1726. *Candida albicans* Virulence Genes Induced During Intra-abdominal Candidiasis (IAC) in the Absence of Antifungal Exposure Mediate Echinocandin Resistance

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Background. We developed and validated a mouse model of *C. albicans* IAC that mimics peritonitis and abscesses (IAA) in humans, and that is amenable to temporal–spatial transcriptional profiling and virulence studies.

Methods. We measured *C. albicans* SC5314 gene expression by RNA-Seq (RiboPure extraction; Illumina MiSeq) in triplicate during early peritonitis (within 30 minutes of infection), late peritonitis (24 hours) and IAA (48 hours). Differential expression was defined by ≥2-fold differences at false discovery rate ≤0.01.

Results. ≥7 million *C. albicans* reads were detected in each experiment. 67% of *C. albicans* reads mapped to coding sequences, covering 93% of open reading frames. The 50 *C. albicans* genes most highly expressed during early peritonitis were associated with pH (including RIM101 and PHR1) and oxidative stress responses, and adhesion/hyphal growth (e.g., ALS3, HWP1, ECM331, SAP6). The corresponding 50 *C. albicans* late peritonitis genes were associated with neutrophil/macrophage responses and nutrient acquisition (glyoxylate cycle, fatty acid β-oxidation, iron homeostasis). Responses within IAA included DNA damage and iron metabolism, reflecting stress response and nutrient/metal limitation. The top 50 core gene responses for all stages were associated with adhesion, stress response, and glucose transport. Among the most up-regulated genes in late peritonitis and IAA compared with early peritonitis were those involved antifungal drug resistance (CDR family, MDR1, FLU1, and ERG family), although mice were not exposed to antifungals. Null and reconstitution mutants for genes involved in adhesion (ALS3), copper transport (CCC2), DNA (DDI1) and cell wall damage responses (DAP1 homologs), and glycerol biosynthesis (RHR2) were attenuated for virulence in temporal-spatial fashion during peritonitis and IAA, and/or hyper-susceptible to phagocytosis and echinocandins (table).

Conclusion. *C. albicans* relies upon diverse biologic processes to cause peritonitis and IAA. Multiple genes induced in response to stress during IAC mediate virulence, phagocyte, and echinocandin resistance. Therefore, pathogenic strategies used by *C. albicans* during IAC may lessen responses to echinocandin treatment, even in the absence of drug exposure or FKS mutations.

***C. albicans* genes implicated in pathogenesis of IAC and echinocandin resistance**

Gene	Description	Phenotypes
ALS3	Adhesin, induced in IAA and PF	Null mutant causes lower tissue burdens at later time points in IAA, but not in early IAA or PF, and is hyper-susceptible to neutrophil phagocytosis
CCC2	Transmembrane transporter involved in copper regulation, induced in IAA	Null mutant is hyper-susceptible to echinocandins, and causes lower tissue burdens late in IAA but not in early IAA or PF
DDI1	DNA damage response, induced in PF	Null mutant causes lower tissue burdens in both PF and IAA
19.489, 19.1034, 19.6867	*DAP1* (cell wall damage resistance) homologs, induced in IAA	Triple null mutant is hyper-susceptible to echinocandins, and has lower tissue burdens in IAA but not in PF
RHR2	Glycerol biosynthesis enzyme, required for biofilm	Null mutant causes lower tissue burdens in PF and IAA

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1727. *Candida albicans* Phosphatidylinositol-(4,5)-Bisphosphate (PIP2) Directs Aberrant Cytokinesis and Septation in Response to Echinocandins, Which Correlates with Fungicidal Activity and Attenuated Virulence

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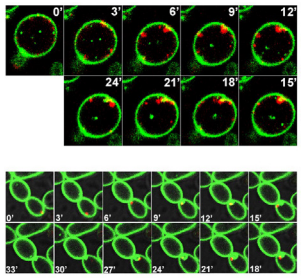
Background. We previously showed that highly dynamic PIP2, septin, and PKC-Mkc1 cell wall integrity pathway responses correlate with echinocandin activity against *C. albicans* and attenuated virulence during invasive candidiasis. Our objectives were to determine whether PIP2 dysregulation in response to an echinocandin results in aberrant localization of the septation and cytokinesis apparatus, and to quantitate aberrant localization.

Methods. Live cell imaging (LCI) was performed for 3 hours (Nikon A1 confocal microscope, NIS Elements software; Tokyo) on *C. albicans irs4* mutant and wild-type SC5314 expressing fluorescently labeled PIP2 and Cdc10 (septin), Act1 (actin), or Myo1 (myosin).

