Trends in Microbiology | Microbe of the Month

Rhizopus arrhizus

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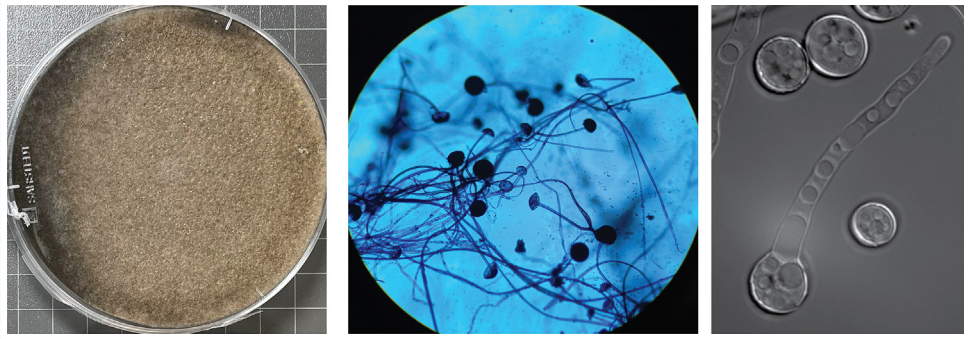
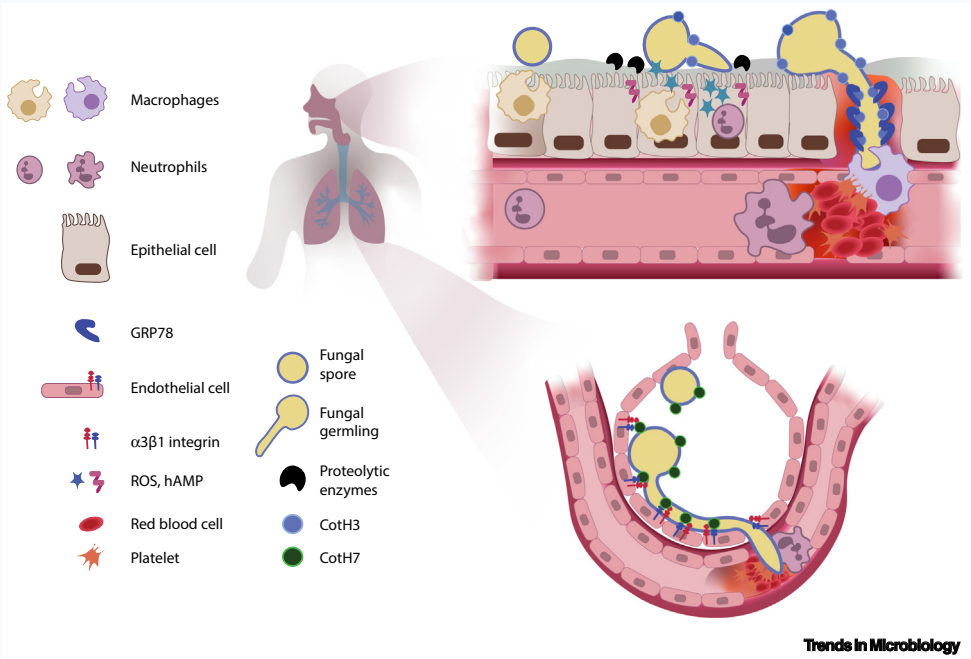
The three-panel image shows *Rhizopus arrhizus* mycelium, hyphae, and germinating spores.



Rhizopus arrhizus is a member of a complex of soil-associated fungal species distributed worldwide that cause spoilage of vegetables and fruit. *R. arrhizus* is also widely used in food industry in the production of fermented food and in other biotechnological industries, such as research and development of new therapeutic compounds. This species has been isolated from plants and animals and can also cause disease in humans.

The fungus *R. arrhizus* (or *R. arrhizus* var. *arrhizus*, also called *R. oryzae* sensu stricto) is among the most frequently reported cause of mucormycosis, together with *Rhizopus microsporus* and *Rhizopus delemar (*formerly *R. oryzae* var. *delemar,* also known as *R. arrhizus* var. *delemar*). *R. arrhizus* var. *arrhizus* and *R. arrhizus* var. *delemar* are sister species that cannot be distinguished morphologically, but can be differentiated by genome content or copy number of the lactate dehydrogenase (LDH) gene and its products. Lactic acid production is indicative of *R. arrhizus* var. *arrhizus*, whereas fumaric acid production is indicative of *R. arrhizus* var. *delemar.*

Schematic showing models of tissue invasion in rhino-orbital sites and within alveoli.



Mucormycosis

Mucormycosis is an invasive fungal infection with high mortality rates. The most affected body sites are rhino-orbital-cerebral regions, lungs, and skin and survivors are often left with extensive disfiguring damage. Infection

KEY FACTS:

Genome size and content vary widely across and within *Rhizopus* species, complicating identification. Spore size does not distinguish *R. arrhizus* var. *arrhizus* from *R. arrhizus* var. *delemar.*

LHD activity distinguishes *R. arrhizus* var. *arrhizus* from *R. arrhizus* var. *delemar.*

The main Mucorales PAMPs are the spore coat protein homologues (CotH), which act as ligands for human receptors.

