A single enzyme plays a critical role in helping the body effectively fight viral infection

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Credit: AI-generated image (disclaimer)

The body's initial response to invading bacteria or viruses is mediated by the innate immune system, wherein cells secrete signaling factors called cytokines that promote inflammation and stimulate a generalized counterattack against targets perceived as 'foreign'. The protein Toll-like

receptor 3 (TLR3), for instance, helps initiate the innate immune response against viruses.

Kong-Peng Lam at the A*STAR Bioprocessing Technology Institute and co-workers have now gained insights into how TLR3 helps 'rally the troops'. They showed that TLR3 recognizes viral genetic material, and subsequently undergoes activation via the enzymatic addition of phosphate chemical groups to specific amino acids — a process known as phosphorylation.

The researchers identified Bruton's tyrosine kinase (BTK) as a TLR3-activating enzyme in this pathway. They found BTK to be a promising candidate based on its prominent role in immune function: mutations in this gene result in X-linked agammaglobulinemia (XLA), a disease characterized by failures in B cell production and function. "These patients are also very susceptible to recurrent bacterial and viral infections," says Lam, "which suggested that BTK might be involved in innate immunity."

To test their hypothesis, the researchers injected mice with polyribocytidylic acid, a molecule that resembles viral RNA and triggers an antiviral immune response. In normal mice, this treatment can trigger a strong inflammatory overreaction that leads to fatal septic shock. However, both BTK-deficient and TLR3-deficient mice proved resistant to septic shock, suggesting these two molecules work together in a common pathway. TLR3 activation also generates signals that stimulate production of the immunostimulatory molecule interferon β, but the absence of BTK effectively crippled this response in mice. Accordingly, BTK-deficient mice proved far less capable of clearing dengue virus from their system than wild-type animals.

Biochemical experiments clearly demonstrated that BTK was required for the phosphorylation of TLR3. Following activation, TLR3 binds to

TRIF, an ‘adapter’ protein that allows it to interact with various other signaling factors. However, without BTK, TLR3 fails to undergo phosphorylation. As a result, TRIF cannot bind to downstream signaling molecules, thus stopping the signaling cascade in its tracks (see image).

Lam now hopes to determine whether BTK represents a general component of innate immunity outside of the TLR3 pathway. In the meantime, he suggests that BTK-targeting drugs could prove a useful tool for immunomodulation. “Conceptually, BTK inhibitors could be used to dampen exaggerated immune responses when the host ‘cytokine storm’ is a curse rather than a blessing, such as in the case of SARS coronavirus infection,” says Lam.

More information: Lee, K. G. et al. Bruton’s tyrosine kinase phosphorylates Toll-like receptor 3 to initiate antiviral response. *Proceedings of the National Academy of Sciences* 109, 5791–5796 (2012). dx.doi.org/10.1073/pnas.1119238109

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