Studying fungi's 'weak link' to fight global rise in deadly fungal infections

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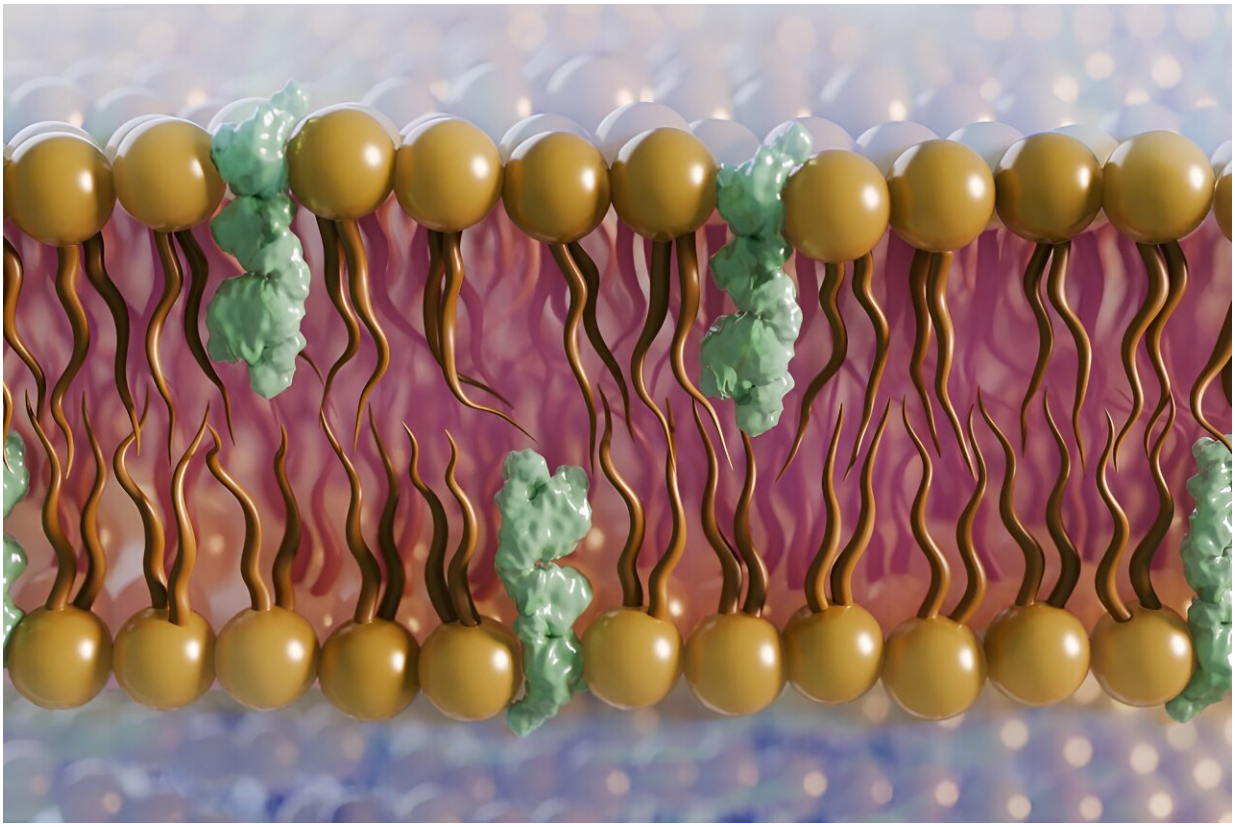

Scientists used neutrons to study the role of ergosterol (green), a cholesterol-like lipid found in the lipid bilayer (yellow) of fungi, which could help in combatting fungal infections that each year cause almost 1.7 million fatalities globally. Credit: Phoenix Pleasant/ORNL, U.S. Dept. of Energy

A group of scientists at the Department of Energy's Oak Ridge National

Laboratory have conducted neutron scattering research to reveal key information about fungus cell membranes that could aid in developing new antifungal treatments.

