2595. Murine Models for the Host Response to Typical and Atypical Pneumonia
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Background: The etiology of pneumonia is difficult to diagnose, with typical bacterial, atypical bacterial, and viral infections being the most common. However, diagnostics that discriminate these infectious etiologies are limited. We, therefore, focused on the host response to identify possible diagnostic markers and better understand these infections. However, atypical bacterial pneumonia is challenging to identify in humans precisely because of this diagnostic difficulty. Therefore, we utilized murine models to define host response differences between typical bacterial, atypical bacterial, and viral pneumonia.

Methods: Mice were intranasally inoculated with S. pneumoniae (n = 38), M. pneumoniae (n = 27), H1N1 pr8 (n = 19), or saline as a control (n = 42). RNA was extracted from peripheral blood collected at 24, 48, 72, 120, or 168 hours and subjected to microarray analysis. Diagnostic signatures were generated using lasso logistic regression and accuracy was assessed using nested leave-one-out cross-validation with feature selection repeated within each iteration. Differentially expressed genes were used to perform gene set enrichment analysis. These murine-derived signatures were externally validated in silico in 487 human subjects found across 5 publicly available data sets.

Results: We generated pathogen-specific murine disease signatures that performed with 91–100% accuracy. Pathway analysis revealed that animals with pneumococcal pneumonia had a robust immune response by 48 hours that continued to 72 hours post-infection. In contrast, animals infected with M. pneumoniae did not show evidence of a strong immune response until 72 hours post-infection. Additionally, the immune response to M. pneumoniae bared greater similarity to the viral response than to the typical bacterial response. H1N1-infected mice showed an anti-viral response at 120 hours that resolved by 168 hours post-infection. The AUC values resulting from independent human validation of our murine signatures ranged from 89 to 98%.

Conclusion: There are discrete host responses to typical bacterial, atypical bacterial, and viral etiologies of pneumonia in mice. These signatures validate well in humans, highlighting the conserved nature of the host response to these pathogen classes.

Disclosures. All authors: No reported disclosures.

2596. Invasive Fungal Disease in Patients with GATA2 Variant Hematologic Malignancy
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Background: Patients with hematologic malignancies (HM) are at risk of invasive fungal disease (IFD). Identification of those patients at the highest risk for IFD would help optimize prophylactic or preemptive treatment decisions in this population. We previously found that among patients with myeloid malignancies who develop invasive aspergillosis, 15% had a mutation in the gene GATA2. Here, we report the incidence of IFD in a cohort of patients with HM related to a pathogenic sequence variant of GATA2.

Methods: We identified 6343 patients cared for at Dana-Farber/Brigham and Women’s Cancer Center between January 2014 and August 2018 who underwent a next-generation sequencing assay of 95 genes recurrently mutated in hematologic malignancy. Those found to have a pathogenic GATA2 sequence variant were selected for retrospective chart review with respect to serious infectious complications including IFD.

Results: We identified 54 patients with a pathogenic GATA2 variant. 5 had a germline mutation related to familial GATA2 deficiency. The other 49 had a HM, mostly (41/49) acute myeloid leukemia or myelodysplastic syndrome. The frequency of the variant GATA2 allele in this group ranged from 2.5 to 92.0% of sequencing reads. 14 patients were excluded due to lack of sufficient follow-up, often related to treatment at another institution. Of the remaining 35 patients, 13 (37%) had proven/probable invasive fungal infection (IFI). Fourteen others had syndromes consistent with possible IFD. In total, 16 of these 35 patients (46%) received antifungal therapy for proven, probable or possible IFD. Four of the patients not treated with antifungals were diagnosed with a serious infection including 2 cases of Staphylococcus aureus bacteremia, and one case of disseminated Mycobacterium avium complex.

Conclusion: We identified a high incidence of IFD among patients with HM related to a pathogenic sequence variant of GATA2. The wide range of variant allele frequency observed raises the possibility that either inherited or acquired GATA2 dysfunction could incur predisposition to infection. These data suggest that personalized genetic diagnostics of patients with HM may be useful for assessment of infectious risk.

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2597. Dolichos biflorus Agglutinin Binds to Pneumococcal Teichoic Acid and Lipoteichoic Acid
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Background: Dolichos biflorus agglutinin (DBA) is a lectin with a binding specificity toward a-linked N-acetylgalactosamine (α-GalNAc). While DBA is known to bind sia, not all pneumococci, its target molecule has not been identified. Pneumococccus teichoic acid (TA) and lipoteichoic acid (LTA) have repeating units with α-GalNAc→3)β-GalNAc decorated with phosphorylcholine (PC) at the O-6 positions. Two PC transferases, LicD1 and LicD2, mediate the attachment of PC to Pneumococcus teichoic acid (TA) and lipoteichoic acid (LTA) have repeating units with α-GalNAc→3)β-GalNAc created by Pce.

Disclosures. Ephraim L. Tašik, MD MHS PhD, Immunexpress: Consultant; Predigen, Inc.: Officer or Board Member, Research Grant.
Methods: Fifteen pneumococcus strains expressing 14 different serotypes, including one non-encapsulated strain (R36A), were studied with flow cytometry (FC) and confocal fluorescence microscopy (CFM) for DBA binding. Pce enzyme activity was detected with a colorimetric assay using p-nitrophenyl-phosphorylcholine as the substrate. Mutant strains with pce knocked-out were constructed in R36A and D39 by replacing pce with Janus cassette. Both licD genes were sequenced for some of the strains.

