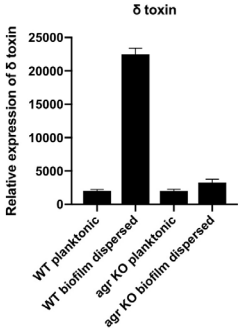

FIGURE 4. Production of the δ toxin PSM is highest in WT biofilm dispersed cells when co-cultured with macrophages

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

2595. Murine Models for the Host Response to Typical and Atypical Pneumonia

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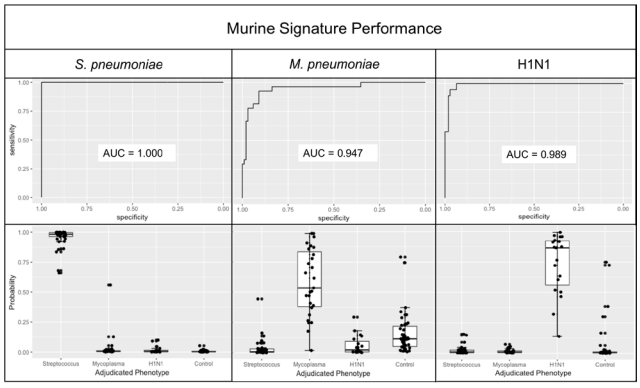
Session: 269. Pathogenesis and Host-Response Interactions
Saturday, October 5, 2019: 12:15 PM

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 it did to the host pneumococcal 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.



Murine-derived Signatures Validated in Five Human Pneumonia Datasets					
			Clinical Assignment		
			Bacterial	Viral	AUC
GSE63990	Classifier-predicted Assignment	Bacterial	67	14	0.9340
		Viral	6	103	
GSE60244		Bacterial	20	14	0.8854
		Viral	2	57	
GSE42026		Bacterial	15	3	0.9241
		Viral	3	38	
GSE40012		Bacterial	55	2	0.9348
		Viral	6	37	
GSE20346		Bacterial	23	1	0.9838
		Viral	3	18	

Disclosures. Ephraim L. Tsalik, MD MHS PhD, Immunexpress: Consultant; Predigen, Inc.: Officer or Board Member, Research Grant.

2596. Invasive Fungal Disease in Patients with *GATA2* Variant Hematologic Malignancy

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Session: 269. Pathogenesis and Host-Response Interactions
Saturday, October 5, 2019: 12:15 PM

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.

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

2597. *Dolichos biflorus* Agglutinin Binds to Pneumococcal Teichoic Acid and Lipoteichoic Acid

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Session: 269. Pathogenesis and Host-Response Interactions
Saturday, October 5, 2019: 12:15 PM

Background: *Dolichos biflorus* agglutinin (DBA) is a lectin with a binding specificity toward α-linked N-acetylgalactosamine (α-GalNAc). While DBA is known to bind some, but not all, pneumococci, its target molecule has not been identified. Pneumococcus teichoic acid (TA) and lipoteichoic acid (LTA) have repeating units with α-GalNAc-(1→3)β-GalNAc decorated with phosphorylcholine (PC) at the O-6 positions. Two PC transferases, LicD1 and LicD2, mediate the attachment of PC to GalNAc residues while phosphorylcholine esterase (Pce) removes PCs attached to the terminal GalNAcs. We examined if DBA binds to the terminal α-GalNAc-(1→3) β-GalNAc created by Pce.

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$^{\triangle}$*pce* and D39$^{\triangle}$*pce*), 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 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

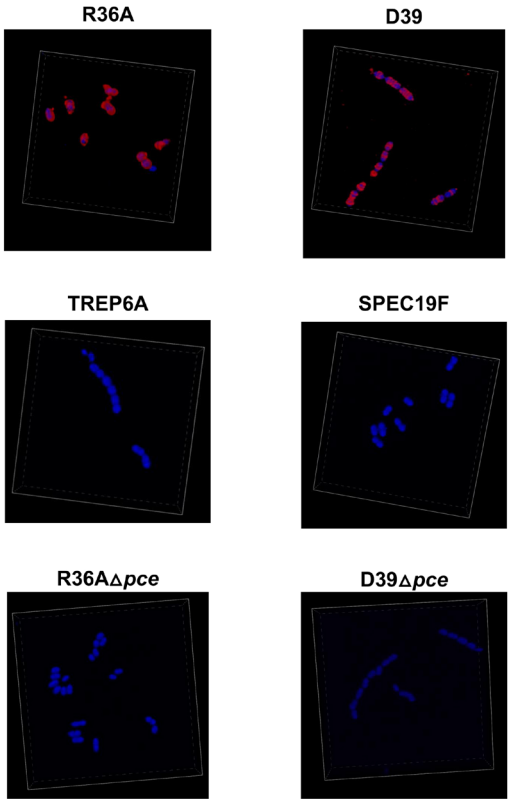

Figure 1. DBA binding results with confocal fluorescence microscopy. R36A and D39 are positive for DBA binding; TREP6A and SPEC19F strains are negative for DBA binding (negative controls); R36A Δ*pce* and D39 Δ*pce* each have an inactivated *pce* gene and are negative for DBA binding. Red: DBA staining; blue: DNA counter-staining.

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

2598. Macrophage Migration Inhibitory Factor May Contribute to Disseminated Coccidioidomycosis Susceptibility

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Session: 269. Pathogenesis and Host-Response Interactions
Saturday, October 5, 2019: 12:15 PM

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 have been associated with granulomatosis with polyangitis (GPA), sarcoidosis and tuberculosis. Despite the overlap between *MIF* and *Coccidioides* immunity, *MIF* has never been studied in coccidioidomycosis.

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 $CATT_{5\text{-}8}$ microsatellite and the -173 G/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 $CATT_{7}$ containing genotype was present in 40% of patients vs. 27% of controls (p = 0.240). Plasma MIF levels were higher in coccidoidomycosis patients with high- vs. low-expression alleles (P = 0.008), but lower in patients vs. controls (P < 0.0001).

Conclusion: *Coccoidioides* 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 expression *MIF* alleles associated with other granulomatous diseases, and may reflect destruction of the granuloma with pathogen dissemination.

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

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

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Session: 269. Pathogenesis and Host-Response Interactions
Saturday, October 5, 2019: 12:15 PM

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* (Af).

Methods: Genes whose products were likely involved in histone modification were deleted in strain Af293 using CRISPR-Cas9. Virulence was assessed in a triamcinolone-treated mouse model of invasive pulmonary aspergillosis. The extent of Af-induced damage to the A549 pulmonary epithelial cell line was determined by Cr^{51} release assay.

Results: Af genes were selected for investigation based on their homology to genes encoding known histone modifying proteins and their high expression level in vivo. The genes were predicted to encode members of the COMPASS histone methyltransferase complex (*cclA/bre2*, *set2*/Afu5g06000), the SAGA histone acetyltransferase complex (*spt3*, *spt8*), and the RPDL histone deacetylase complex (*hosA*). The Δ*cclA* and Δ*set2* mutants had significant growth defects on rich media and were not tested further. The Δ*spt3* and Δ*spt8* mutants grew normally and had mild conidiation defects. The Δ*hosA* 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 Δ*spt3,* Δ*spt8,* and Δ*hosA* mutants had only 40% mortality by 21 days. The Δ*hosA* mutant also had impaired capacity to damage pulmonary epithelial cells in vitro.

Conclusion: Ccla 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 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.

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

2600. Mannose-Binding Lectin Polymorphisms are Important Modulating Factors in Community- and Hospital-Acquired Pneumonia Caused by *Legionella* spp.

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