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BACKGROUND

With increased rates of resistance to the major classes of antifungals, there is a need for novel antifungals. SCY-078 (SCY) is a first-in-class oral/IV triterpenoid glucan synthase inhibitor (GSI) antifungal that exhibits potent activity against *Candida* species, including echinocandin-resistant (ER) strains (1). Unlike echinocandins, SCY is orally bioavailable, which could potentially lead to better patient compliance and tolerability. In this study, we evaluated the effect of SCY and caspofungin (CAS) on the morphology of *C. albicans* (CA), *C. auris* (CAu), and *C. glabrata* (CG) using scanning and transmission electron microscopy (SEM/TEM).

METHODS

- The minimum inhibitory concentration (MIC) of CAS-resistant CA, CAu, and CG strains against SCY and CAS were determined according to CLSI M27-A3 methodology.
- Strains having an MIC₅₀ ≥ 1 (for CA) and ≥ 0.5 (for CG) were considered CAS-resistant.
- Cells exposed to MIC₅₀ concentrations of SCY or CAS were collected along with untreated cells (UC), fixed in glutaraldehyde, and prepared for SEM and TEM as previously described (2).
- Briefly, cells were fixed, stained, dehydrated, and placed in a desiccator box for 48 hours.
- Cells were coated with palladium for 60 seconds and viewed with the Helios NanoLab 650 electron microscope.

RESULTS

- SEM analysis showed that untreated cells exhibited normal morphology and ultrastructure (Fig. 1 A, D, and G), whereas cells treated with SCY were swollen, with loss of the classic yeast elliptical appearance (Fig. 1 B, E, and H). Cells treated with CAS showed only minor swelling (Fig. 1 C, F, and I).

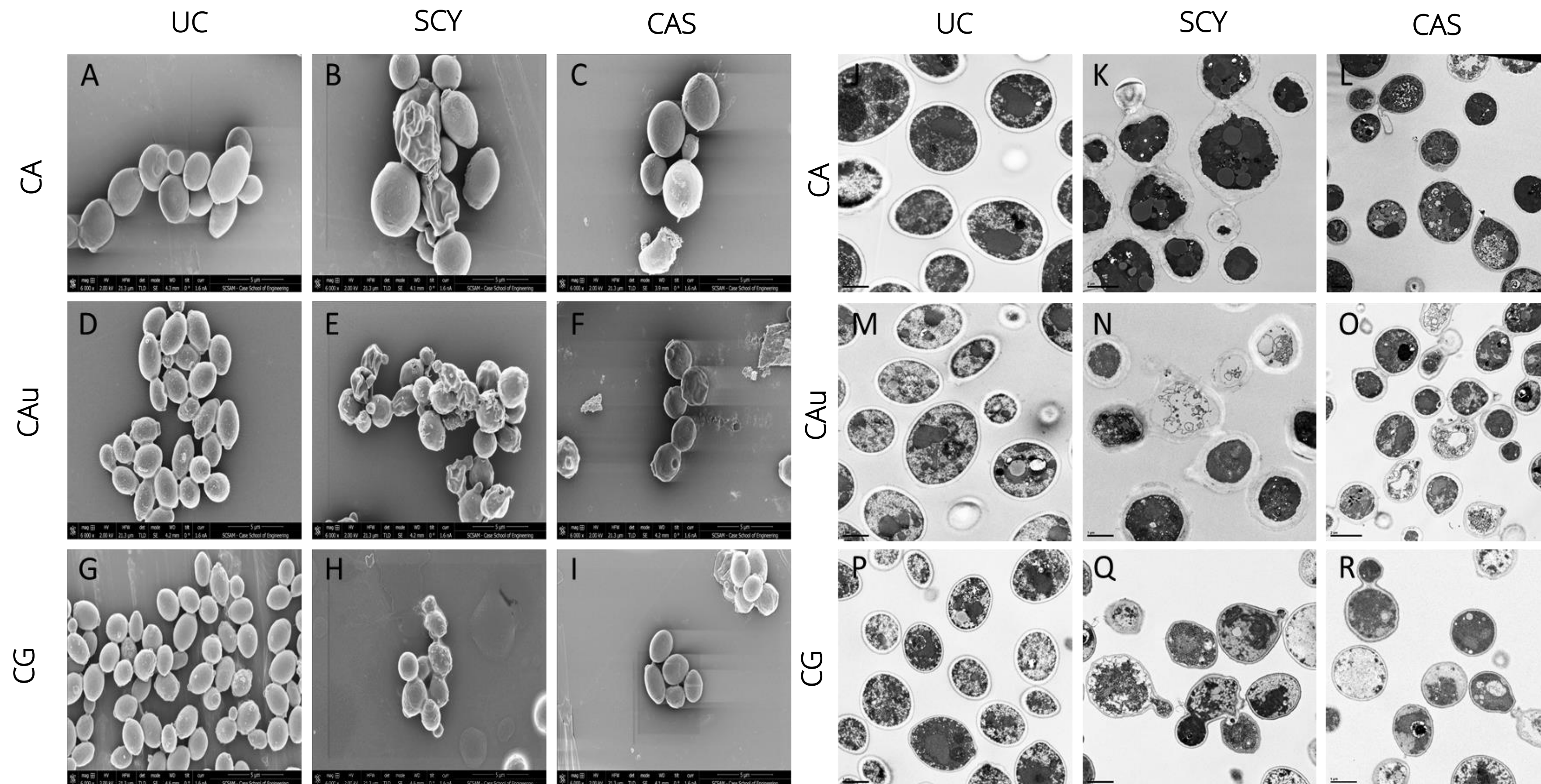


Figure 1. SEM of CA UC (A), SCY treated CA (B), CAS treated CA (C), CAu UC (D), SCY treated CAu (E), CAS treated CAu (F), CG UC (G), SCY treated CG (H), CAS treated CG (I), and TEM of CA UC (J), SCY treated CA (K), CAS treated CA (L), CAu UC (M), SCY treated CAu (N), CAS treated CAu (O), CG UC (P), SCY treated CG (Q), and CAS treated CG (R).

- TEM analysis of untreated cells showed normal morphology, including an intact outer cell envelope and healthy cytoplasmic structures (Fig. 1 J, M, and P), whereas SCY treated cells revealed a swollen cell envelope and loss of cell membrane, leading to destruction of the internal structures (Fig. 1 K, N, and Q). Lipid-like structures were also noted within the cytoplasm.
- In contrast, CAS treated cells appeared to have intact cell walls and undisturbed internal structures (Fig. 1 L, O, and R).

CONCLUSIONS

The findings indicate that when evaluated at respective MIC₅₀ levels, SCY-078 exhibits a profound effect on cellular morphology in CAS-resistant organisms, which may be indicative of a difference in target engagement from the echinocandins.

References:

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