**2887. Identifying Candida albicans Transcription Factors (TFs) That Regulate Pathogenesis of Intra-abdominal Candidiasis (IAC) by Screening a Deletion Mutant Library**

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**Session:** 308. Fungi: Blood, Sweat, and Genes

**Saturday, October 5, 2019: 3:45 PM**

**Background.** IAC is a common manifestation of invasive candidiasis, but its pathogenesis is poorly understood. We developed a mouse model of *C. albicans* IAC, in which disease progresses from peritonitis to abscesses (IAA) in a manner that recapitulates human infection. Our goal was to use the model to identify *C. albicans* TFs that regulate virulence during IAC.

**Methods.** We screened a signature-tagged library (48 unique oligonucleotide markers) of homozygous deletion mutants for 165 *C. albicans* TF genes, created in duplicate in strain SC5314 (S. Noble). Mice were infected intra-peritoneally in triplicate with pools of 24 mutants and wild-type, and strains harvested at 72 hours in IAA.

**Results.** Twenty-one TF mutants were significantly attenuated for virulence in both libraries, and 2 TF mutants were significantly more virulent in both libraries, as measured by tissue burdens (figure). Biologic processes over-represented among attenuated mutants were regulation of pH responses, biofilm, hyphal formation, echinocandin responses, and copper metabolism. pH responses are likely to be crucial to pathogenesis of IAC, as *C. albicans* transitions from pH 8.6 during peritonitis to pH 6.8 within IAA. 9 pH response regulators contributing to virulence included RIM101, STP2 (alkaline), ASH1, SFL1, SFL2 (neutral), MN1, SKO1, PHO4 (weak acid), and CSR1 (acid). We created rim101 null mutant and reconstitution strains, and demonstrated that the gene was essential for complete virulence during peritonitis and IAA. Transcriptional profiling of strains by RT-PCR during peritonitis and in vitro showed both conserved and rewired Rim101 targets. SAP5, which encodes an aspartyl protease, is a major Rim101 target in vivo and in vitro; over-expression of SAP5 in rim101 restored virulence during peritonitis and IAA formation are being explored through epistasis approaches.

**Conclusion.** Screening of a *C. albicans* TF mutant library identified pH responses and other biologic processes as important during pathogenesis of IAC. Rim101, an alkaline pH response regulator, contributes to both peritonitis and IAA, the latter at least in part through its effects on Sap5.

**Disclosure.** All Authors: No reported Disclosures.

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**2888. STAT4 Mutation in Three Generations with Disseminated Coccidioidomycosis (DCM) also Exhibits Increased Susceptibility to Coccidioidal Infection in Transfected Mice**

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**Session:** 308. Fungi: Blood, Sweat, and Genes

**Saturday, October 5, 2019: 4:00 PM**

**Background.** Reported coccidiomycosis has increased with case rates of 198/100,000 in Arizona (2012). In California alone, 2000–2011 hospitalizations were ~2.2B. Dissemination occurs in 8% of reports with significant morbidity and occasional deaths. DCM was found in 3 generations: grandmother (skin), mother (skin) and son (bone). Whole exome sequencing identified a heterozygous (het) STAT4 mutation (p.E626G) in all three. This mutation alters the phosphotyrosine binding pocket and is predicted to impair STAT4 function, interfering with (i) receptor binding and phosphorylation, (ii) nuclear localization, and/or (iii) transcription. Expression profiling of antigen-stimulated peripheral blood mononuclear cells from one patient showed dampening of known STAT4 targets compared with controls.

**Methods.** STAT4 p.E626G was generated and confirmed in C57BL/6NJ (WT) mice using CRISPR-Cas9. With continued breeding, neither homozygous (hom) nor het mice had gross abnormalities. There were normal spleen and lung lymphoid cell numbers, thymus and bone marrow had normal development of lymphoid subsets. We performed intranasal infection with reduced virulence *C. posadasii* strain 1038 or with *F. tularensis* live vaccine- strain (LVS). Naïve or Δcps1-vaccinated mice were tested for resistance to *C. posadasii* strain Silveira.

**Results.** At day 21 post Cp 1038 infection, hom, het, and WT mice had similar lung fungal burdens (~10^7 cfu). All p.E626G mice died between days 31 and 39 with lung burden significantly higher (~9 × 10^7 cfu) than WT sacrificed on day 44 (7 × 10^7 cfu, P = 0.015). After LVS infection, p.E626G mice had increased lung bacterial cfu and all had dissemination to the spleen compared with WT lung bacterial burden and no splenic dissemination. Immunized het and WT mice all had significantly reduced lung cfu 14 days following *C. posadasii* infection compared with unvaccinated WT mice.