Secreted factors of both fungal (mucoricin) and endosymbiotic bacterial (rhizoxin) origin may contribute to fungal pathogenesis and disease.

DISEASE FACTS:

Zygomycosis is the old name for the infections caused by Mucorales. This name is no longer in use due to updates in taxonomy in this group.

Iron overload is a marker of susceptibility and angioinvasion.

Diabetic individuals with ketoacidosis and neutropenic individuals are at highest risk.

The biggest fungal outbreak ever documented was due to mucormycosis and occurred in India during the coronavirus disease 2019 (COVID19) pandemic, affecting up to 45 000 individuals.

Pulmonary mucormycosis represents a major diagnostic challenge.

Mucormycosis treatment requires both surgical intervention and antifungal therapy with amphotericin B, along with isavuconazole or posaconazole.

Despite treatment, the mortality rate for mucormycosis remains higher than 50%.

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is caused by fungi of the order Mucorales, which includes *R. arrhizus* and related *Rhizopus* species. It affects primarily immunocompromised and diabetic individuals.

During infection via damaged mucosal barriers, *R. arrhizus* spores and germlings adhere to nasal and alveolar epithelial cells and endothelial cells lining blood vessels. This angioinvasion is a key feature of mucormycosis. The fungus can secrete proteolytic enzymes to degrade mucosal barriers and can then invade and damage epithelial and endothelial layers. Hyphal growth and invasion will cause tissue damage, blood vessel obstruction, and thrombosis, all leading to tissue necrosis.

Fungal tissue invasion and dissemination are controlled by phagocytic macrophages and neutrophils, which produce reactive oxygen species (ROS) and human antimicrobial peptides (hAMPs) to kill the pathogen. Acute hyperglycaemic conditions, such as diabetic ketoacidosis, impair phagocyte chemotaxis and intracellular killing. Acidosis also induces dissociation of iron from iron sequestering hAMPs, causing iron overload that decreases interferon (IFN)γ and neutrophil-mediated fungal killing. Moreover, *R. arrhizus* uses this free iron as a key micronutrient. In diabetic and neutropenic mice models, chelating iron decreases *R. arrhizus* burden, increases IFNγ and tumour necrosis factor (TNF)α, and improves survival.

The keystone in mucormycosis treatment is the early combination of surgical intervention and antifungal therapy. The antifungal of choice is amphotericin B (AMB) in any formulation, however, liposomal AMB is usually preferred. Isavuconazole and posaconazole are also recommended.

Modes of pathogenesis

The glucose-regulated protein 78 (GRP78) is the main human receptor for *R. arrhizus* on endothelial and nasal epithelial cells. High glucose, iron overload, or acidotic environments increase GRP78 expression, increasing fungal binding and uptake. These conditions are found during hyperglycaemic conditions such as acute diabetic ketoacidosis or chronic uncontrolled diabetes. Highly expressed GRP78 in endothelial and nasal epithelial cells would explain the presentation as rhino-orbital-cerebral mucormycosis seen mainly in individuals with diabetes. However, in alveolar epithelial cells, *R. arrhizus* germlings bind to an α3β1 integrin heterodimer instead of GRP78, and α3β1 integrin is considered the specific receptor for Mucorales in the lung. Further, β1 integrin signalling triggers the activation of the epidermal growth factor receptor (EGFR), allowing endocytosis of germlings by alveolar cells and subsequent cell damage.

The main Mucorales pathogen associated molecular patterns (PAMPs) are the spore coat protein homologues (CotH), which confer the ability to invade host cells (invasins). CotH3 in *R. arrhizus* germlings is the fungal ligand for GRP78, while CotH7 is the cell surface ligand for α3β1 integrin in alveolar cells. The different anatomic distribution of receptors and their corresponding fungal epitopes has been proposed to explain the differences in clinical syndromes seen between individuals living with haematological malignancies and individuals with diabetes.

R. arrhizus can secrete toxins such as mucoricin, which has structural and functional similarities to ricin and can inactivate host ribosomes. In addition, bacteria are observed as endosymbionts of 30–50% of Mucorales isolates. Bacterial-derived secondary metabolites can influence fungal behaviours and impact interactions with soil micropredators, such as amoeba and nematodes, as well as host phagocytes. The impact of bacterial endosymbionts on Mucorales pathogenesis remains an area of investigation.

TAXONOMY AND CLASSIFICATION:
KINGDOM: Fungi
PHYLUM: Mucoromycota
SUBPHYLUM: Mucoromycotina
ORDER: Mucorales
GENUS: *Rhizopus*
SPECIES: *Rhizopus arrhizus* (also *Rhizopus arrhizus* var. *arrhizus)*

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Declaration of interests

We declare that no authors have a conflict of interest with this manuscript.

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