A common mechanism involving the TORC1 pathway can lead to amphotericin B-persistence in biofilm and planktonic Saccharomyces cerevisiae populations - DTU Orbit (13/12/2018)

Fungal infections are an increasing clinical problem. Decreased treatment effectiveness is associated with biofilm formation and drug recalcitrance is thought to be biofilm specific. However, no systematic investigations have tested whether resistance mechanisms are shared between biofilm and planktonic populations. We performed multiplexed barcode sequencing (Bar-seq) screening of a pooled collection of gene-deletion mutants cultivated as biofilm and planktonic cells. Screening for resistance to the ergosterol-targeting fungicide amphotericin B (AmB) revealed that the two growth modes had significant overlap in AmB-persistent mutants. Mutants defective in sterol metabolism, ribosome biosynthesis, and the TORC1 and Ras pathways showed increased persistence when treated with AmB. The ras1, ras2, and tor1 mutants had a high-persister phenotype similar to wild-type biofilm and planktonic cells exposed to the TORC1 pathway inhibitor rapamycin. Inhibition of TORC1 with rapamycin also increased the proportion of persisters in Candida albicans and Candida glabrata. We propose that decreased TORC1-mediated induction of ribosome biosynthesis via Ras can lead to formation of AmB-persister cells regardless of whether the cells are in planktonic or biofilm growth mode. Identification of common pathways leading to growth mode-independent persister formation is important for developing novel strategies for treating fungal infections.