In vitro Evolution of α-(1,3)-glucan and Virulence in *Histoplasma* spp.

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Histoplasma is a dimorphic fungal pathogen transitioning from mycelium to the yeast form that persists in mammalian hosts. *Histoplasma* is a primary pathogen, although histoplasmosis is most common in the immunocompromised. The polysaccharide α-(1,3)-glucan is both a cell wall constituent and virulence factor in many fungal pathogens. In *Histoplasma,* the presence or absence of α-(1,3)-glucan in the yeast cell wall yields a rough or smooth colony morphology, respectively.

We designed an *in vitro* evolution experiment selecting for smooth mutants in ten strains across 4 species of *Histoplasma*, plus *Blastomyces dermatitidis* and *Paracoccidioides brasiliensis.* Using DNA extractions, we derived ~200 high molecular-weight DNA samples. Genome sequencing will identify which mutations/genes beget the smooth phenotype, and its conservation relating to α-glucans production and virulence across the genus. From rough wild-types, smooth mutants predominated the population of *Histoplasma* within 10 passages; in *Blastomyces* and *Paracoccidioides,* passages 20 and 25. Macrophage virulence assays novelly confirmed α-(1,3)-glucan necessity for *in vitro* virulence in *H. suramericanum* and the African clade.

The elements required for α-(1,3)-glucan biosynthesis represent important targets for antifungal drug development. We will evaluate how the absence of α-(1,3)-glucan influences virulence in animal infections, and how this impacts overall immunity.

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