How mitochondria deploy a powerful punch against life-threatening bacteria

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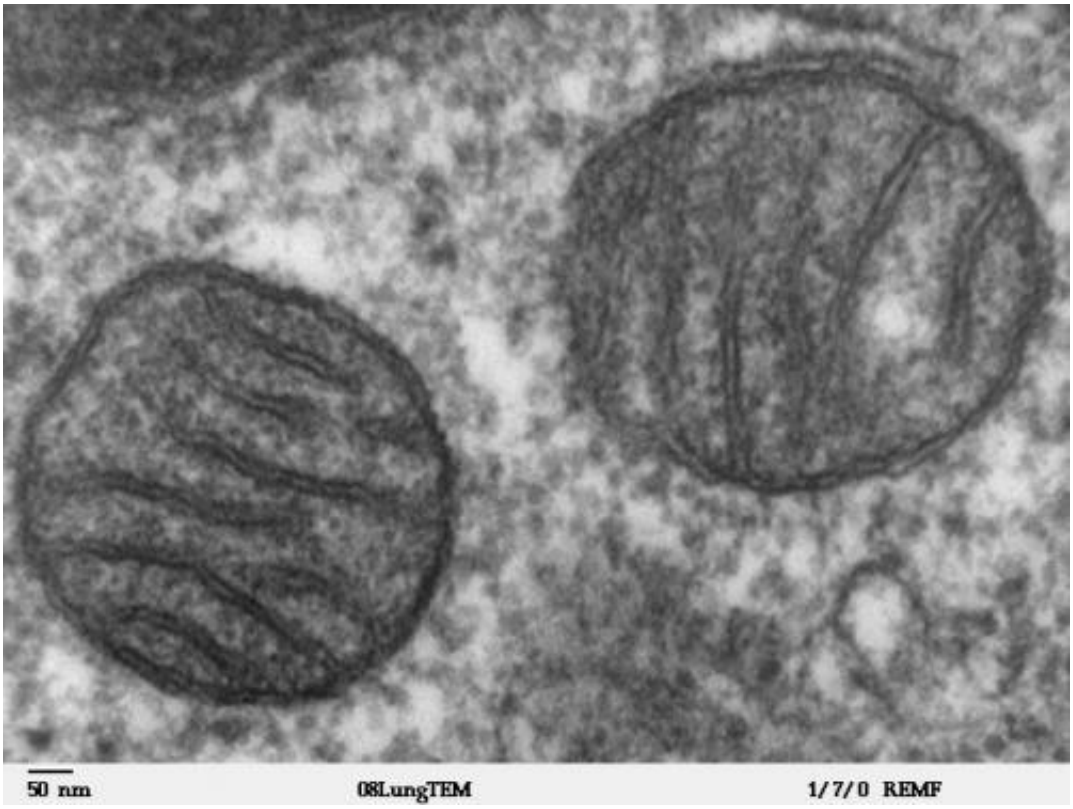

Mitochondria. Credit: Wikipedia commons

The constant battle for dominance between disease-causing bacteria and our immune systems has led to the evolution of some crafty warfare tactics on both sides.

One particularly nasty bacteria: methicillin-resistant Staphylococcus

aureus, or MRSA.

Common in schools and health-care settings, MRSA has been known to cause occasionally life-threatening infections. This has recently led Michigan Medicine researchers to investigate how immune system cells deliver their deadly payloads to destroy invading organisms such as MRSA.

Their work is published in the journal *Cell Host & Microbe*.

When alerted of an invasion, immune cells called macrophages surround and engulf bacteria, quarantining them inside a compartment called a phagosome. The cell then destroys them with weapons called reactive oxygen species (ROS).

"One example of a reactive oxygen species is bleach," says Mary O'Riordan, Ph.D., a professor of microbiology and immunology at the University of Michigan and the study's principal investigator. "Just like you don't want bleach on your skin, bacteria don't want reactive oxygen to damage their outside surface."

Immune cells usually deploy ROS inside their phagosomes using a well-known mechanism, which involves dumping oxidants into the compartment to kill the bacteria.

But many bacteria—including salmonella and MRSA—have found ways to avoid this form of attack.

Mitochondria: a power player

O'Riordan and her colleagues, research investigator Basel Abuaita, Ph.D., and Tracey Schultz, sought to discover what backup system immune cells employed to fight these bacteria.

In doing so, they found an unexpected player: mitochondria.

"We discovered that macrophages sense invading MRSA and turn on the machinery to increase mitochondrial development of ROS," Abuaita says.

ROS is a natural byproduct of mitochondria's normal job in cells, the production of energy.

And the team found that when placed under stress, such as invasion by a foreign agent, chemical signals from the endoplasmic reticulum—an organelle in the cell that acts as sort of a post office, packaging and sending substances around the cell—notifies mitochondria to ramp up production of ROS.

Still, a question remained: how do mitochondria deliver their ROS to the phagosome?

"ROS are also damaging to our own cells, so we hypothesized that there must be some delivery mechanism," O'Riordan says. "Mitochondria have not traditionally been known to package and deliver substances to different parts of the cell."

Targeted delivery methods

Their studies revealed that the ROS were delivered in tiny mitochondrial vesicles, recently discovered as a way that mitochondria could talk to other parts of the cell.

To find these payloads, Abuaita used florescent tags and live high-resolution imaging techniques to watch the process unfold in real time.

He infected a cell with MRSA under a microscope and inserted a dye

that would glow in the presence of ROS. Mitochondria in the infected cell began to glow, as did the macrophage when the bacteria touched its outside membrane.

Once the macrophage ate the MRSA, he witnessed a glowing hot spot as the ROS was delivered to the phagosome.

Why, though, would a cell have two different methods for deploying ROS?

"The immune system is full of redundancies," O'Riordan says. "It has to, by definition; every bacteria, virus, or parasite that we know is a pathogen is one because it has evolved ways to avoid the immune system.

"The immune system also has a real diversity of purpose and mechanism," she adds. "Being open to different ways of asking questions about the immune system and understanding the biology of these pathogens helped us to find the right experimental system to use."

More information: Basel H. Abuaita et al, Mitochondria-Derived Vesicles Deliver Antimicrobial Reactive Oxygen Species to Control Phagosome-Localized Staphylococcus aureus, *Cell Host & Microbe* (2018). DOI: 10.1016/j.chom.2018.10.005

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