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Putting the brakes on cell's 'engine' could give flu and other vaccines a boost

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A relatively unknown molecule that regulates metabolism could be the key to boosting an individual's immunity to the flu - and potentially other viruses - according to research reported today in the journal *Immunity*.

The study, led by University of Vermont (UVM) College of Medicine doctoral student Devin Champagne and Mercedes Rincon, Ph.D., a professor of medicine and an immunobiologist, discovered that a protein called methylation controlled J - or MCJ - can be altered to boost the immune system's response to the flu.

Metabolism is a crucial function that helps keep cells alive. It plays a role in a range of bodily processes - from the conversion of food into energy to the ability to fight off infection. MCJ is the part of the cell that produces energy and enables metabolism.

"It's the engine of the cell," says Rincon, who adds that previously, researchers assumed that the mitochondria were constantly active.

She and Champagne discovered that MCJ acts as a braking system in the mitochondria, slowing these organelles down. Without MCJ, the mitochondria are hyperactive.

In the T cells of the body's immune system, specifically the CD8 T cells that fight viruses and infections, metabolism helps ensure that those bug-fighting cells remain active and don't tire out. When a virus attacks, CD8 cells detect and kill it while leaving the healthy cells intact.

MCJ controls the metabolism of the CD8 cells. It prevents the mitochondria from generating too much energy and making the CD8 cells so overactive that they kill healthy cells.

A vaccine, such as a flu shot, trains the CD8 cells to identify that virus and destroy it. With a good vaccine, the CD8 cells will "remember" and protect against that virus for a long time.

"The metabolism of immune cells is very important," explains Rincon. "It is critical to determining effective protection against infection, but also if vaccines will work," she says.

For their study, Champagne and Rincon generated mutant mice without MCJ and infected both normal mice and mice lacking MCJ with flu virus - imitating a vaccine, so the animals' CD8 cells would learn to recognize the bug. After four weeks, they took the CD8 cells from the infected mice and injected those cells into other mice. One group received normal CD8 cells; the other group got cells without MCJ.

The researchers gave those new mice very high doses of the same flu virus. The mice with normal CD8 cells all died from the virus, indicating that the "educated" CD8 cells did poorly in protection. In contrast, the mice injected with MCJ-deficient CD8 cells had proper protection and all survived.

Champagne and Rincon concluded that with normal MCJ levels, CD8 cells are not as efficient in fighting virus because their mitochondrial metabolism is not strong enough, so the removal of MCJ (the "mitochondrial brake") can improve the CD8 cells protection capability - and thus the efficacy of a vaccine.

"Nothing has been shown to do what this protein does," says Rincon. "Suppressing MCJ will enhance your immune response and protection

from an influenza virus and, most likely, protection from other threatening viruses."

The researchers are now testing potential therapies for fatty liver disease by eliminating MCJ in liver cells. That action speeds up the metabolism process of breaking down lipids and converting fat into energy, thus reducing the presence of the disease, which affects 15 to 20 percent of humans, Rincon says.

Provided by University of Vermont