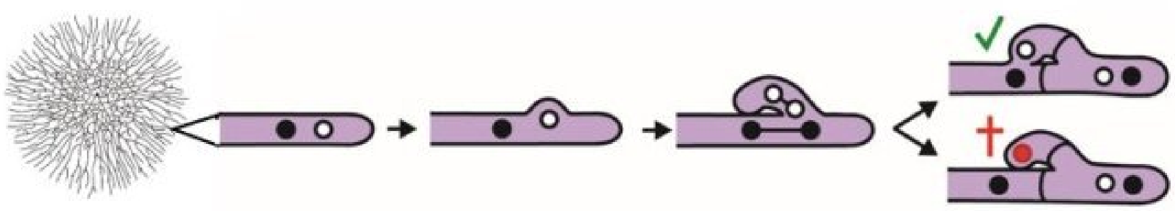
Researchers explain how mushrooms can live for hundreds of years without getting cancer

July 10 2023



Schematic representation of a clamp connection. Credit: Wageningen University

The risk of cancer increases with every cell division. As such, you would expect long-lived species like elephants to get cancer more often than short-lived species like mice. In 1975, however, Richard Peto discovered that this is not the case, and that there is very little variation in lifetime-cancer risk between animal species. This is known as Peto's paradox.

In a new publication, three researchers from Wageningen University & Research (WUR) propose a hypothesis to explain the variation in cancer risk in fungi. Some fungi seem to deploy a special type of cell division to prevent selfish mutations from being selected, drastically reducing the risk of cancer. The results of the study were published in the journal *Microbiology and Molecular Biology Reviews*.

Peto's paradox can be explained by the more stringent anti-cancer mechanisms that long-lived species have in comparison with short-lived species. This theory applies to animals that develop cancer when rapidly dividing mutant cells decrease the fitness of the animal. WUR researchers previously revealed that a type of "nucleus cancer" can develop in fungal networks.

"Mutations can occur in fungal mycelia—the below-ground network of fungal filaments—that give the nucleus a competitive advantage in the mycelium," explains Duur Aanen, one of the involved researchers. "Because these mutations are selected within the mycelium, but reduce the fitness of the mycelium as a whole, you can think of them as a kind of 'nucleus cancers.'"

Clamp connection in fungi

In their publication, the WUR researchers (Aanen and his colleagues Anouk van 't Padje and Ben Auxier) reason that long-lived, slowly-growing fungi, such as fairy ring-forming species that can live for hundreds of years, must have mechanisms that reduce the risk of such nucleus cancers.

Species that typically grow fast—but have short lives—do not need such a mechanism. Indeed, these species are prone to develop nucleus cancers if you culture them longer in the lab than they would normally grow under natural conditions. Previous research had revealed that, without exception, the selected mutants had lost the ability to fuse as fungal filaments (hyphae), and that this loss of fusion was responsible for the competitive advantage of the fungal mycelium.

According to the researchers, the mechanism responsible for resistance to these kinds of mutants in long-lived species is the clamp connection. This structure occurs only in mushroom-forming fungi and its function lacked a satisfactory explanation until now.

A clamp connection forms during cell division of a mycelium in mushroom-forming fungi. This mycelium is called dikaryon, because the cells have two genetically distinct haploid nuclei (haploid cells contain only one copy of each chromosome). When a terminal cell divides, one of the two nuclei takes a "detour" to the daughter cell, by first migrating to a temporary side cell, which later fuses with the daughter cell. After fusion, this side cell remains visible as a clamp connection.

"If the cell cannot fuse, it means a dead end for the cell and thus the end of its nucleus," explains Aanen. "My colleagues and I have now proposed a new hypothesis: that the fusion of the clamp connection is a test moment for one of the haploid nuclei. Since our previous research revealed that loss of fusion is the main route to nucleus cancers, we hypothesized that the clamp connection acts as a screening devise for the quality of the nucleus, with both nuclei continuously testing each other for the ability to fuse, a test that nuclei with mutations in fusion genes fail. We therefore argue that mycelia have a constant and low risk of nucleus cancers, regardless of their size and lifespan."

More information: Duur K. Aanen et al, Longevity of Fungal Mycelia and Nuclear Quality Checks: a New Hypothesis for the Role of Clamp Connections in Dikaryons, *Microbiology and Molecular Biology Reviews* (2023). DOI: 10.1128/mmbr.00022-21

Provided by Wageningen University