SOUTHWESTERN NEWS

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New protein vital for immune response is found in surprise location

DALLAS – Aug. 25, 2005 – A newly discovered protein not only is vital to the immune system's ability to fight off viral infections but also has been found in an unexpected location within the cell, causing researchers to rethink previous notions about the workings of the human immune system.

Researchers at UT Southwestern Medical Center said their findings may lead to new therapies aimed at preventing and treating viral diseases such as the flu, hepatitis, West Nile virus and SARS. The study is available online and will appear in the Sept. 9 issue of the journal *Cell*.

Working with cultured cells, researchers found that the protein, made by a gene they discovered and named MAVS, is located in an unexpected place within the cell – in the membrane of an organelle called the mitochondrion, which until now was best known for generating energy required for daily life.

"This is the first mitochondrial protein known to be involved in immune defense against any microbial infection," said Dr. Zhijian "James" Chen, associate professor of molecular biology at UT Southwestern and the study's senior author. "This discovery puts mitochondria on the map in terms of immunity, and it opens up a new avenue of research in immunology."

The researchers modified normal cells so that the cells could not produce the MAVS protein, which is short for Mitochondrial Anti-Viral Signaling protein. Without MAVS, the cells were highly vulnerable to infection with two common viruses in a class called RNA viruses Other RNA viruses include hepatitis C, West Nile, SARS and the flu viruses.

Cells altered to produce an overabundance of MAVS were protected from dying from viral infection.

"These results raise the possibility that variations in the expression levels of MAVS may endow different individuals with varying ability to fight off viral diseases," said Dr. Chen, who also is an investigator with the Howard Hughes Medical Institute. "Viruses have evolved along

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with humans and have developed strategies to evade the host's immunity. It's quite possible that some viruses may target MAVS in order to achieve successful infection. In those cases, therapies that enhance MAVS expression or activity may be a viable option for boosting immune responses against viral diseases."

The fact that MAVS is located within the membrane of the mitochondrion makes sense for a couple of reasons, Dr. Chen said.

First, proteins housed within the mitochondria have been shown by researchers, such as UT Southwestern biochemist Dr. Xiaodong Wang and others, to play a role in apoptosis, or programmed cell death. The fact that MAVS is located in the membrane of mitochondria suggests it may play a role in coordinating cell death and immune response, Dr. Chen said.

Secondly, many scientists believe that mitochondria originally evolved from bacteria that lived within a host organism's cells, eventually developing a symbiotic relationship with host cells. Now that mitochondria are an integral part of our cells, Dr. Chen speculated that mitochondria may have acquired new functions by serving as a sentinel to detect invading pathogens and other stressful signals, ensuring that the host cells survive and thrive even in adverse environments.

Dr. Chen and his research group are currently working to determine how the MAVS protein functions within the complex series of biochemical reactions that takes place when the body is infected with a virus.

Researchers at UT Southwestern, led by microbiologist Dr. Michael Gale, and elsewhere have previously found that when an RNA virus invades a cell, a protein called RIG-I first intercepts the virus and binds to viral genetic material. That interaction starts a cascade of biochemical reactions that eventually triggers the cell to make a protein called interferon, which in turn fights off the virus.

But the chain of events between RIG-I's encounter with the virus and the interferon response is not known. Researchers have been trying to identify and characterize the proteins involved in an effort to better understand the nature of viral infection and how to combat it.

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Dr. Chen said he and his group believe MAVS is among a group of molecules that play a role in activating other proteins – including IRF-3 and NF-kappaB – that prod the cell into making interferon. He also said there is evidence that MAVS binds with RIG-I, but more experiments are needed to determine just how MAVS functions within the cell.

Other UT Southwestern researchers involved in the studies were lead authors Rashu Seth, a graduate student research assistant, and Dr. Lijun Sun, a postdoctoral researcher in molecular biology, and Chee-Kwee Ea, a graduate student research assistant.

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