408. Single-cell Sequencing Identifies Variability in Host Response Among Different Genera of Influenza Viruses
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Background. Seroprevalence and surveillance studies indicate that influenza C virus (ICV) infection is common among humans, and initial exposure occurs early in life. ICV often causes milder disease than influenza A and B viruses, but the mechanisms underlying differences in pathogenicity remain poorly understood.
Methods. To compare early events of infection in natural target sites, we cultured primary human tracheal/bronchial epithelial cells under air-liquid interface conditions to allow differentiation. We infected these cells with human strains of influenza A, B or C virus. Cells were infected at low MOI (0.1) to ensure populations of directly infected cells and uninfected neighboring cells. To compare the same immune response and cell tropism among these viruses, we performed single-cell RNA sequencing of mock- and influenza-infected cells. In parallel, we infected cells pretreated with interferon to mimic later rounds of infection after an early immune response is initiated.
Results. Infection of primary cells by all three viruses was confirmed by RT-qPCR of bulk cell lysates. As expected, prior exposure to interferon β results in reduced levels of viral transcripts. At the single-cell level, we identified expression of genes associated with specific cell types, including basal, ciliated and secretory cells. We also identified expression of interferon stimulated genes, but these genes were not homogeneously expressed among all cell subpopulations and varied among cultures infected with different influenza viruses. We also found different patterns in gene expression in cells previously exposed to interferon, suggesting that host environment varies over subsequent rounds of infection.
Conclusion. Single-cell sequencing is an important tool for studying the host response to influenza infection in complex cellular environments such as the respiratory tract, in which cells vary in their susceptibility to infection and antiviral response. Further analysis will characterize differences among directly infected vs. neighboring cells and correlate responses with pathogenicity.
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407. The Effect of Streptococcus pneumoniae Pneumonia on Atherosclerosis
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Background. Clinical studies consistently find an increase in the risk of acute coronary syndrome (ACS) in the weeks following pneumonia, although the mechanisms underlying this finding are unknown. ACS most commonly occurs as a result of thrombosis at the site of ruptured atherosclerotic plaques. We hypothesized that the systemic inflammatory response to pneumococcal pneumonia leads to acute localized inflammatory changes within established atherosclerotic plaques, favoring plaque instability and rupture, thereby resulting in ACS.
Methods. Male ApoE-/- mice, a well-established model of atherosclerosis, were fed an atherogenic diet for 7–8 weeks before intranasal infection with Streptococcus pneumoniae or mock infection. Mice were sacrificed 2 or 8 weeks post-infection. Formalin-fixed, paraffin-embedded aortic sinus plaque sections were analyzed to assess markers of plaque vulnerability to rupture. To characterise post-pneumonic plaque macrophage phenotype, aortic sinus plaque cryosections 2 weeks post pneumonia/mock infection were immunostained for MAC-3 to identify macrophage-rich areas. These plaque regions were collected using laser capture microdissection and RNA extracted for microarray analysis.
Results. S. pneumoniae infection was associated with increased aortic sinus ath erosclerotic plaque macrophage content (18.1 vs. 8.0%; P < 0.05) at 2 weeks post infection, but no significant difference in aortic sinus plaque burden, plaque smooth muscle or collagen content. There was no significant difference in any of these plaque vulnerability markers at 8 weeks post infection. Microarray analysis of laser capture micro-dissected plaque macrophages identified downregulation of the expression of three genes coding for specific E3 ubiquitin ligases following pneumonia. Pathway analysis identified a significant perturbation in the ubiquitin proteasome system pathway as a result.
Conclusion. In this murine model, pneumococcal pneumonia resulted in increased atherosclerotic plaque macrophage content, a marker of plaque instability, at 2 weeks post infection. Pneumonia may therefore lead to an increased propensity for atherosclerotic plaques to rupture soon after pneumonia, due to infiltration of macrophages into the plaque.
410. Influence of Pre-season Antibody Titers to Influenza Virus Risk in a Cohort of Healthcare Personnel

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Background. Influenza (flu) and other respiratory viruses circulate regularly throughout healthcare systems, often placing healthcare personnel (HCP) at high risk for illness. Hemagglutination inhibition (HAI) titers are associated with protection from flu illness, though few studies have characterized HAI in HCP. The Respiratory Protection Effectiveness Clinical Trial (ResPECT), provided HAI titers and data to assess infection risk based on four flu seasons. Participants from multiple outpatient settings were respiratory protection within six feet of symptomatic patients.

