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Pitt study provides clues to body's defense against common oral ailment

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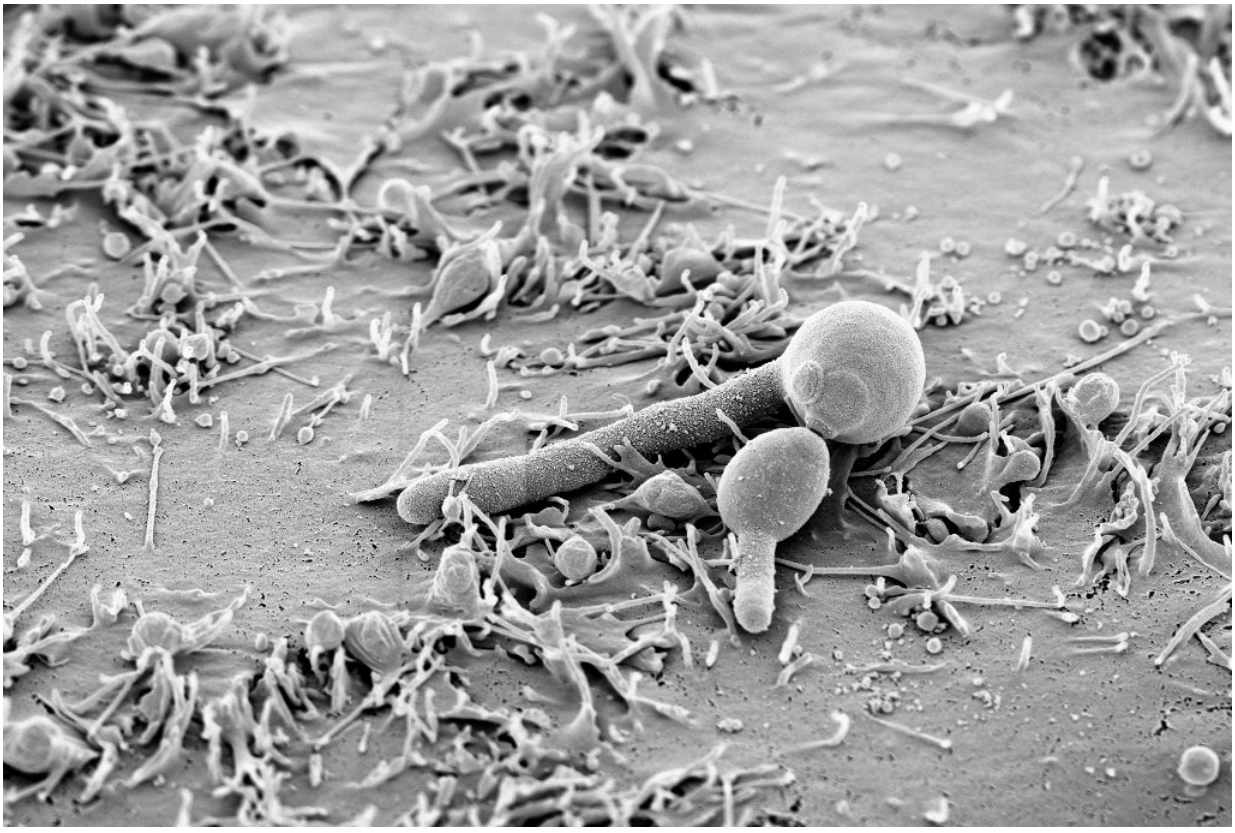

Image of the fungus *Candida albicans* on the surface of a skin cell that is in the process of growing into its filamentous form. Credit: Bernhard Hube, University of Jena, Germany

An international team, led by researchers at the University of Pittsburgh

School of Medicine, has identified the mechanism by which the immune system first learns that the fungus *Candida albicans*, which causes oral thrush, has invaded the body. The culprit is a fungal toxin called Candidalysin, which punches holes in cells lining the mouth and is sensed by the immune system, which then begins to mount a defense.

The new findings, published today in the journal *Science Immunology*, could eventually lead to better treatments for oral thrush, which can produce pain severe enough to cause difficulty eating and swallowing, as well as other fungal infections.

The mouth is home to a large number of microbes, termed commensals, which are harmless in healthy individuals. However, suppression of the immune system can lead to severe and reoccurring painful oral infections from these organisms, explained the study's co-senior author Sarah Gaffen, Ph.D., who holds the Gerald P. Rodnan Endowed Chair in the Division of Rheumatology & Clinical Immunology at Pitt.

One such example is the fungus *Candida albicans*. The harmless commensal form exists as a small single-celled organism, but when the immune system is compromised, *Candida* elongates into an invasive form, characterized by long filaments called hyphae, that causes a pervasive infection called oral candidiasis, or "thrush."

The immature immune systems of infants make them particularly susceptible to thrush, which can lead to a failure to thrive and nutritional deficiencies. The infection also is prevalent among HIV/AIDS patients, denture wearers and those on immunosuppressants, including chemotherapy and drugs to prevent the rejection of transplanted organs. In fact, at least 50 percent of HIV patients struggle with repeated thrush infections.

However, surprisingly little is known about how fungal immunity in the

mouth operates, and, until now, it was unclear why *Candida* does not establish an invasive infection in healthy humans, said Gaffen.

Her lab previously showed that an immune hormone called interleukin-17 (IL-17) and the specific cells that make it—a subclass of immune cells called helper T cells—are essential to immunity against oral thrush.

Oral epithelial cells (OECs), which are part of the mucous membrane lining the inside of the mouth, are the first cells in the body to encounter *Candida*. They ignore the yeast until it begins to grow hyphae, at which point the OECs stimulate helper T cells to produce IL-17.

In the new study, the researchers used a combination of human OECs cultured in laboratory dishes and mice infected orally with *Candida*, to show the central importance of Candidalysin, a toxin secreted by *Candida* that allows the fungus to create holes in OECs and invade the tissue. Further experiments revealed that IL-17 and Candidalysin act in a synergistic manner to amplify antifungal signals in cultured OECs.

Candidalysin was discovered in 2016 by the study's other co-senior author, Julian Naglik, Ph.D., professor of fungal pathogenesis and immunology, King's College London, United Kingdom.

"To use a Game of Thrones analogy: the oral epithelial cells form a protective 'wall' that keeps the marauding *Candida* invaders at bay. Patrolling the wall are the helper T cells, which use IL-17 as their weapon to protect the kingdom," said the paper's first author, postdoctoral fellow Akash Verma, Ph.D.

Despite millions of fungal infections worldwide, there are no commercially available anti-fungal vaccines. "Our research provides vital clues to understand the immune defense network at barrier sites of the

body. This knowledge may ultimately be harnessed to design antifungal vaccines," Gaffen said.

More information: A.H. Verma el al., "Oral epithelial cells orchestrate innate type 17 responses to Candida albicans through the virulence factor candidalysin," *Science Immunology* (2017). immunology.sciencemag.org/look … 6/sciimmunol.aam8834

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