Results. *C. albicans irs4*, in which PIP2 5'-phosphatase is disrupted, mislocalizes PIP2 and septins, and over-activates the PKC-Mkc1 pathway in a manner similar to echinocandin-exposed *C. albicans* SC5314. LCI revealed that PIP2 co-localized with Act1 and Myo1 at aberrant sites in *C. albicans irs4*, similar to PIP2-Cdc10 co-localization. 83% of co-localizing patches were in cells undergoing active cytokinesis. 78% of patches were at sites of cytokinesis, which reflected both normal budding and abnormal, wide-necked budding; 5% of patches localized to aberrant plasma membrane sites during cytokinesis. 17% of co-localizing patches were in cells that were not undergoing active cytokinesis. 6% of patches were at old cytokinesis sites; 11% of patches were at aberrant plasma membrane sites. Similar PIP2-septin-actin-myosin dysregulation was observed in *C. albicans* SC5314 immediately upon 4x MIC caspofungin exposure (Figure; videos).

Conclusion. Dysregulated *C. albicans* PIP2 recruits the septation and cytokinesis apparatus, including septins, actin, and myosin, to sites of incomplete cytokinesis at bud necks and to sites of aberrant, ectopic septation in plasma membranes of both dividing and non-dividing cells. Our data support a model in which a dysregulated PIP2 response is triggered immediately upon echinocandin exposure, over-activates the PKC-Mkc-1 pathway, and correlates with the extent of fungicidal activity and attenuated virulence. PIP2-septation-cytokinesis dysregulation is likely to lead to *C. albicans* death by promoting cell lysis, or selecting cells to undergo apoptosis.

Time lapse co-localization of PIP2-GFP and Act1-RFP (top) or Myo1-RFP (bottom) in *C. albicans* SC5314 in response to 4xMIC caspofungin.



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1728. A Retrospective Analysis of 49 Cases of Histoplasmosis in Inflammatory Bowel Disease Patients on Tumor Necrosis Factor-α Antagonists

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Session: 165. Mycology
Friday, October 4, 2019: 12:15 PM

Background. Tumor necrosis factor (TNF)-α antagonist therapy has revolutionized the practice of management of inflammatory bowel disease (IBD); however, these medications carry a boxed warning from the Food and Drug Administration for risk of serious infection. We aimed to study the invasive fungal infection, histoplasmosis, in the setting of TNF-α antagonist therapy.

Methods. We performed a retrospective review of patients with IBD receiving TNF-α antagonist therapy who developed histoplasmosis during the time period January 2001–May 2018 at the Mayo Clinic, Rochester, MN. The medical records of patients were reviewed for demographics, medications, symptoms, diagnosis, treatment, and outcomes including mortality. IBD was diagnosed by biopsy, radiographic, or endoscopic evidence of disease.

Results. We identified 49 patients (age range 19–74; median 44 years) with a confirmed diagnosis of histoplasmosis while receiving a TNF-α antagonist. 73.5% of cases were classified as disseminated. Median time from starting TNF-α antagonist to histoplasmosis diagnosis was 2.1 years. Liposomal amphotericin B was given in 17 cases as the initial treatment. Itraconazole was given to all 49 patients. Initial treatment was split evenly between inpatient (49%) and outpatient (51%) locations with 6 patients (12%) requiring ICU-level care. Median length of stay was 9.5 days. The total length of treatment for all antifungals was 38.4 weeks, with 20.4% of patients developing documented antifungal side effects. TNF-α antagonist was continued in 9 patients (18.4%) and another 10 patients resumed TNF-α antagonist. Half of those who resumed TNF-α antagonists were on antifungal therapy. There was one histoplasmosis recurrence while off TNF-α antagonist, and three deaths (6%).

Conclusion. Histoplasmosis outcomes in IBD patients on TNF-α antagonists were mostly favorable; however, approximately half required hospitalization. Many patients were young with few co-morbidities, and over one-third were able to continue or resume TNF-α antagonists without documented recurrence of histoplasmosis. Practitioners should be vigilant for histoplasmosis infections in this patient population who reside in histoplasma-endemic regions.

Table 1 Patient Demographic and Characteristics

Characteristic	No. (%), n=49
Age, years, median (range)	44 (19 – 76)
Sex	
Female	20 (40.8%)
Male	29 (59.2%)
Race	N=47
Caucasian	46 (99%)
Middle Eastern	1 (1%)
Charlton Comorbidity Index, median (IQR)	0 (0, 3.5)
Smoking	
Current	4 (8.5%)
Former	12 (25.5%)
Never	31 (66%)
Previous transplant	0
IBD History	
Crohns	41 (83.7%)
UC	7 (14.3%)
Indeterminate	1 (2%)
TNF-α antagonist	
Infliximab	35 (71.4%)
Adalimumab	13 (26.5%)
Certolizumab	1 (2.0%)
Additional immunosuppression	
Prednisone	12 (24.5%)
Azathioprine	13 (26.5%)
Methotrexate	6 (12.2%)
Tacrolimus	1 (2.0%)
Budesonide	1 (2.0%)
Time (years) from IBD diagnosis to TNF-α antagonist, median (IQR)	9.24 (2.1, 18.2)

Disclosures. **All authors:** No reported disclosures.

