MedicalXpress

Starving fungi could save millions of lives each year

June 22 2018

Researchers have identified a potentially new approach to treating lethal fungal infections that claim more than 1.6 million lives each year: starving the fungi of key nutrients, preventing their growth and spread.

The team from the Westmead Institute for Medical Research found that stopping fungi from producing transporters that carry essential nutrients, like phosphate, starved the fungi.

Despite high levels of phosphate in the human body, the research showed that the infecting fungi are very poor at absorbing it. This causes the fungi to produce more transporters to try to bring in more phosphate—a process known as the 'phosphate starvation response'.

By blocking this phosphate starvation response—and stopping the fungi from producing more transporters to get more nutrients—the research team starved the fungi, preventing their spread of infection in mice.

Lead researcher, Associate Professor Julianne Djordjevic, is optimistic this discovery will provide a new avenue to develop safer and urgently needed antifungal drugs.

"Death rates due to fungal infections are similar to those of tuberculosis and greater than those due to malaria," Associate Professor Djordjevic said.

"Current antifungal drugs are toxic, poorly absorbed by the body, and

not fully effective. Drug-resistance is also emerging as a serious problem.

"Although new therapies are desperately needed to reduce the high global morbidity and mortality of infectious fungal diseases, no new classes of drug have been introduced into clinical medicine since 1986.

"If we can stop fungi from absorbing nutrients during infection, this could provide a novel treatment avenue for fungal infections. This is particularly important in patients with weakened immune systems, such as those with HIV/AIDS or leukaemia, and in organ transplant recipients who require life-long immunosuppressive therapy," she said.

The first author on the study, Dr. Sophie Lev, expanded the findings using bioinformatics.

"We found that the phosphate starvation response in fungal pathogens has expanded its function to transport other essential nutrients, like sugars and amino acids, not just phosphate. We also identified that this starvation response occurs because phosphate transporters do not function properly at human pH.

"The combined effect of poor nutrient absorption at human body pH and the expanded nutrient starvation response means that blocking this response could be the key to starving fungi of a range of key nutrients and treating these potentially lethal infections," Dr. Lev said.

"This finding is particularly exciting, because we may not need to start from scratch to identify drugs that block the fungal nutrient starvation response.

"FDA-approved drugs like Foscarnet, which are used to treat viral infections in transplant patients, have been shown to inhibit the

phosphate starvation response in fungi.

"When used in combination with antifungal drugs prescribed in the clinic, these drugs work more effectively, reducing treatment dose and potentially side effects," Dr. Lev concluded.

More information: Sophie Lev et al, Why is a functional PHO pathway required by fungal pathogens to disseminate within a phosphate-rich host: A paradox explained by alkaline pH-simulated nutrient deprivation and expanded PHO pathway function, *PLOS Pathogens* (2018). DOI: 10.1371/journal.ppat.1007021

Provided by Westmead Institute for Medical Research