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Cellular Power Plants Also Fend Off Viruses

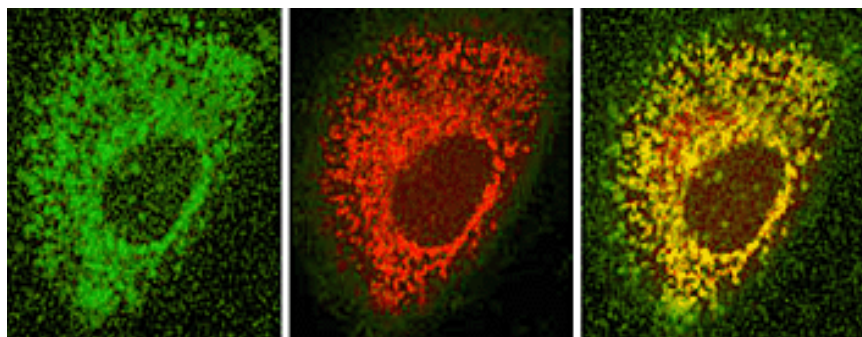


Image Title: Three confocal microscopic images of a cell stained with an antibody that detects the protein MAVS (left), Mito-Tracker (center), and an overlay of the green and red images (right) that indicates the mitochondrial localization of MAVS. - Courtesy of Zhijian 'James' Chen, HHMI at UT Southwestern Medical Center

Researchers have discovered a surprise lurking inside mitochondria, the power plants that are present in every cell. It turns out that these powerhouses also contain a protein that triggers the immune system to attack viral invaders.

According to the researchers, the new role makes perfect biological and evolutionary sense because it fits well with another function of mitochondria as executioners of a biochemical cascade that causes programmed cell death, or apoptosis.

“This is the first protein known to be involved in the immune response that is found in mitochondria,” said Zhijian ‘James’ Chen, a Howard Hughes Medical Institute investigator at the University of Texas Southwestern Medical Center. Chen and his colleagues reported the discovery on August 25, 2005, in an immediate early publication of the journal *Cell*.

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- Zhijian "James" Chen

In their studies, Chen and his colleagues were seeking a regulatory molecule that would provide a missing link in the activation of two important triggers of the innate immune system—NF- κ B and IRF3. Somehow, these molecules are activated in response to a receptor molecule, called RIG-I, which detects viral genetic material. RIG-I binds to the RNA of viruses such as the influenza virus, hepatitis C virus, West Nile virus and SARS virus.

The researchers knew the molecule they were seeking was present in a biochemical pathway somewhere between RIG-I and other “downstream” regulatory molecules. They initiated a search for this missing molecule by searching for proteins in the cell that contain a characteristic molecular domain, called a CARD domain, which mediates interactions between different regulatory proteins. Their search yielded a protein, which they called MAVS for mitochondrial antiviral signaling.

Their experiments revealed that MAVS activated NF- κ B and IRF3 in cell cultures. They also found that in order for MAVS to function, it requires both the CARD domain and another domain that anchors it to the mitochondrial membrane. Studies using fluorescent tracers revealed that MAVS was present in the mitochondria of cells. And when the researchers altered the MAVS molecule in such a way that it prevented MAVS from attaching to mitochondria, the molecule did not function properly.

The researchers demonstrated the importance of MAVS in immune responses by showing that cells without MAVS were vulnerable to viral infection; while those with excess MAVS were resistant to such infections.

Chen speculated that the mitochondria might have evolved into immune sentinels because of their location near internal cell membranes where viral replication takes place. “By having MAVS in the mitochondrial membrane, it provides a strategic position for cells to sense the presence of viruses, especially viral replication,” said Chen.

“In addition, MAVS is unique in that it has both a mitochondrial targeting sequence, as well as a CARD domain sequence,” said Chen. “CARD domain proteins are known to be involved in apoptosis, and the mitochondria are also known to be involved in apoptosis. So, while at this point this is still pure speculation, but perhaps combining these two domains in one protein, MAVS, might allow the cells to integrate signals somehow and coordinate apoptotic responses or immune responses, depending on the type of viral

infection.” Apoptosis is triggered when a cell is no longer needed during development or is damaged beyond repair. It serves to protect the body from the accumulation of damaged or malfunctioning cells.

Chen said that the newly discovered immunological service rendered to the cell by mitochondria makes good biological and evolutionary sense. “Evolutionarily, it is believed that mitochondria originated from ancient bacteria, which formed a symbiotic relationship with eukaryotic cells,” said Chen. “For symbiosis to evolve, the bacteria and the host must be beneficial to one another. Mitochondria have long been known to serve the major function of producing chemical energy for the cell, as well as to sense damage and trigger apoptosis. Now, I think our discovery reveals another important function of the mitochondria, and that is in immunity,” he said.

Understanding how boosting MAVS function causes cells to resist viral infection could have important clinical implications, said Chen. “Treatments that enhance the activity of MAVS may prove to be useful in boosting immunity against viruses,” he said. “Furthermore, we suspect that MAVS might be a prime target for some viruses that can evade immune surveillance. If those suspicions prove out, then treatments that counteract this evasion could provide therapeutic benefits,” he said. Chen also speculated that subtle variations in the MAVS protein might explain why people may respond differently when infected with the same virus.

Chen and his colleagues are now exploring such questions, as well as teasing out further molecular details of the signaling mechanism by which MAVS triggers the immune system. “Over the long term, we would like to understand the host-viral interactions that function through MAVS, and how MAVS gives the cell immunity to viruses and how viruses try to evade this function of MAVS. We would like to exploit these findings to develop more effective antiviral strategies.”