1729. Profiling Human Neutrophil Functional Responses From Solid-Organ and Stem Cell Transplant Recipients to *Candida albicans*

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Session: 165. Mycology

Friday, October 4, 2019: 12:15 PM

Background. Solid-organ (SOT) and stem cell transplant (SCT) recipients are at increased risk of invasive fungal disease despite normal neutrophil counts in peripheral blood. However, the neutrophils function against fungi has not been completely defined. In this study, we measure human neutrophil anti-*candida* activity in SOT and SCT recipients.

Methods. SOT and SCT patients were identified and consented from September 2018 until April 2019. Healthy control patients (HC) were identified at primary care clinics. EDTA-anticoagulated peripheral blood was obtained from healthy and transplant patients 2–4 months post-transplant. Neutrophils were isolated by negative selection. *C. albicans* was incubated for 2 hours with and without human neutrophils at multiplicity of infection (MOI) of 10, 5 and 1. Following neutrophil cell lysis, percent remaining live *Candida* was measured using a viability dye. In addition, growth inhibition of *C. albicans* by neutrophil swarming to *C. albicans* spotted onto glass slide arrays was also assessed by live cell imaging.

Results. 22 SOT (15 kidneys, 7 livers), 20 SCT (allograft) and 22 HC were enrolled. Neutrophils from SCT and SOT had lower *C. albicans* killing percentages compared with HC at MOI 10 (HC: 47%, SOT: 29%, SCT 24% $P = 0.0041$); MOI 5 (HC: 72%, SOT: 35%, SCT 38% $P < 0.0001$) and MOI 1 (HC: 91%, SOT: 48%, SCT: 45% $P < 0.0001$). Neutrophil swarming and fungal control of *C. albicans* spots was significantly inhibited by neutrophils from SCT when compared with SOT and controls ($P < 0.0001$). Analysis of medications, including tyrosine kinase inhibitor (TKI) use, did not demonstrate significant differences of a specific drug class when patient groups are compared (SCT vs. SOT).

Conclusion. Our study indicates that despite normal circulating numbers, neutrophils from SOT and SCT recipients are dysfunctional and show profoundly impaired anti-Candida activity. There were no medications or laboratory values that predicted functional neutrophil outcome. These data strongly support the use of functional neutrophil profiling to risk stratify those individuals at higher risk for invasive fungal infections.

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1730. Invasive Fusarium Species in Mayo Clinic Patients with Hematologic Malignancies

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Background. The epidemiology of fungal infections in hematologic malignancies has changed in the past decade. Triazole prophylaxis has decreased Candida spp infections while infections due to other molds such as *Aspergillus* and *Fusarium* species have increased. Fusariosis has very poor prognosis, and after aspergillosis, is the most common invasive fungal infection in this patient population. We sought to describe fusariosis in patients with hematologic malignancy at the Mayo Clinic.

Methods. We performed a retrospective review of patients with culture-positive *Fusarium* infection from January 2003 to October 2016 at the Mayo Clinic, Rochester, MN. The records of patients were reviewed for demographics, diagnosis, treatment, and outcomes including mortality. Patients without a diagnosis of hematologic malignancy were excluded. Patients were classified with proven or probable Fusariosis based on the Revised Definitions of Invasive Fungal Disease from the EORTC/MSG Consensus Group.

Results. We identified 14 patients with hematologic malignancies (age range 17–76 years; median 60 years) with a confirmed culture diagnosis of Fusarium infection classified as proven (9 patients) or probable (5 patients). Two cases were isolated pulmonary infections, 3 extra-pulmonary, and 9 disseminated cases. Two patients had previously undergone stem cell transplantation. Eight patients (57%) were receiving antifungal prophylaxis at the time of diagnosis: 2 on voriconazole, 1 on posaconazole, 1 on fluconazole, 3 on echinocandins, and 1 on Amphotericin B. Nine patients (64%) were neutropenic at the time of diagnosis. Amphotericin was the initial treatment in 7 (50%) patients, with voriconazole added for 4 patients for combination therapy the first week. Voriconazole monotherapy was given initially in 5 patients. Seven patients (50%) were deceased at 6 weeks after culture positivity, with an additional 2 patients deceased by 12 weeks.