The research is published in *The Journal of Physical Chemistry Letters*.

The number of reported fungal cases has been slowly but steadily increasing in recent years. According to a study conducted by scientists at the Institute of Molecular Biosciences at the University of Graz in Graz, Austria, a rise in severe fungal infections has resulted in over 150 million cases annually and almost 1.7 million fatalities globally.

The ORNL team focused on ergosterol, a lipid (fat), found in fungi. Ergosterol is similar to but less studied than cholesterol found in animal cells.

Lipids form much of the basic structure of cell membranes, which are primarily made up of a double wall of lipids called a lipid bilayer. Among other functions, ergosterol and cholesterol help make the cell membrane more stable and flexible. Learning more about the differences between the two could increase the understanding of how to fight fungal infections.

"There has been significantly less research conducted on ergosterol compared to cholesterol, yet many people assume these sterols behave the same," said Shuo Qian, a staff scientist for ORNL's Second Target Station project to upgrade the Spallation Neutron Source, or SNS. "This study has shown us that ergosterol requires its own specific research. Better understanding this important facet of fungi could help in understanding how to combat its infections."

Qian explained that fungal infections can be especially harmful to the elderly and those with weakened immune systems, and unfortunately,

these infections are on the rise worldwide. Noting the scarcity of effective and nontoxic antifungal drugs available on the market and the limited fundamental knowledge about many aspects of fungi, Qian and his team decided to look for a possible solution within fungus cell membranes, a target for many antifungal drugs.

To simplify the experiments, the team studied a membrane model that accurately represented the fungal membrane. This strategy allowed them to better isolate and observe how ergosterol embeds itself less deeply than cholesterol and causes significantly less membrane thickening. Their results point to distinct differences in the interactions of ergosterol with membranes compared with those of cholesterol.

According to Qian, the team's findings could only have been obtained using neutrons: "Neutron techniques allowed us to look at individual molecules and how they move around in the membrane. Only neutrons can give us these multiscale, multilength and multi-timescale results."

The team performed both wide- and small-angle neutron scattering diffraction and spectroscopy experiments using five different instruments at SNS and the High Flux Isotope Reactor, or HFIR, including the Neutron Spin Echo Spectrometer, or NSE, and the Backscattering Spectrometer, or BASIS, at SNS and the Biological Small-Angle Neutron Scattering, or BIO-SANS, the Extended Q-Range Small-Angle Neutron Scattering Diffractometer, or EQ-SANS, and the Wide-Angle Neutron Diffractometer, or WAND2 at HFIR. ORNL's SNS and HFIR provide researchers with a wide range of complementary neutron scattering techniques in a single location.

"I think that's one of the beautiful things about this study," said Gergely Nagy, a neutron scattering scientist at SNS. "We were able to use several different techniques to study the material from various complementary perspectives."

Both neutron diffraction and small-angle neutron scattering are techniques used to study the structure of materials, just at different scales. Neutron diffraction looks at samples at the atomic and molecular level, whereas small-angle neutron scattering allows researchers to view larger, nanometer-sized structures in samples.

"The neutron spin echo technique is the only one that allows us to extract the mechanical properties of the membranes," said Piotr Zolnierczuk, a neutron scattering scientist at SNS. "There is no other method that offers the correct energy resolution."

The team used a large reference pool of data with dozens of different membranes, additives, and cholesterol. They found that ergosterol affects lipids unlike anything they have seen before in terms of the way it changes the movement of other lipid molecules.

Learning more about the differences between ergosterol and cholesterol is essential to proving that not all sterols have the same behavior. Future research on this subject could provide more clues about ergosterol's unique interactions in membranes. This fundamental understanding will help develop new approaches to battling fungal infections.

More information: Shuo Qian et al, Nonstereotypical Distribution and Effect of Ergosterol in Lipid Membranes, *The Journal of Physical Chemistry Letters* (2024). DOI: 10.1021/acs.jpclett.4c00385

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