

How a deadly fungus evades the immune system

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Candida albicans. Credit: Wikipedia.

New research from the University of Toronto has scientists re-thinking how a lethal fungus grows and kills immune cells. The study hints at a new approach to therapy for *Candida albicans*, one of the most common causes of bloodstream infections.

Previously, scientists thought that *Candida albicans* spread by changing from a single, round cell to a long string of cells, or filaments. They

thought this shape change allowed the [fungus](#) to move through the bloodstream and let its filaments penetrate tissues and destroy immune cells.

But the new study, published today in *Nature Communications*, shows that a little bit of sugar on the surface of [fungal cells](#) triggers the death of immune cells that would otherwise kill the fungus.

"It's not the shape-change per se that enables the fungus to kill the immune cell, but what happens along with it," says Professor Leah Cowen, lead researcher on the study who holds the Canada Research Chair in Microbial Genomics and Infectious Disease in U of T's Department of Molecular Genetics. "The addition of glycosylated proteins, which are proteins with a sugar attached, re-models the surface of the fungal cells."

Cowen and her lab found that *Candida albicans* can kill immune cells even after its cells have died. They let [immune cells](#) called macrophages consume the fungus, and after an hour they removed the fungal cells from the macrophages. Then they exposed new macrophages to fungal cells that had been consumed and those that had not, and they compared the results.

"The fungal cells that were never internalized by macrophages couldn't kill the fresh macrophages, but those that had been inside a macrophage could kill beautifully," says Cowen. That finding was a clue. The researchers reasoned that the change in the fungal cells that turned them into killers was probably on their surface, since [dead cells](#) have no active internal processes.

The researchers then used an enzyme called Endo H to snip off sugars on the glycosylated proteins attached to the dead fungal cells. The change completely blocked the ability of the fungus to kill—a strong lead on a

new and needed therapeutic strategy for *Candida albicans*.

Globally, fungi kill more than 1.5 million people a year. In the U.S., *Candida* fungi account for almost 90 per cent of hospital-acquired fungal infections, and in Canada they're the third most common cause of [bloodstream infections](#) in intensive care units. More than 40 per cent of people with a systemic *Candida albicans* infection will die.

A therapy that targets the ability of fungal cells to outfox the immune system would be promising, says Cowen, because it might minimize effects on healthy microbes and avoid spurring drug resistance.

As well, some anti-fungals in development—including one in Cowen's lab—are hindered because the target proteins are present in both fungi and humans. That means a drug has to distinguish between the fungal and human versions of the target. "If you develop a drug that targets something that's only found in fungi, it's less likely to have side effects in a human," says Cowen.

In her *Nature Communications* study, Cowen used a powerful *Candida albicans* mutant library, which the pharmaceutical company Merck recently made public. The library let Cowen and her team test the function of almost all genes in the *Candida albicans* genome, where before they could test just 10 per cent. "It really let us approach this pathogen from a holistic perspective and evaluate the role of all its genes in disease," says Cowen.

The researchers used the library to do the first genome-scale analysis of the fungus's ability to change shape and grow, and they discovered more than 800 regulators of this process, which they published today with their other findings.

"It's cool because we have a ton of new biology to explore, hundreds of

possible drug targets and a new appreciation of how [fungal pathogens](#) interact with immune systems," says Cowen. "It's been a lot of fun."

Provided by University of Toronto

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