Genome-wide study reveals how key immune sensors arrive at the front lines of infection

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In a healthy immune system, invading pathogens trigger a cascade of alerts and responses to fight off the infection. Sensors called toll-like receptors, or TLRs, act as one of the first lines of defense. Two of these sensors, known as TLR7 and TLR9, specifically recognize and respond to microbial RNA and DNA, respectively. But what determines how these TLRs get where they need to be and sound the alarm for pathogen infection?

To answer this question, a team led by Sumit Chanda, Ph.D. and colleagues at Sanford-Burnham Medical Research Institute (Sanford-Burnham) used a technique known as RNA interference (RNAi) to silence each gene in the human genome one by one. In doing so, they were able to determine which genes are crucial for TLR7 and TLR9 functions and which are dispensable. In their study, published March 14 in *Cell Host & Microbe*, the team identified 190 proteins that contribute to our ability to detect and respond to microbial infection. These findings could help scientists develop new strategies to manipulate immune responses for treatment of autoimmune disorders and microbial infections.

Cellular sentinels

While most TLRs sit on the cell's surface, monitoring the surrounding environment for signs of infection, TLR7 and TLR9 are found in the cell's endosomes, membrane-bound compartments that normally shuttle

proteins from one place to another. During infection, many bacteria and viruses use endosomes to gain access to cellular machinery and hide from other components of the body's immune system.

"Our cells use TLR7 and TLR9 as policemen to inspect the endosomes, a critical gateway for a microbe's border crossing into the cell," said Chanda, associate professor in Sanford-Burnham's Infectious and Inflammatory Disease Center and senior author of the study. "These receptors can initiate cellular communications that set an anti-microbial defense mechanism into motion, both in the cell that's being invaded and in the cells around it. In this study, we wanted to better understand the network that regulates that response once a foreign agent is detected in the endosome."

TLRs have been widely studied and work in the field garnered a Nobel Prize in 2011. Many pathogens, including HIV, Group A streptococcus, and the influenza virus, elicit a response from TLR7 or TLR9 in the endosomes of cells. However, TLR7 and TLR9 can end up mistakenly triggering an immune response against the host, instead of the invader, if there are breakdowns in this first-responder network.

The search for TLR7/9 co-factors

In their study, Chanda and his team used an RNAi screen to identify 190 genes that cells rely upon to coordinate a response to a pathogen that has breached the endosome. Using advanced computational methods, they were able to reconstruct a molecular blueprint that revealed the intricate wiring of this critical immune defense network.

"We then drilled down and looked at one gene from the RNAi screen—called HRS—which was shown to play a fundamental role in localizing these receptors to the endosomes," said Chih-yuan Chiang, Ph.D., a postdoctoral associate in Chanda's laboratory and co-first author

of the study.

Proper functioning of the immune system depends on these critical receptors getting to right place—the endosome. Send TLR7 and TLR9 to the wrong place, and the host is not only susceptible to infection, but also to autoimmune diseases. The team found that without this HRS protein, TLR9 can't do its job because it isn't delivered to the right location. HRS is part of a larger complex that recognizes and sorts other proteins into various internal vesicles (including endosomes).

"This study provides important biological insight into how one protein directs cellular sentinels to their guard posts," said Amanda Opaluch, Ph.D., also a co-first author of the study. "But overall, the study provides a 30,000-foot view of how the front line of our immune system carefully balances the need for a strong defense against pathogens and an over-reactive response that can trigger autoimmunity. The novel regulatory mechanisms that we have uncovered will be the subject of many further investigations for their impact in disease."

Chanda's group now plans to search for chemical compounds that might shut down errant signaling in the TLR7 and TLR9 system, which is implicated in several autoimmune diseases, including lupus, diabetes, inflammatory bowel disease.

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