Researchers examine human immune response to virus at the atomic level

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A team of biochemists has identified the molecular mechanism by which an immune response is triggered by the invading viruses, according to recent research.

The results could eventually lead to new therapies for many different kinds of viral infections, from the common cold to hepatitis and AIDS, according to Dr. Pingwei Li, Texas A&M University's department of biochemistry and biophysics.

"This work provided insight into how our immune system recognizes viral RNA at the atomic level," Li said.

The results of the team's research were published on July 15 by *Structure* of Cell Press, said Li, who is one of a 10-member team, four of who are with Li's department.

In the last few years, Li's group studied an enzyme called "RIG-I" that senses the presence of foreign RNA and triggers an innate immune response.

Unlike an adaptive immune response, innate immune response gives immediate protection against infection. Adaptive immune responses are learned by the body -- or "taught" as with inoculation, Li said. But innate immunity is built right into the cell's genetic structure and is ready to respond whenever a pathogen invades the host.

The innate immune system can rapidly respond to an entirely novel virus or bacteriological threat, while the adaptive immune system has to go through a kind of learning process that may take weeks to be effective sometimes. Just as important, the adaptive immune system is coupled to innate immunity, Li said.

Because of this connection to immune response, learning exactly how RIG-I senses foreign viruses promises great rewards in treating a host of diseases, he said.

"It is a very exciting and hot topic among researchers these days," Li said. "A couple of labs were racing to figure out how RIG-I works, but our team was the first to show how RIG-I recognizes the terminal triophosphate of viral RNA. We determined the structure almost a year ago and the result was presented at the Keystone Symposium for Structural Biology early this year."

Viruses contain RNA, which are molecules similar to DNA in many ways but which play different roles. The RNA molecules from virus often have structures that do not exist in human RNA. RIG-I specifically targets these unique structures and launches an immune response by triggering the secretion of interferon, Li said

Interferons are proteins produced and released by the infected cells to fight pathogens such as viruses or bacteria.

But exactly what was the mechanism by which RIG-I triggers the antiviral immune responses? Though there were some clues offered by previous research, it was not clear how it worked at the molecular level, Li said.

Researchers knew, for example, that the RIG-I enzyme specifically targets the structural unit called "5' triphosphate," which is unique to

viral RNA. Furthermore, it was known what a particular part of the RIG-I binds to the viral RNA.

"This crucial part is its 'C-terminal domain,' a small RNA binding module capable of recognizing RNA from many different kinds of viruses," he said.

To examine the molecular mechanism of viral RNA sensing by RIG-I, the team used human RIG-I C-terminal domain, and examined the binding action through several different techniques. First, they used gel-filtration chromatography to figure out what kind of RNA binds to RIG-I. Then, using surface plasmon resonance, a biosensor-based technonolgy, they examined how tightly RIG-I binds viral RNA and how fast it "gets on and gets off the enzyme," Li said.

Surface plasmon resonance uses a laser beam to detect molecular bindings, he said.

Next, the team used a sophisticated analytical tool called "X-ray crystallography" to determine the three-dimensional structure of RIG-I bound to viral RNA.

Much like CAT scan used in hospitals, X-ray crystallography uses an X-ray beam diffracted through a crystal to image the atomic structure of molecules.

"Using a series of X-ray diffraction patterns, a crystallographer produces a 3D image of a molecule," Li said. "The image shows how a protein looks and how it recognizes the other molecules such as proteins or RNA."

Li noted the structure and mechanisms described in the article concerned only a fragment of the RIG-I protein that is responsible for binding to

viral RNA. The team is currently working to analyze the full-length protein to gain further insight into how RNA binding activates signaling by RIG-I.

Li received a $1.5 million grant from the National Institutes of Health early this year to continue the research on RIG-I, he said.

"The ultimate goal of this research is to understand how our immune system fights viral infections. Findings from this research will facilitate the development of novel antiviral and anticancer reagents and more effective vaccines."

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