**Objectives**

*Candida auris* is an emerging multidrug-resistant human fungal pathogen, often refractory to treatment by all classes of antifungal drugs. Amphotericin B (AmB) is a fungicidal drug that, despite its toxic side effects, remains a drug of choice for the treatment of drug-resistant fungal infections, including those caused by *C. auris*. However, the molecular mechanisms underlying AmB resistance are poorly understood. Therefore, the objective of this study is to understand the mechanism(s) of AmB resistance in *C. auris*.

**Methods**

To determine the plausible cause(s) of increased AmB resistance, we performed RNA-seq analysis of logarithmically growing AmB resistant isolates in comparison to AmB susceptibleisolates in the Yeast Extract Peptone Dextrose broth medium (YPD; 1% yeast extract, 2% peptone, and 2% dextrose) at 37°C. Four independent AmB-resistant and a two AmB susceptible isolate belonging to the South Asian clade were used in this study.

**Results**

For RNA-seq experiments we used four independent AmBresistant isolates in comparison to two susceptible *C. auris* isolates. Prior to RNA isolation, all strains were grown to logarithmic growth phase in YPD broth at 370C. From the RNA-seq analysis, we found ~750 DEGs common to all AmBresistant isolates vs two distinct susceptible isolates. Importantly, gene expression pattern varies very little between the two unrelated AmB sensitiveisolates of distinct patient origin. These data strongly suggest that AmB resistance may be regulated by a set of “core” genes across distinct clinical *C. auris* strains in all clades. From the RNA-seq experiments, we have identified *SSK1,* a two-component response regulator, to be highly expressed in AmBresistant *C. auris* strains. Additionally, we observed that Ssk1 modulates susceptibility to caspofungin and AmB and was required for fungal survival when challenged with primary murine macrophages and neutrophils *ex vivo*. Furthermore, disruption of *SSK1* causes virulence attenuation in a murine model of disseminated candidiasis. Thus, based on these data, we hypothesize that Ssk1 is an important regulator of AmB resistance and host-*C. auris* interactions.

**Conclusions**

Collectively, these data identify differences in the transcriptional landscapes of AmB-resistant vs AmB- susceptible isolates and provide a framework for the mechanistic understanding of AmB resistance and host-*C. auris* interactions.