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/pce and D39/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 and four SNPs in licD2, compared with R36A and D39.

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. TRREP6A and SPEC19F strains are negative for DBA binding (negative controls). R36A Δpce and D39 Δpce each have an inactivated pce gene and are negative for DBA binding. Red: DBA staining; blue: DNA counter-staining.

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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 polymorphism has been associated with granulomatous sarcoidosis with polyangiitis (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 4bp CATTs were stimulated with 50 μg/ml of inactivated C. posadaii 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 -173C 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 CATTT 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 = 0.008), 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 (Af).

Methods: Genes whose products were likely involved in histone modification were deleted in strain A293 using CRISPR-Cas9. Virulence was assessed in a triamcinolone-treated mouse model of invasive pulmonary aspergillosis. The extent of AI-induced damage to the A549 pulmonary epithelial cell line was determined by Cr5 assay.

Results: Al 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 acetyltransferase complex (ccla set2/afu5g06000), the SAGA histone acetyltransferase complex (spt3, spt8), and the RPDL histone deacetylase complex (hosk). The CcLaA and DΔcA mutants had significant growth defects on rich media and were not tested further. The Δspt3 and Δspt8 mutants grew normally and had mild conidiation defects. The ΔhoskA 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 ΔhoskA mutants had only 40% mortality by 21 days. The ΔhoskA mutant also had impaired capacity to damage pulmonary epithelial cells in vitro.

Conclusion: CcLaA 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. HoskA, a part of the RPDL complex, is necessary for maximal virulence and induction of host cell damage. Our results suggest that the HoskA histone deacetylase may be a promising drug target for treating invasive aspergillosis.

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