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 pareticiotis 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 corresponding 50 C. albicans late peritonitis genes were associated with neutrophil/macrophage responses and nutrient acquisition (glucose oxidase cycle, fatty acid β-oxidation, iron homeostasis). Residues within IAA included DNA damage and iron metabolism, reflecting stress response and nutrient/metal limitation. The top 50 core genes 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, Flul, and Erg family), although mice were not exposed to antifungals. Null and reconstituting mutants for genes involved in adhesion (Als3), copper transport (Ccc2), DNA (Ddr1) 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 pareticitiis and IAA. Multiple genes induced in response to cellular stress during IAC mediate virulence, phagocytosis, 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   | Adhesion, 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 (A) | Null mutant is hyper-susceptible to echinocandins, and causes lower tissue burden at IAA but not in early IAA or PF |
| Ddr1   | DNA damage response, induced in PF | Null mutant causes lower tissue burdens in both IAA and PF and IAA |
| 19.489 | DNA damage response, induced in IAA | Null mutant causes lower tissue burdens in both IAA and PF |
| 19.1034, 19.1049 | DNA damage response, induced in IAA | Triple null mutant is hyper-susceptible to echinocandins, and has lower tissue burden in both IAA and 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 Fungal Activity and Attenuated Virulence
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Background. We previously showed that highly dynamic PIP2, septin, and PKC-Mkc-1 cell wall integrity pathway responses correlate with echinocandin activity during IAC, mediating virulence, phagocytosis, 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 irs4 in response to 48-hour echinocandin exposure

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

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monly used as initial treatment, with many physicians recommending combination therapy the first week. Voriconazole monotherapy was given initially in 5 patients. Seven patients (50%) patients, with voriconazole added for 4 patients for combination therapy the first week. Amphotericin was the initial treatment in 6 patients who were neutropenic at the time of diagnosis. Voriconazole was added for 1 patient. Seven patients (50%) were receiving immunosuppressive medications or had undergone stem cell transplantation. Eight patients (57%) were receiving corticosteroids or immunosuppressive medications at the time of diagnosis. Voriconazole was added for 6 patients for combination therapy. The percentage of patients with neutropenia and neutrophil dysfunction 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 infection from January 2003 to October 2016 at the Mayo Clinic, Rochester, Minnesota.

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 C. albicans 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 SOT and SCT 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: 52%, SCT: 54%, 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 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 SCT and SOT recipients are dysfunctional and show profoundly impaired fungicidal 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 are more commonly seen. 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; mean age 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 anti-fungal 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 at the Mayo Clinic have changed in recent years. Fusariosis in patients with neutropenia were more likely to be disseminated, with high mortality rates. Amphotericin B is 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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Background. Mucormycosis is a fatal fungal infection with unique predisposition to diabetic patients. 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 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 CD25+ cells was significantly high in patient before treatment when compared with healthy control and diabetics. and at the 6-month challenge dose. The percentage of CD25+ cells was highest in healthy control when compared with others. CD161+ cells was occasionally similar in patient before treatment and diabetics but we found a higher percentage, in patients after treatment.

Conclusion. The findings in this study immminently 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 diabetes.

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

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Background. The preferred efficacy design for licensing a vaccine for animal use is 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 coccidiodomycosis vaccine, an infection 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 ABL3. 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 radiographic, 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. Sera were 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, monocytes and weight loss were present in all infected dogs. Radiographic and histopathological examinations were very extensive at the high challenge dose. The percent 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 immminently 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 diabetes.