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Could fungi seeThe Last of Us? - Why and how we should study antifungal drugs using neutron reflection and lipidomics

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Millions of people suffer life-threatening fungal infections, but there are no vaccines, and only a few antifungal agents, whose application is often restricted by toxicity, resistance and low bioavailability. Most antimycotic drugs target ergosterol residing in fungal membranes, but their precise mechanisms of action, toxicity and resistance development are still unclear. A fuller understanding of the function of the current drugs is critical for designing better, safer therapeutics in a world where climate change is a driving factor in the adaptation of pathogenic fungi to new geographical areas.

Candida glabrata is a non-pathogenic yeast in healthy humans, but the number of infections it causes has increased, making it urgent to understand its virulence and resistance. We have combined RNA interference to produce well-defined genetic modifications in C. glabrata strains (1) with lipidomic analysis to study the link between lipid composition and antifungal drug resistance.

Amphotericin (AmB) is a WHO essential medicine that has the broadest antifungal spectrum and has been used as the last line of defense against systemic fungal infections for more than 50 years, but its mechanism of action and resistance are still not well understood. We have used neutron reflection to elucidate the mechanism by which fungal cells become resistant to AmB in model fungal membranes (2,3) and membranes from C. glabrata strains with increased or decreased AmB resistance. Our integrative approach demonstrates how neutron techniques can provide insight into the molecular basis of antimicrobial activity and resistance with the long-term aim to improve therapies.

(1) Ishchuk et al. Front Microbiol (2019) doi:10.3389/fmicb.2019.01679.
(2) de Ghellinck et al., BBA-Biomembranes, 2015 doi:10.1016/j.bbamem.2015.06.006
(3) Delhom et al. Nanomaterials 2020 doi:10.3390/nano10122439

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