Results: Ten of the 15 strains had Pce activity and all of them bound DBA (Table 1). When the pce gene was inactivated in two normally Pce-positive strains (R36A and D39), the strains did not show DBA binding by CFM (Figure 1). Thus, expression of Pce appears to be sufficient for expressing the DBA antigen. Of the five strains that had no Pce activity, two bound DBA. Sequencing of the licD genes in these two strains with positive DBA binding and negative Pce activity revealed one SNP in licD1 and four SNPs in licD2, resulting in a single amino acid difference each for LicD1 and LicD2, compared with R36A and D39.

Conclusion: DBA can bind to the terminal α-GalNAc-(1→3)β-GalNAc of pneumococcal TA and LTA, which is created by Pce. DBA binding is independent of capsule type. The unexpected binding of DBA to the two Pce-negative strains suggests that there is a Pce-independent mechanism for generating the target for DBA binding. Since LicD1 and LicD2 are involved in attaching PC to a α-GalNAc-(1→3)β-GalNAc, we are now investigating their role in creating DBA targets independent of Pce.

Table 1. Summary of DBA binding (DBA +/−) by FC and CFM, and associated Pce enzyme activity (Pce +/−)

|   | DBA (+) | DBA (-) | Total |
|---|---------|---------|------|
| Pce (+) | 10      | 0       | 10   |
| Pce (-) | 2       | 3       | 5    |
| Total   | 12      | 3       | 15   |

2600. Mannose-Binding Lectin Polymorphisms Are Important Modulating Factors in Community- and Hospital-Acquired Pneumonia Caused by Legionella spp. (Program Number: 502)

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Background: Disseminated coccidioidomycosis occurs in <1% of cases, and genetic polymorphisms may account for some of the variability in infection severity. Macrophage migration inhibitory factor (MIF) is an inflammatory cytokine with two promoter polymorphisms linked to variability in expression. High expression MIF polymorphisms may have been associated with granulomatous immune responses.

Methods: A549 cells transfected with MIF promoter/luciferase plasmids of 0 or 8 CATT repeats were stimulated with 50 µg/mL of inactivated C. posadasii spherule lysate, and luciferase expression was measured as relative units (RU) of luminescence. Genomic DNA from patients with disseminated coccidioidomycosis (n = 37) and healthy controls (n = 371) was analyzed for the 794 CATT, microsatellite and the -173 C SNP. Cohorts were divided into self-identified African Americans and Caucasians, and allele frequencies were compared using Fisher exact test. Plasma MIF levels were analyzed by enzyme-linked immunosorbant assay using specific antibodies, and levels were compared by T-test.

Results: Human lung epithelial cells exposed to Coccidioides spherules had significantly higher MIF expression than unexposed cells (3.94 ± 0.44 vs. 3.02 ± 0.24 RU, P = 0.0162). Among Caucasians (n = 26), the high MIF expression ~173C containing genotype was present in 50% of the coccidioidomycosis patients vs. 40% of healthy controls (P = 0.396). The -794 CATT containing genotype was present in 40% of patients vs. 27% of controls (p = 0.240). Plasma MIF levels were higher in coccidioidomycosis patients with high- vs. low-expression alleles (P = 0.0088), but lower in patients vs. controls (P < 0.0001).

Conclusion: Coccidioides spherules stimulated MIF expression in human lung epithelial cells supporting the hypothesis that MIF is involved in immunity against this pathogen. In Caucasian subjects, the higher MIF expression genotypes were more common in patients with disseminated coccidioidomycosis when compared with healthy controls, although significance was limited by sample size. This is consistent with high MIF expression alleles associated with other granulomatous diseases, and may reflect destruction of the granuloma with pathogen dissemination.

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2599. Studying the Effects of Altering Histone Modification on Aspergillus fumigatus Virulence

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Background: As there are few drugs for treating invasive aspergillosis, there is an urgent need for new antifungal agents. Enzymes involved in histone modification are possible antifungal drug targets. We set out to investigate whether genes whose products are involved in histone modifications influence the virulence of Aspergillus fumigatus (A). Histone deacetylases (HDAcs) are required for normal conidiation and virulence. HosA, part of the RPD3L complex, is necessary for maximal virulence and induction of host cell damage. Our results suggest that the HosA histone deacetylase may be a promising drug target for treating invasive aspergillosis.

Methods: Genes whose products were likely involved in histone modification were deleted in strain AF293 using CRISPR-Cas9. Virulence was assessed in a triad of models: 1) wild-type infected mice; 2) mice infected with Δspt8, Δspt3, Δspt4, Δspt6, Δspt7, strain AF293 was used as the wild-type (WT) control. Mice infected with the Δspt8 mutant had wild-type (WT) growth and conidiation in vitro. Mice infected with the WT strain had 100% mortality within 9 days whereas mice infected the Δspt3, Δspt8, and ΔhosA mutants had only 40% mortality by 21 days. The ΔhosA mutant also had impaired capacity to damage pulmonary epithelial cells in vitro.

Conclusion: Spt8 and Set2, components of the COMPASS complex, are required for normal growth in vitro. Spt3 and Spt8, members of the SAGA complex, are required for normal condensation and condensation. HosA, a part of the RPD3L complex, is necessary for maximal virulence and induction of host cell damage. Our results suggest that the HosA histone deacetylase may be a promising drug target for treating invasive aspergillosis.

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