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Cell's recycling team helps sound alarm on pathogens

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Just as households have garbage disposals and recycling bins for getting rid of everyday waste, the cell has its own system for cleaning up unnecessary or defunct components. This process, known as autophagy, is also an efficient method of eliminating unwanted visitors like viruses, bacteria, and parasites.

But when it comes to combatting a fungal invader, Duke researchers have found that the cleanup crew takes a less straightforward approach. Rather than killing fungal invaders directly, autophagy is used to chew up a molecule that would otherwise hold back the immune response. It's sort of like breaking the glass on an alarm to allow the button to be pushed.

The finding appears January 22 in *Nature Communications*.

"The real frontline killers of fungi are (white blood cells called) neutrophils, but they are kept at bay by a molecule called A20," said Mari L. Shinohara, Ph.D., senior study author and assistant professor of immunology, molecular genetics and microbiology at Duke University School of Medicine.

"We found that when there is a fungal infection, the sentinels of war—a special group of cells called tissue-resident macrophages—use autophagy to get rid of the A20 molecules to quickly release an emergency signal," Shinohara said.

The term autophagy (literally self-eating) was coined half a century ago by the Nobel laureate Christian de Duve to describe the process used by cells to break down and recycle their components. This self-digestion and recycling helps cells survive times when nutrients are low, and also enables them to remove dysfunctional organelles and proteins that could damage the cell.

In recent years, scientists have discovered that autophagy plays a role in the immune response as well. They showed that the same cellular machinery that degrades unused proteins can also destroy viruses, bacteria and parasites. But it wasn't clear whether autophagy could target fungi for destruction.

To explore this question, Shinohara and her colleagues started with a group of mice genetically engineered to lack a tiny spherical structure called the autophagosome that is responsible for engulfing unwanted materials for degradation—the recycling bin. They infected these mice with Candida albicans, a fungal pathogen that causes opportunistic oral and genital infections in humans.

The researchers found that mice lacking autophagosomes and unable to perform autophagy were more susceptible to fungal infection than normal mice. Masashi Kanayama, a postdoctoral fellow in Shinohara's lab and lead author of the study, then dissected the mouse mutants to determine what was happening at the cellular level. He discovered that fewer neutrophils had been recruited to fight off the infection.

Neutrophils and macrophages are usually called to arms by a protein complex called NF-kappaB, which is a key regulator of the immune response. Because autophagy is known to specifically sequester certain proteins, Shinohara wondered whether it might be soaking up a protein that blocks NF-kappaB as a roundabout way to induce the immune response.

Through a series of molecular biochemical assays, Shinohara and colleagues found that autophagy was indeed depleting A20, a known inhibitor of NF-kappaB. With A20 out of the picture, NF-kappaB was free to send out chemical signals known as chemokines to activate the antifungal arsenal to respond to the infection.

"We believe that autophagy provides an effective means of combating fungal infections," said Shinohara. "First, having a negative regulator like A20 ensures that there are fewer false alarms, and that fighters are only brought in when needed. Second, removing A20 is a quick and efficient way to induce an immune response, because it sets off a chain of actions that is already in place. Creating a protein from scratch would take much more time."

More information: "Autophagy enhances NF-kappaB activity in tissue-dependent macrophages by sequestering A20 to boost anti-fungal immunity," Masashi Kanayama, Makoto Inoue, Keiko Danzaki, Gianna Hammer, You-Wen He and Mari L. Shinohara. *Nature Communications*, Jan. 22, 2015. DOI: NCOMMS6779

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