2592. Lung Function as an Indicator of Vaccine Enhanced RSV Disease in Cotton Rats
Crystal Jones, PhD; Xiaolan Shen, MS; Xiaoli Ping, Catherine Gallagher; Jeremy Beech; Cameron M. Douglas, PhD; Michael Citron, MS; Amy Espeholt, PhD; Merck & Co., Inc., West Point, Pennsylvania
Session: 269. Pathogenesis and Host-Response Interactions Saturday, October 5, 2019: 12:15 PM

Background: Respiratory syncytial virus (RSV) infection is the leading cause of lower respiratory tract infections in infants and young children. Seronegative children previously vaccinated with formalin-inactivated live RSV formulated with aluminum (FIRSV) developed vaccine enhanced RSV disease (VERD), which is characterized by fever, wheezing, bronchoconstriction, and airway hyperresponsiveness (AHR). We investigated whether impaired lung function can serve as a marker for VERD in an animal model of RSV infection.

Methods: Uninfected and RSV-infected cotton rats intranasally challenged with 10^6 pfu of RSV A2 were anesthetized with pentobarbital and tracheostomized. A cannula was placed in the trachea and animals were connected to flexVent™ (Scrieg), which is a computer-controlled piston ventilator that analyzes pressure and volume signals in response to an oscillatory waveform applied at the animal’s airways. Vercuronium bromide was administered to ventilated animals to prevent independent breathing. To measure AHR, animals were exposed to increasing doses of inhaled methacholine, and methacholine-induced bronchoconstriction was measured.

Results: Two independent studies showed that RSV-infected cotton rats (n = 4) exhibited increased total respiratory system resistance (Rrs) and airway resistance (Rn) following methacholine challenge on days 4 and 6 post-infection compared with uninfected cotton rats (n = 4).

Conclusion: RSV-induced impairment in lung function can be exploited for the development of a more robust and objective method for assessing vaccine safety in a cotton rat model of respiratory disease compared with traditional histopathological analysis.

Disclosures. All authors: No reported disclosures.

2593. Human Monoclonal Antibodies Potentially Neutralize Enterovirus D68 in both a Clade-Specific and -Independent Manner
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Background: Enterovirus D68 (EV-D68) causes worldwide outbreaks of human respiratory illness with spatio-temporally related outbreaks of acute flaccid myelitis (AFM), a polio-like illness. Numerous seroepidemiology studies show that nearly all humans older than 2 years have EV-D68 neutralizing antibodies in their serum, even in serum collected prior to large outbreaks. However, little else is known about the human antibody response to this virus. We sought to isolate human monoclonal antibodies (mAbs) from B cells in peripheral blood mononuclear cells (PBMCs) of the human antibody response to this virus. We sought to isolate human monoclonal antibodies (mAbs) from B cells in peripheral blood mononuclear cells (PBMCs) of healthy, Bethesda, Maryland; National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, Maryland; University of Colorado Anschutz Medical Campus, Aurora, Colorado
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Background: Staphylococcus aureus biofilms are a common cause of persistent, life-threatening infections. Dispersal of S. aureus cells from established biofilm-based infections is crucial for dissemination within the host, but is poorly understood. We tested the hypothesis that biofilm dispersed S. aureus cells have distinct physiology from planktonic cells and are better equipped to evade host immunity in an agr-dependent manner.

Methods: Primary murine bone marrow-derived macrophages (BMDMs) were infected with planktonic and biofilm dispersed cells from S. aureus USA300 LAC wild type (WT) and USA300 LAC-agr knockout (KO). Biofilm dispersed cells were collected via glycerol deprivation. Gentamicin protection assays were used to enumerate phagocytosed bacteria and fluorescence microscopy to quantify macrophage viability. A 26-plex immunoassay was used to screen for cytokines and chemokines. Reversed phase high-performance liquid chromatography was used to measure relative phe- nol-soluble modulin (PSM) levels from macrophage co-cultures.

Results: Compared with planktonic cells, biofilm-dispersed cells in both S. aureus WT and KO backgrounds exhibited: (1) ~10-fold less phagocytosis by BMDMs (p = 0.0003; Figure 1); (2) increased macrophage killing (23% vs. 8%; p = 0.0038; Figure 2); (3) stronger pro- (e.g., IFN-γ, IL-2, IL-6, IL-17; Figure 3A) and anti- (e.g., IL-10, IL-4, IL-22; Figure 3B) inflammatory cytokine responses from macrophages (P < 0.05 for all); (4) significantly higher δ toxin PSM production (P = 0.0090; Figure 4) in WT biofilm dispersed only.

Conclusion: S. aureus biofilm dispersed cells are physiologically distinct from planktonic cells and have a unique interaction with the host immune system. Dispersed cells are more resistant to phagocytosis, have a greater propensity to kill macrophages, and mount stronger pro- and anti-inflammatory responses in an agr-independent manner. Dispersed cells also have the ability to produce more δ toxin PSM via well-known agr-dependent pathways.

2594. Biofilm-Dispersed Staphylococcus aureus Exhibits a Distinct agr-Independent Host Interaction
Spencer Chang, BS; Vance G. Fowler, Jr, MD, MHS; Batu K. Sharma-Kuinkel, PhD; Felix Medie, PhD; Larry Park, PhD; Yue Zheng, PhD; Michael Otto, PhD; Alexander Horwill, PhD; Duke University School of Medicine, Durham, North Carolina; Duke University Medical Center, Durham, North Carolina; Duke University, Durham, North Carolina; Duke University, Durham, North Carolina; National Institutes of Health, Bethesda, Maryland; National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, Maryland; University of Colorado Anschutz Medical Campus, Aurora, Colorado
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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. Additionally, differentially expressed genes were used to perform gene set enrichment analysis. These murine-derived signatures were externally validated in silico in 487 human subject samples 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 had a robust immune response by 48 hours that continued to 72 hours post-infection. Additionally, the immune response to M. pneumoniae bore 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.

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. 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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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 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 these infections. However, atypical bacterial pneumonia is challenging to identify in volunteers.

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

Murine-derived Signatures Validated in Five Human Pneumonia Datasets

| Clinical Assignment | Bacterial | Viral |
|---------------------|-----------|-------|
| GS6E3990            | 67        | 14    |
| GS6E0244            | 20        | 14    |
| GS6E2026            | 15        | 3     |
| GS6E0012            | 55        | 2     |
| GS2E0346            | 23        | 1     |

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