Probing morphogenesis and drug susceptibility in a human fungal pathogen

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The human fungal pathogen, *Candida albicans* can switch from an oval yeast form to a filamentous form, a transition critical for its virulence. To investigate this process, we have been using live-cell microscopy to analyze the morphological and molecular changes, including that of key proteins and lipids, associated with this transition. More recently, we have been investigating the biophysical characteristics of the cytoplasm, using a genetically encoded micro-rheological probe [1], and we observe a striking increase in mesoscale cytoplasmic diffusion during morphogenesis. This increase in cytoplasmic fluidity is due to a decrease in ribosome concentration, which results in part from an inhibition of ribosome biogenesis, combined with an increase in cytoplasmic volume, leading to dilution of a major cytoplasmic crowder. Furthermore, our results suggest that inhibition of ribosome biogenesis can trigger morphogenesis in this fungal pathogen. Given that cytoplasmic crowding varies with stress, we also investigated, using a similar approach, whether changes in the biophysical characteristics of the cytoplasm are associated with tolerance of *C. albicans* to the most commonly used antifungal drug, fluconazole. Indeed, antifungal tolerance, which is a major issue when combating infections, is not genetically encoded. In contrast to the situation during morphogenesis, we observe a dramatic decrease in cytoplasmic fluidity associated with tolerance to fluconazole. This striking alteration in the physical characteristics of the cytoplasm occurs upon depletion of the sterol ergosterol and is reversible. Reducing ribosome levels restores this antifungal drug-induced decrease in cytoplasmic fluidity and reduces drug tolerance. Intriguingly, we observe that extended growth in fluconazole does not result in an increase in ribosome concentration, but instead an increase in cytoplasmic protein concentration and condensate formation. Hence, our results reveal how cytoplasmic fluidity is altered during morphogenesis and during tolerance in presence of an important antifungal drug, both processes critical for a persistent *C. albicans* infection.

[1] Delarue M et al. Cell 2018 **174**:338-49.