus infected B cells. They discovered that LMP1 needs the cellular protein Tumor Necrosis Factor Receptor-Associated Factor 6 (TRAF6) to promote its B cell activation signaling pathways.

The study, published recently in the Journal of Biological Chemistry, also shows that LMP1 and CD40 – a normal activating receptor of B cells – both use TRAF6 as a key signaling protein, but in different ways. LMP1 mimics CD40 in delivering activation signals to B cells, but LMP1's signals are amplified and sustained, resulting in B cell hyper-activation.

B cells are a type of white blood cell. They normally mature into plasma cells that produce proteins called antibodies necessary to fight off infections. But in the process of modifying antibody genes, mistakes can cause mutations. With an accumulation of such mutations, B cells can become cancerous, which is why B cell malignancies are relatively common.

"We found that TRAF6 is essential for LMP1 functions, and that it interacts with LMP1 in a way that is distinct from the way in which TRAF6 interacts with CD40," said lead author Kelly Arcipowski, a Ph.D. candidate in the UI Molecular and Cellular Biology Interdisciplinary Graduate Program. "Thus, it might be possible to target LMP1 signaling without disrupting normal immune function. This information is valuable to the development of new therapies to target LMP1-mediated pathogenesis, including B cell lymphomas and autoimmune disease."

B-cell lymphomas include Hodgkin's lymphomas and most non-Hodgkin's lymphomas. Examples of autoimmune diseases in which LMP1 is implicated are rheumatoid arthritis and systemic lupus erythematosus (SLE).

LMP1 is produced by a normally latent gene that is expressed when Epstein-Barr virus, a herpes virus that infects greater than 90 percent of humans, becomes reactivated from its inactive state. This can occur in flares of autoimmune disease, and in people who are immune-deficient. Epstein-Barr virus can thus become activated in cases of late-stage AIDS or organ and bone marrow transplant recipients who are immunosuppressed to prevent rejection of the transplant.

While LMP1 contributes to the formation of a tumor, it isn't an ideal target for therapeutics. LMP1 is a protein that is being constantly internalized from the cell surface, prompting researchers to instead target the signaling pathway.

"(Researchers) first thought you would be targeting the normal protein (CD40), too," said senior study author Gail Bishop, Ph.D., professor of microbiology at the UI Carver College of Medicine and director of the Immunology Interdisciplinary Graduate Program. "What our lab has discovered over the years is that LMP1 produces CD40-like effects

using the same proteins in different ways, and therefore that opens a window to targeting just LMP1."

Arcipowski currently is researching how TRAF6 is activating the LMP1 signaling pathway.
"If you figured out exactly which part of TRAF6 was binding to LMP1, you could target that specific interaction while leaving TRAF6's association with CD40 intact," Arcipowski said.

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