Disclosures. All authors: No reported disclosures.

969. GRP78 and Integrin β1/α3 Play Disparate Roles in Epithelium Invasion During Mucormycosis Abdallah Aljaribi, MS; Talclegiorgis Gebremariam, MS2; Sondus Alkhazraji, PhD3; Priya Uppuluri, PhD1; John E. Edwards, Jr, MD, FIDSA1 and Ashraf S. Ibrahim, PhD1, 2Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, California, 2Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, California and 1Harbor-University of California at Los Angeles Medical Center, Torrance, California

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Background. Mucormycosis is a lethal fungal infection caused by Mucorales. Inhalation is the major route of entry resulting in rhino-orbital or pulmonary infection. Nasal and lung epithelial cells are among the first cells that encounter inhaled spores. We sought to identify the nasal and lung epithelial cell receptors interacting with Rhizopus during tissue invasion.

Methods. R. delemar-induced nasal (CCL30) or lung epithelial (A549) cell invasion was studied using Uvetix dye, while host cell injury was determined by Sytox Green staining and assessed by SEM and immunofluorescent labeling of NET-associated proteins. Fungal viability was evaluated using microbiological counts and viability stains. We utilized a zebrafish larva infection model to evaluate neutrophil-Candida interactions in vivo.

Results. Imaging revealed the phagocytosis of C. albicans by human neutrophils followed by the formation of NETs. In contrast, neutrophils encountering C. auris rarely engaged in phagocytosis or produced NETs. By Sytox Green staining, C. auris triggered negligible NET release by human neutrophils, with levels 7-fold lower when compared with C. albicans (Figure A). C. auris did not induce neutrophils to generate ROS, a key signaling mechanism for NET formation. The ineffective neutrophil response to C. auris correlated with diminished fungal killing (Figure B). Imaging of neutrophils in a zebrafish model of invasive candidiasis revealed the recruitment of approximately 50% fewer neutrophils in response to C. auris when compared with C. albicans (Figure C).

Conclusion. C. auris evades neutrophils by altering multiple aspects of their usual anti-candidal responses. We propose that this diminished innate immune response may contribute to the unexpected virulence of C. auris.

Disclosures. All authors: No reported disclosures.

971. Breakthrough Invasive Fungal Infections (IFI) in Acute Leukemia (AL) Patients Receiving Antifungal Prophylaxis

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Background. A major challenge in patients with AL receiving chemotherapy is to decrease the risk of IFI during the prolonged neutropenic period. Even with antifungal prophylaxis, the incidence of breakthrough IFI can be as high as 14%. Our objectives were to determine the incidence of all IFI and breakthrough IFI, to define risk factors associated with IFI and to assess outcomes.

Methods. Single-center retrospective cohort analysis of all adult patients admitted to the University of Michigan for AL from January 1, 2010 to December 31, 2013. Chart review determined co-morbidities, chemotherapy regimens, antifungal prophylaxis, occurrence of IFI as determined by EORTC/MSG criteria, and outcomes. Chi-square, Fischer’s ANOVA, and binary logistic regression tests were performed when appropriate.

Results. Of 363 patients, all but 4 had acute myeloid leukemia (AML); 124 had a stem cell transplant (SCT). A total of 103 (28%) had proven (n = 13), probable (n = 22), or possible (n = 68) IFI. Considering only those 35 patients who had proven or probable IFI, the only risk factor for development of IFI by logistic regression analysis was IFLAG chemotherpay (P = 0.06). Mold infections occurred in 27 patients: Aspergillus (19), Mucorales (5), both Aspergillus and Mucorales (1), Alternaria (1), and Scedosporium (1). Additionally, 5 patients had invasive candidiasis and 3 had Pneumocystis. Eighteen of 35 patients (51%) had breakthrough IFI while on posaconazole suspension (6), fluconazole (5), micafungin (5) or voriconazole (2). Factors significantly associated with breakthrough IFI were SCT (P = 0.04), neutrophils <500, 210 days at diagnosis (P = 0.002) and prophylaxis with posaconazole suspension (P = 0.003). Twelve-week mortality in proven and probable IFI was 31% (11/35). Nine of 11 deceased patients had breakthrough IFI; 8 of whom (5 with mold IFI and 3 with invasive candidiasis) died of the fungal infection.

Disclosures. All authors: No reported disclosures.

970. Emerging Pathogen Candida auris Evades Neutrophil Attack

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Background. Candida auris, an emerging fungal pathogen, causes hospital-associated outbreaks of invasive candidiasis with mortality near 60%. Little is known about the pathogenesis of this species that has newly arisen in the last 10 years, and it is unclear why this species is rapidly spreading worldwide. Neutrophils, critical for control of invasive candidiasis, kill fungi through phagocytosis or release of neutrophil extracellular traps (NETs), which are structures of DNA, histones, and proteins with antimicrobial activity. The objective of this study was to delineate the neutrophil response to C. auris.

Methods. We examined interactions of human neutrophils with C. auris and included C. albicans for comparison. Neutrophil-Candida interactions were visualized by time-lapse fluorescence microscopy and scanning electron microscopy (SEM). We utilized oxidative stress indicator CM-H2DCFDA to measure the generation of reactive oxygen species (ROS) in neutrophils. NET formation was quantified by Sytox Green staining and assessed by SEM and immunofluorescent labeling of NET-associated proteins. Fungal viability was evaluated using microbiological counts and viability stains. We utilized a zebrafish larva infection model to evaluate neutrophil-Candida interactions in vivo.

Results. Imaging revealed the phagocytosis of C. albicans by human neutrophils followed by the formation of NETs. In contrast, neutrophils encountering C. auris rarely engaged in phagocytosis or produced NETs. By Sytox Green staining, C. auris triggered negligible NET release by human neutrophils, with levels 7-fold lower when compared with C. albicans (Figure A). C. auris did not induce neutrophils to generate ROS, a key signaling mechanism for NET formation. The ineffective neutrophil response to C. auris correlated with diminished fungal killing (Figure B). Imaging of neutrophils in a zebrafish model of invasive candidiasis revealed the recruitment of approximately 50% fewer neutrophils in response to C. auris when compared with C. albicans (Figure C).

Conclusion. C. auris evades neutrophils by altering multiple aspects of their usual anti-candidal responses. We propose that this diminished innate immune response may contribute to the unexpected virulence of C. auris.

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