Mild-mannered metabolic helper rushes to fight invading viruses, researchers report

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Within cells, an ancient antiviral duo can deliver a one-two knockout to thwart invading viruses, report researchers who have just unmasked the cellular sidekick that throws the first punch. The findings mean scientists must rethink the design of antiviral immunity and how the body fends off viruses of all types, including influenza and HIV.

In the study, Children's Hospital Boston researchers found, mild-mannered organelles inside the cell known as peroxisomes can detect virus invasion signals and launch a limited antiviral offensive. Other organelles, the mitochondria, follow up with a more definitive antiviral counterattack.

"This is the first demonstration that peroxisomes are involved in immunity," said Jonathan Kagan, staff scientist in the gastroenterology division and senior author of the paper published May 6 in the online journal *Cell*. "This work has implications for our understanding of how we interact with infectious viruses and even bacteria."

The paper establishes a new function for peroxisomes as a cellular compartment that promotes a rapid response to viral infection. With this discovery, the researchers say, scientists need to look for other cellular parts that may do double duty as pathogen detectors. A larger volunteer army may be lurking in cells as needed for the innate immune system.

In a clinical implication, the findings suggest a new approach to rare and largely untreatable conditions known as peroxisome biogenesis

disorders, Kagan said. In the most common manifestation, Zellweger syndrome, children suffer from major developmental abnormalities and die as infants. The milder disorders allow children to live into their teens. Many affected children die of lung infections such as pneumonia, which may arise from problems in the antiviral signaling scaffold due to the absence of peroxisomes, Kagan speculates. Previously, the disorders have been considered developmental and metabolic.

When they are not fighting invading microbes, peroxisomes are busy mopping up the potentially damaging free radical byproducts produced by their larger distant cousins, mitochondria, the power plants of the cell. In other house-keeping duties, peroxisomes also make and attach the lipids that grease the cellular machinery so proteins can slide into or through membranes. Both organelles grow, multiply, and shrink in response to metabolic demands.

Peroxisomes acquire their virus-fighting power from a cloak of mitochondrial antiviral signaling protein, or MAVS. Five years ago, MAVS proteins were discovered on mitochondria, a surprising location for which they were named, and shown to be vital to the immune system's ability to fight infections.

MAVS proteins are found in all cells in the body, Kagan said, but until now they were only known to be draped around mitochondria. The latest study started as a search for MAVS on peroxisomes, an idea born from recent reports of other proteins shared by peroxisomes and mitochondria. On a graduate studies sabbatical from Vienna, first author Evelyn Dixit stained cells for MAVS and found the proteins on peroxisomes.

Next, she observed, the same MAVS proteins activated different antiviral immune responses, depending upon the organelle they adorned. "The difference was that the antiviral response was quicker and transient

when it originated from peroxisomes compared to mitochondria," Dixit said.

In another difference, the peroxisomal MAVS turned on a subset of antiviral genes without a secreting interferon. By contrast, mitochondrial MAVS triggers interferon production and release, which alerts both the cell and its neighbors to mount a larger immune response.

"Seeing interferon-stimulated genes but no interferon was at first quite aggravating," Dixit said. "We thought we did something wrong. Then we had to turn our thinking around 180 degrees and accept that it was not a mistake. Peroxisomal MAVS leads to interferon-stimulated genes while bypassing interferon secretion."

The differential response may be a way that different kinds of cells can customize their antiviral responses to the special needs of different tissues, Kagan suggests. For example, the interferon response shuts down protein synthesis, promotes inflammation, and causes a general toxic effect that some tissues may be able to handle better than others, such as the intestines.

Without interferon, peroxisomes could mount a limited response in sensitive tissues, such as nerves, eyes, or heart muscle. "We have speculated that certain tissues may only use mitochondria or only use peroxisomes," Kagan said.

"At the end of the day, we found antiviral signaling can occur from peroxisomes and from mitochondria," he said. "Only from the peroxisome do we see a rapid response, and that is sufficient to control viruses, but it cannot eliminate them. Signaling from both is needed to effectively knock them out."

More information: Evelyn Dixit, et al., "Peroxisomes Are Signaling

Platforms for Antiviral Innate Immunity", Cell.

Provided by Children's Hospital Boston

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