**Conclusion.** The STAT4 p.E626G mutated mouse recapitulated patients’ increased susceptibility to coccidioidal infection. The decreased fungal burdens seen in Δcps1-vaccinated mice suggest that vaccination may be effective in those persons genetically susceptible to DCM. Given the increasing frequency and economic burdens of coccidiomycosis, pursuit of vaccination strategies should continue.
2889. Skin Niche Conditions Trigger C. auris to Form Robust Biofilms That Resist Desiccation

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Session: 308. Fungi: Blood, Sweat, and Genes
Saturday, October 5, 2019: 4:15 PM

Background. Emerging pathogen Candida auris, the first fungus to be labeled as a public health threat, causes nosocomial outbreaks of invasive candidiasis with mortality as high as 60%. Little is known about the pathogenesis of this species that has newly arisen in the last 10 years. It is unclear why this species readily colonizes the skin and transmits efficiently in healthcare settings. We considered the possibility that C. auris may proliferate in conditions of the skin niche.

Methods. We analyzed the growth of C. auris (B11203) in synthetic sweat media that was designed to mimic human axillary sweat. We included C. albicans SC5314 as a comparison. To simulate sweat evaporation, we examined fungal growth in sweat media that had been concentrated up to 2.5-fold. We utilized OD600 readings to quantify planktonic and biofilm growth. Biofilm architecture was assessed by scanning electron microscopy. To determine the resilience of biofilms, biofilm viability was assessed by viable burden following desiccation.

Results. In the various concentrations of sweat media, C. auris formed biofilms that were 3.5- to 5-fold greater than those observed for C. albicans (A). In contrast, C. auris biofilms formed in RPMI-MOPS were approximately half the density of the C. albicans biofilms. During planktonic growth in synthetic sweat media, C. auris and C. albicans replicated similarly, including in media that had been concentrated 2.5-fold. This suggests that the various media conditions differently trigger biofilm formation for the two species. The C. auris biofilm formed in sweat media was approximately 100-fold more resistant to 1 week of desiccation (B).

Conclusion. Skin niche conditions trigger C. auris to form resilient biofilms that resist desiccation. We propose that this unique characteristic may account for the propensity of this species to colonize the skin and for its capacity to persist on the surface of contaminated medical devices.

Disclosures. All Authors: No reported Disclosures.

2890. Antibiotic Overuse at Discharge in Hospitalized Patients with Bacteriuria or Treated for Pneumonia: A Multi-Hospital Cohort Study

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Session: 309. Glass Half Full or Half Empty? Trends in Antimicrobial Prescribing
Saturday, October 5, 2019: 3:15 PM

Background. Antibiotics prescribed at hospital discharge account for half of antibiotic use related to hospitalization for urinary tract infection or bacterial pneumonia. It is unclear how much antibiotic use at discharge represents overuse, and thus, could potentially be improved through antibiotic stewardship.

Methods. From July 2017 to December 2018, trained abstractors at 46 Michigan hospitals collected detailed data on a sample of adult, nonintensive care, hospitalized patients with bacteriuria or treated for community-acquired or healthcare-associated pneumonia (discharge diagnosis of pneumonia plus antibiotic treatment). Antibiotic prescriptions at discharge were assessed for overuse using a guideline-based hierarchical algorithm: evaluating first for unnecessary antibiotic (noninfectious/nonbacterial syndrome), then excess duration (antibiotics needed, but prescribed for longer than necessary), and finally avoidable fluoroquinolones (safer alternative antibiotic available) (Figure 1). For each disease state, descriptive results are shown with comparisons by t- or Fisher’s exact tests.

Results. Of 17,157 patients (7,283 with bacteriuria; 9,874 treated for pneumonia), 30.1% of patients with bacteriuria had asymptomatic bacteriuria and 11.4% of patients treated for pneumonia did not meet diagnostic criteria for pneumonia. The most common antibiotics prescribed at discharge were fluoroquinolones. Nearly half (43.6%) of patients had antibiotic overuse at discharge (33.8% bacteriuria, 50.9% pneumonia), with a median 4 days of overuse after discharge (Table 1). For bacteriuria, 45.0% of overuse days at discharge were due to unnecessary antibiotics; for pneumonia, 61.2% were due to excess antibiotic duration (Figure 2). Patients with community-acquired pneumonia and those with sepsis on admission had the highest rates of antibiotic overuse at discharge (Table 2).

Conclusion. In the largest assessment of antibiotics at discharge to-date, antibiotic overuse at discharge was extremely common. Specific targets for discharge stewardship vary by disease state. Notably, interventions may be more effective at reducing fluoroquinolone prescribing at discharge indirectly by stopping treatment for asymptomatic bacteriuria and reducing excess duration in pneumonia.

Disclosures. All Authors: No reported Disclosures.