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# Study reveals insight into how key protein protects against viral infections

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Scientists from the University of Utah School of Medicine have discovered that a mouse protein called IFITM3 contributes to the body's defense against some types of viral infections by binding to an enzyme responsible for regulating the pH of a cell's waste disposal system. This finding, published in the March 30, 2012, issue of *Innate Immunity*, sheds light on the cellular mechanisms involved in flu resistance and opens up potential new avenues of research for anti-viral medications.

"Previous research has shown that IFITM3 proteins play an important role in human resistance to viruses such as influenza and HIV," says John H. Weis, Ph.D., professor of pathology, George J. Weber Presidential Chair at the University of Utah School of Medicine, and senior author on the study. "But, until now, we didn't know exactly how IFITM3 was providing that protection."

By comparing normal mouse cells to those obtained from mice without the Ifitm3 gene, Weis and his colleagues, including graduate research assistant Yin Shen Wee, Ph.D., discovered that IFITM3 proteins play a critical role in the structural stability and function of a protein complex known as vacuolar ATPase (v-ATPase). The v-ATPase complex is responsible for regulating the pH of the endosomes and lysosomes that make up the cellular waste disposal pathway. Resistance to certain types of viral infection depends on an acidic pH. Weis and his team found evidence that IFITM3 binds directly to v-ATPase, and that absence of IFITM3 adversely affects the ability of v-ATPase to acidify the pH of endosomes.

"IFITM3 proteins help to protect against viral infection by preventing viral replication," says Weis. "Our studies demonstrate that IFITM3 does this by supporting the function of endosomes and lysosomes that trap and destroy virus particles."

Weis' team also found that loss of the IFITM3 protein affects the appropriate localization of key cell membrane components following activation by interferon, a cell signaling molecule released in response to the presence of viruses. Normal cells use a protein called clathrin to build small bubbles used for transporting substances, including some viruses, in and out of the cell. Typically, clathrin localizes in the cell membrane in response to interferon activation. However, in cells lacking the IFITM3 protein, clathrin remains within the cell cytoplasm and clathrin-dependent uptake is decreased.

"To our knowledge, this is the first report in the scientific literature describing clathrin sequestration in the cytoplasm," says Weis. "Taken together, our findings suggest that the anti-viral role of IFITM3 may be to maintain clathrin within the cell membrane by stabilizing v-ATPase, but further studies are needed to define the specific molecular interactions involved."

Provided by University of Utah

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