Structures involved in communication among pathogenic fungi could be targets for novel treatments

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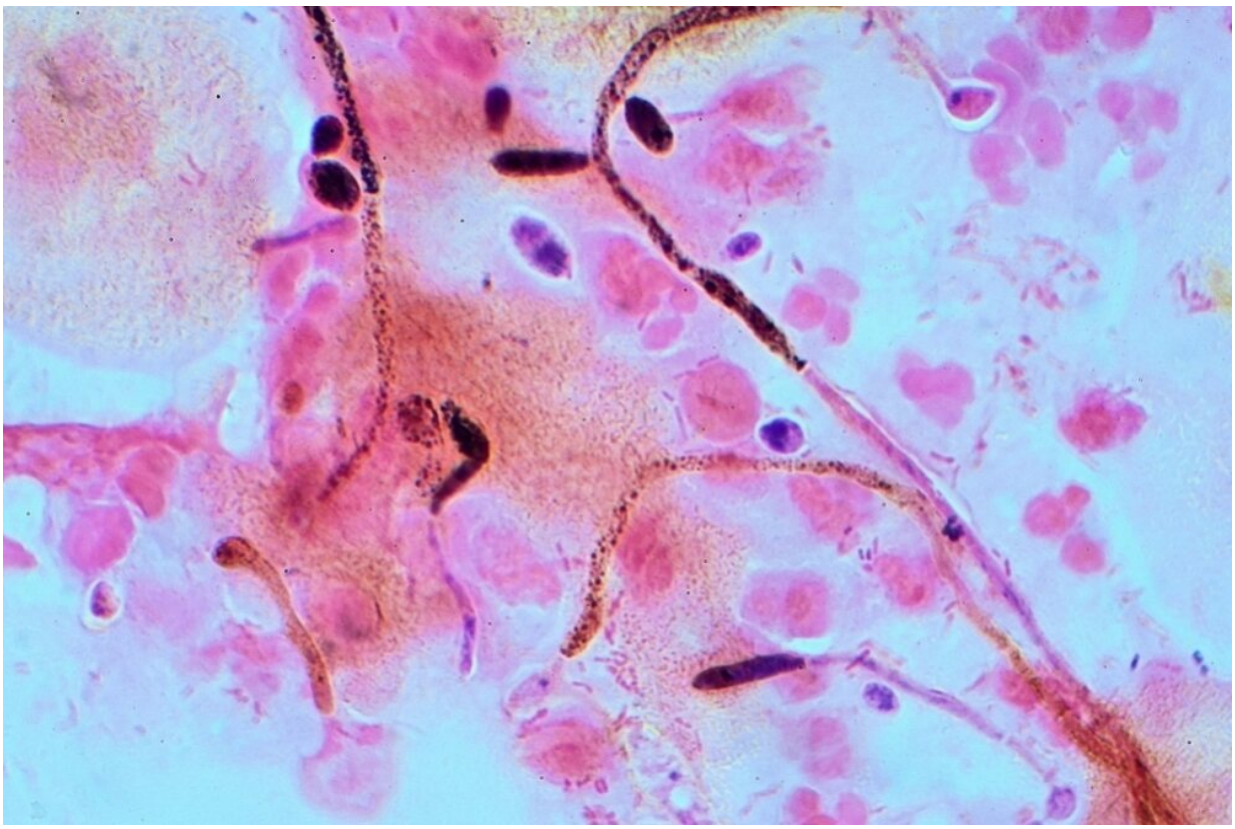

A study shows how extracellular vesicles share information among cells in the same species, enabling the colony to respond in a coordinated manner to the host organism's defenses. C. albicans seen under an optical microscope. Credit: Graham Beards/Wikimedia Commons

A group of scientists in Brazil and the United States has revealed the role played by certain structures in intermediating communication among individual fungi of the same species. The discovery, detailed in an article published in the journal *mBio*, could serve as the basis for development of more effective therapies to combat fungal infections.

