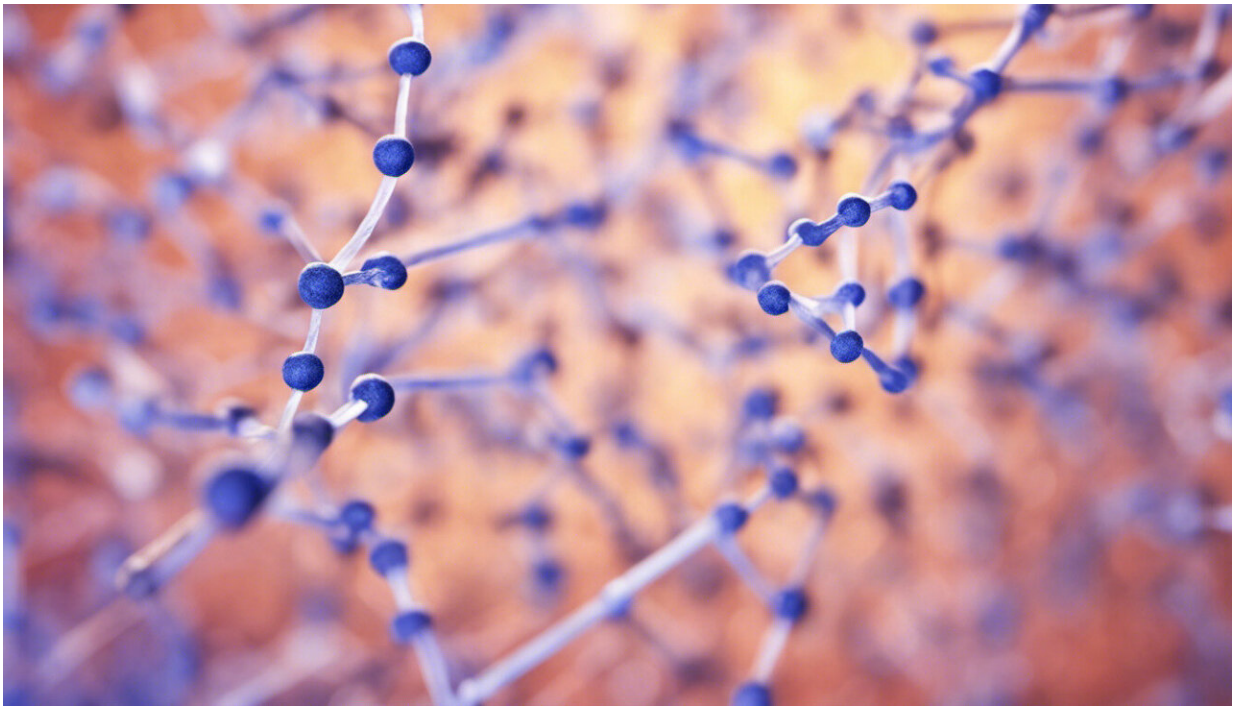
Enzyme helps detect foreign DNA

September 11 2015



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The human immune system responds to DNA from pathogens by triggering the production of a defense molecule known as interferon. A research team led by A*STAR scientists has now pinpointed an enzyme integral to this process, called Bruton's tyrosine kinase (BTK), which provides a potential new target for drug development.

The presence of bacterial and viral nucleic acids inside the cell is

generally undesirable, so a protein called DDX41 responds to microbial invaders by binding this foreign DNA. DDX41 then recruits another protein called STING to help launch an immune defense. STING, an acronym for stimulator of interferon genes, does what its name suggests and turns on the genes that code for interferon, a type of cytokine.

However, a team led by Kong Peng Lam, executive director of the A*STAR Bioprocessing Technology Institute, discovered this pathway from DNA sensing to interferon production also relies on BTK.

"Our findings indicate that agents targeting BTK activation could yield new and broad-based antimicrobial agents," says Lam.

Lam's lab group at A*STAR, together with scientists from the National University of Singapore, studied mouse cells that lacked the gene necessary for making BTK. They treated these cells with bacterial DNA or infected them directly with pathogens such as Listeria and malaria. In each instance, interferon production was impaired, indicating the essential role for BTK in fighting off infections.

The researchers then looked at human cells to identify the mechanism by which BTK works with DDX41 and STING to promote antimicrobial immunity. They showed that when pathogens invade cells, BTK physically attaches to DDX41 and adds a phosphorylation tag to a residue of the protein. This phosphorylation primes DDX41 to bind the foreign DNA and also stabilizes DDX41's interaction with STING, which in turn activates the genes necessary to generate interferon.

Pharmaceutical companies are already working on drugs that modulate BTK activity. One BTK inhibitor, called ibrutinib, has been approved for the treatment of leukemia and lymphoma. Others, which are for people suffering from autoimmune diseases such as rheumatoid arthritis and lupus, are undergoing clinical trials.

According to Koon-Guan Lee, an immunologist at A*STAR and first author of the study, the discovery that BTK also plays a role in warding off pathogens "further suggests that BTK inhibitors could potentially be used to dampen the cytokine storms seen in sepsis or in severe infections that could otherwise kill the host."

More information: "Bruton's tyrosine kinase phosphorylates DDX41 and activates its binding of dsDNA and STING to initiate type 1 interferon response." *Cell Reports* 10, 1055–1065 (2015). dx.doi.org/10.1016/j.celrep.2015.01.039

Provided by Agency for Science, Technology and Research (A*STAR), Singapore