Who goes there? Novel complex senses viral infection

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Double-stranded (ds) RNA viruses are a diverse group of viruses that include rotaviruses, a common cause of gastroenteritis. The ability of the immune system to detect and destroy viruses is critical for human health and survival. Now, a study published by Cell Press in the June 23rd issue of the journal *Immunity* identifies a novel sensor that is necessary to activate the immune response to viral infection. The research enhances our understanding of the complex and overlapping mechanisms our immune cells use to thwart infection.

Viruses are infectious agents composed of nucleic acid (DNA or RNA) and a protective protein coating. Viruses infect all types of organisms and can hijack host cell machinery to replicate (make many copies of themselves). The innate immune system is the body's first line of defense against viruses and detects infection by sensing viral nucleic acids. Detection of a virus leads to activation of the type 1 interferon (IFN) response, a powerful weapon that is named for its ability to "interfere" with viral replication.

"During the past decade, major efforts using genetic approaches have identified three major classes of innate immune receptors for sensing microbial nucleic acids," says senior study author, Dr. Yong-Jun Liu from the University of Texas MD Anderson Cancer Center. "However, there is a major gap in our understanding of how these receptors bind nucleic acids and whether additional receptors or coreceptors exist. For example, Toll-like receptor 3 (TLR3) has been known as the only TLR that sense dsRNA and use adaptor molecule TRIF to trigger antiviral

immune responses. Intriguingly, macrophages and dendritic cells from TLR3-deficient mice but not from TRIF-deficient mice could still make significant antiviral IFN responses to dsRNA, suggesting the presence of additional TRIF-dependent dsRNA sensors"

Dr. Liu and colleagues investigated this issue by isolating and characterizing proteins that bound to a synthetic form of double-stranded viral RNA called poly I:C. Looking inside myeloid dendritic cells that are known to play a key role in pathogen detection, the researchers found two known dsRNA sensors as well as a previously unknown viral sensor complex that consists of three RNA helicases, DDX1, DDX21 and DHX36, and the adaptor molecule TRIF. This multi-helicase-TRIF complex bound directly to poly I:C and triggered an immune response. Dr. Liu's team went on to show that DDX1 directly bound to poly I:C while DDX21 and DHX36 served as bridges to TRIF and that each of the four components was essential for the appropriate immune response. Importantly, interference with the complex impaired the immune response to influenza A and a type of rotavirus.

"Our study suggests that the DDX1-DDX21-DHX36 complex represents the missing poly I:C sensor and may represent an early sensor of poly I:C that triggers initial IFN production," concludes Dr. Liu. "This initial IFN production may help to activate other know dsRNA sensors which will serve to further amplify the IFN response. This may explain the overlapping functions of the known dsRNA sensors." A better understanding of the complex mechanisms our immune system uses to detect viruses will contribute to the future design of more effective antiviral therapeutics.

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