Conclusion. *Fusarium* infection outcomes in patients with hematologic malignancies are poor. Neutropenia was common in those diagnosed, and infections were more likely to be disseminated, with high mortality rates. Amphotericin was commonly used as initial treatment, with many physicians recommending combination therapy with two agents, commonly voriconazole.

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1731. Immune Dysregulation in Mucormycosis

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Session: 165. Mycology

Friday, October 4, 2019: 12:15 PM

Background. Mucormycosis is a fatal fungal infection with unique predisposition to infect diabetics. Dysregulated adaptive immunity contributes to the pathogenesis in all fungal diseases, but activated Th17 cells have laid a new dimension to chronic inflammatory response which was previously attributed to uncontrolled Th1 response. We attempted to study the Th17 and T regulatory (Treg) immune response in diabetic patients with mucormycosis and compared the data with a healthy control and a T2DM case without fungal infection. In addition we could follow-up one patient post 6-month treatment and performed immunological studies.

Methods. 2 mL of blood samples were collected in EDTA vial from two patients who were suffering from diabetes with mucormycosis for immunological investigations. Samples were also taken from age-matched T2DM patient without fungal infection and a healthy volunteer as controls for T-cell parameters. Repeat blood sample was taken to study immune parameters in one patient who was followed up after 6 months. The expression of various T-cell markers was analyzed by immunostaining with the antibodies against CD3, CD4, CD25, CD161, IL-23R [Becton Dickinson (BD) PharMingen]. Fluorescence profiles were analyzed using Flow Jo software (BD Biosciences). The results are expressed as a percentage of positive cells.

Results. The percentages of CD4+ cells were low in both patients when compared with and healthy control but it is much higher in diabetes case when compared with others. CD161+ cell population was higher in both patients when compared with healthy control and diabetic patient without fungal infection. The percentage of IL23R+ cells was significantly high in patient before treatment when compared with, healthy control and diabetics. and decline after treatment. The percentage positivity of CD25+ cells was highest in healthy control when compared with others. The profile of CD25+ cells was comparatively similar in patient before treatment and diabetics but we found a higher percentage, in patients after treatment.

Conclusion. The findings in this study imminently indicate the mechanism of immune dysregulation involving Th17 and Treg pathways in mucormycosis and provide evidence that restoration of Th17/Treg may be considered as a therapeutic option for long-term benefit in diabetics.

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1732. A Canine Target Species Challenge Model to Evaluate Efficacy of a Coccidioidomycosis Vaccine

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Session: 165. Mycology

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Background. The preferred efficacy design for licensing a vaccine for animal use (United States Department of Agriculture (USDA)) is a prospective, placebo-controlled, randomized, and double-blinded vaccination-challenge trial. In such studies, each subject receives the same exposure to the virulent pathogen by active challenge. To test a cps1, live avirulent canine coccidioidomycosis vaccine, an inhalation disease model was developed in beagle dogs.

Methods. 6-month old male beagle dogs were housed according to PHS standards. All procedures, approved by the Institutional Animal Care and Use Committee for Colorado State University, were performed at ABSL3. Dogs were infected by nebulization with low, medium or high counts of arthroconidia of *Coccidioides posadasii*, strain Silveira, delivered via endotracheal tube under injectable anesthesia. Thoracic radiographs, CBC, and serum chemistries and body weights were obtained at 2- or 3-week intervals and dogs were euthanized 8 weeks p.i., or earlier if necessary. Approximately 1 gram lung specimens from each lobe were cultured for fungal burden. Fixed tissues were examined histologically. Serum was tested for antibodies.

Results. Ten of 11 dogs were successfully infected; 5 required early removal at 33 to 48-days p.i. Elevated globulin, decreased albumin, decreased A/G ratio, monocytosis and weight loss were present in all infected dogs. Radiographic and histopathological lesions were very extensive at the high challenge doses. Medium doses had the most consistent scoring and clinical findings, including some early removal, without overwhelming disease, while the low dose produced the least consistent quantifiable features. All dogs developed antibodies.

Conclusion. Nebulized aerosol delivery of spores reproducibly produced significant coccidioidomycosis in 10 of 11 dogs. Overall, the challenge model demonstrated consistent characteristic findings sufficient to assess vaccine efficacy in dogs during an 8-week period post challenge without producing a potentially overwhelming infection. The aerosol nebulization of arthroconidia in beagle dogs should provide a vaccination-challenge experimental design in line with Chapter 9 Code of Federal Regulations, parts 102.5 and 104.5.

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