Researchers uncover new mechanism of immune-cell activation

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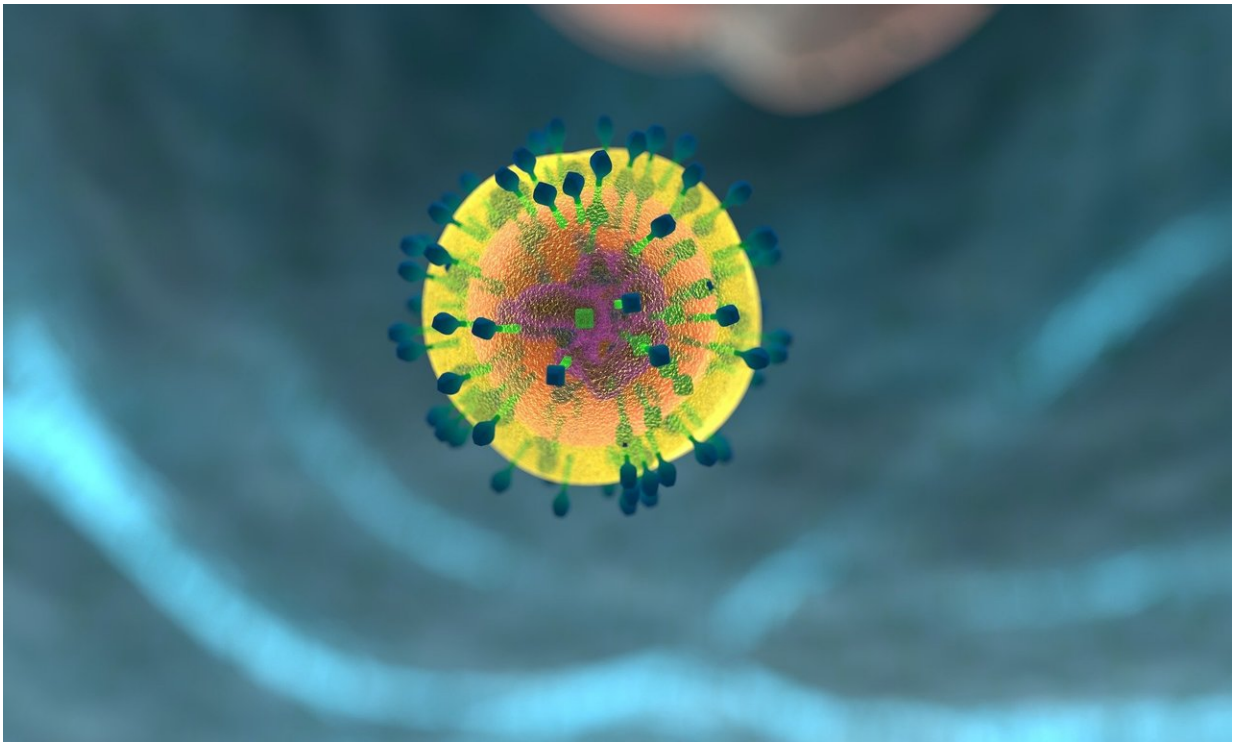

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When antibody-producing immune cells encounter infectious pathogens for the first time, they engage a signal cascade to generate a massive activation signal within seconds. The mechanisms underlying this acute initial activation have not been fully understood. In a new study by Yale Cancer Center, scientists have identified the short endosomal protein

interferon-inducible transmembrane protein 3 or IFITM3 as a central amplifier to supercharge activation of immune cells. The findings are published online today in the journal *Nature*.

IFITM3 functions like glue to rapidly assemble and tighten up large complexes of signaling molecules that together generate the activation signal. Without IFITM3, antibody-producing B-cells cannot vigorously fight infections and do not generate immunological "memory" of the infectious particles that they encountered.

"Genetic deletion of IFITM3 in B-cells did not affect their survival, but when the B-cells encountered foreign pathogen, their response was sluggish," said Markus Müschen, MD, Ph.D., Director of the Center of Molecular and Cellular Oncology, Arthur H. and Isabel Bunker Professor of Medicine (Hematology) at Yale Cancer Center, and senior author of the study. "Unexpectedly, we discovered IFITM3 at the center of a new signaling cascade that B-cells in the immune system need to mount a vigorous immune response."

Unfortunately, the novel IFITM3 signal amplifier functions as a double-edged sword. While this mechanism helps immune cells to fight infections, the new study also showed that cancer cells use the exact same mechanism for activation and explosive growth.

"Studying patients with B-cell malignancies in three clinical trials, we found high expression of IFITM3 among the strongest predictors of poor clinical outcome," said Müschen. "This was unexpected because this tiny protein was known ability to make cell membranes more rigid, but we had no idea what its function could be in B-cell tumors."

On the upside, loss of IFITM3 did not only impact immune cells, but also headed off the development of cancer. In the absence of IFITM3, normal cells that acquire cancer-causing mutations are protected from

malignant transformation and cannot initiate the critical signal cascade that is needed for cancerous growth.

"Interestingly, the first step of this cascade, the initial activation of IFITM3 can be blocked by kinase inhibitors that are already available in the clinic," added Müschen. "Going forward, we will test whether some of these kinase inhibitors are effective in blocking IFITM3-dependent signal amplification in cancer."

More information: Jaewoong Lee et al. IFITM3 functions as a PIP3 scaffold to amplify PI3K signaling in B cells, *Nature* (2020). DOI: 10.1038/s41586-020-2884-6

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