"There was a hypothesis that cells in the same species could communicate via these structures, called extracellular vesicles. We showed, using different methodologies, that this occurs in three species," said Fausto Almeida, last author of the article. Almeida is a professor at the University of São Paulo's Ribeirão Preto Medical School (FMRP-USP) in Brazil.

The investigation was supported by FAPESP. Researchers at Carlos Chagas Institute in Curitiba (Brazil) and Johns Hopkins Bloomberg School of Public Health in Baltimore (USA) collaborated.

Extracellular vesicles are nanostructures produced by all living cells to transport proteins, genetic material and metabolites, among other molecules, to the extracellular space. They are involved in both pathological and normal phenomena, such as regulation of physiological processes and responses to specific environmental conditions.

"In performing this communication and modulating certain phenomena, extracellular vesicles become potential targets for therapies. If we can alter or even interrupt this communication channel, we'll be able to achieve interesting results in future," Almeida said.

In a previous article, published in *Nature Communications*, the group had analyzed the role of extracellular vesicles in infection by the fungus Cryptococcus neoformans.

Their most recent study shows how extracellular vesicles are used by the

pathogenic fungi Candida albicans, Aspergillus fumigatus and Paracoccidioides brasiliensis. These species are responsible for a large proportion of the fungal infections that occur worldwide. The third is particularly relevant in Brazil. All three are notorious for the severity of the infections they can cause.

This is one of the factors that lead to the 1.6 million deaths reported worldwide as being due to this type of infection. The number is probably an underestimate, according to a study by the group published in 2019.

Enigma of fungi

"Extracellular vesicles and their contents are able to regulate gene expression not only in individuals but also in neighboring cells [of the same species]. As a result, they prepare the entire colony to respond to and overcome the host's antagonism in trying to eliminate the infection," said Tamires Bitencourt, first author of the article. The study was conducted while she was on a postdoctoral internship at FMRP-USP.

The researchers demonstrated that the communication promoted by extracellular vesicles involves different cellular signaling pathways depending on the species, which is highly promising for the search for broad-spectrum treatments.

The experiments conducted with the three types of pathogenic fungus consisted of triggering a stimulus that would cause a response. The extracellular vesicles were then removed and transferred to a new culture of the same species that had not been subjected to intervention of any kind. These control colonies displayed the same responses as the ones that had received stimuli.

In the case of P. brasiliensis, the researchers used tunicamycin, a drug known to cause stress in the cell's endoplasmic reticulum, an organelle

that processes proteins produced by the fungus, among other functions. They observed that when the extracellular vesicles treated with tunicamycin were transferred to untreated cells, a cellular signaling pathway called UPR was activated in these cells in an attempt to restore a balance in the fungal organism.

A. fumigatus, which causes invasive pulmonary aspergillosis, a severe disease, was exposed to ultraviolet light. The species is known to adapt to this type of stress, which damages DNA. When the extracellular vesicles were absorbed by the fungi not exposed to UV light, they made cells reduce colony growth. In addition, the gene akuA, which is involved in DNA repair, was expressed with significant intensity.

Interventions in C. albicans consisted of altering cell morphology by means of stimuli that converted them from yeast to filament, enabling the fungus to occupy different niches in the host and augment its virulence. In response, it developed hyphae, long filamentous branches that invade tissue and maintain virulence, showing that it responded to the stimuli.

The researchers now plan to cause alterations to proteins carried by extracellular vesicles in an attempt to kill the fungi or weaken their resistance to existing antifungals, among other possible interventions.

"It's as if we had discovered the secret code whereby fungi communicate. We'll now use it to attack the enemy," Almeida said.

More information: Tamires A. Bitencourt et al, Fungal Extracellular Vesicles Are Involved in Intraspecies Intracellular Communication, *mBio* (2022). DOI: 10.1128/mbio.03272-21

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