Methods. Serological samples obtained at the beginning and end of each season and anterior nasopharyngeal swabs were taken randomly and when participants reported respiratory symptoms were assessed. Our primary outcome was PCR-confirmed influenza.

Results. During 5,180 participant-seasons of observation, 128 PCR-confirmed influenza A infections (20 H1N1, 108 H3N2) and 34 PCR-confirmed influenza B infections (4.041 (IQR) reported receiving an annual influenza vaccine. Each log base 2 increase in titer subtype-specific titer reduced the hazard of influenza infection with A/ H3N2 by 18% (Relative Risk (RR) 0.82 95% CI 0.72,0.94), by 28% for influenza B (RR 0.72 95% CI 0.56,0.92 and by 25% for influenza A H1N1 (RR 0.75 95% CI 0.57–1.0). After adjusting for HAI titers, age was not significantly associated with risk for any of the subtypes.

Conclusion. In this prospective cohort of monitored HCPs, these findings support the current literature demonstrating that HAI titers are associated with protection from influenza infection. The relationship between HAI titers, influenza, and vaccination is complex, however. Vaccination was not shown to be associated with infection risk based on four flu seasons. Participants from multiple outpatient settings were respiratory protection within six feet of symptomatic patients.

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411. Does an Early Cytokine Response During Ebola Virus Disease Improve the Duration of Survival in Rhesus Macaques?

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Background. Ebola virus disease results in a severe cytokine release resulting in organ failure and disseminated intravascular coagulation, often leading to death. An early post-exposure immune response may improve outcomes but that remains poorly characterized. Therefore, we evaluated select serum cytokine markers of immune activation in nonhuman primates (NHPs) for their association with duration of survival.

Methods. This was a post-hoc analysis of an interventional supportive care NHP study in which 13 rhesus macaques were inoculated intramuscularly with a target dose of 1000 PFU Zaïre ebolavirus (Kikwit). We measured cytokines with a Luminex MAGPIX panel at baseline and daily starting day 3 post-exposure until euthanasia.

Based on human clinical data, 10 cytokines and proteins were included in our analysis: IL-1a, IL-6, IL-10, GM-CSF, MCP-1, MIP-1a, MIP-1β, IFN-γ, TNF-α, and C-reactive protein levels. After NHPs were divided into two groups by k-means clustering, we developed Kaplan–Meier curves for time to death (Figure 1). We visually explored Pearson’s correlation and kinetics of serum cytokines and log10 viral load (Figure 1; Figure 2). We fitted cox regression models with each cytokine to evaluate the risk of early death for each cytokine log10 level or log-fold change. We performed a sensitivity analysis for MIP-1β centering the data at dpe 0.

Results. Among NHPs with temperature data, 83% (N = 10) developed fevers (>3 SD baseline) from dpe 3 to 4. The macrophage marker MIP-1β was associated with an increased risk of early death (per log10 pg/mL increase, HR= 52.83 at dpe 3, adjusted P = 0.045). Surprisingly, this association was also observed at dpe 0 (HR= 36.88 at dpe 0, adjusted P = 0.044). Other cytokine levels or changes were not associated with an increased hazard of death.

Conclusion. Our findings did not support a role for early systemic cytokine release in improving survival. However, elevated baseline levels of the MIP-1β may predispose NHPs to early death from EVD. This finding could represent a target for therapeutic strategies and should be further researched.

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412. Host Response Biomarkers Predict Clinical Failure in Patients with Staphylococcus aureus Bacteremia (SAB) Treated with Flucloxacinillin (FLU) or Vancomycin (VAN)

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Background. Imbalance among innate mediators such as IL-1β, IL-10, and TNF-a portends poor outcomes of persistence and death in patients with SAB. Previous studies did not consider the role of antibiotic treatment in this important host–pathogen relationship. In this study of SAB, we determined cytokine signatures that correlate with the composite endpoint of clinical failure (bacteremia duration >4 days or 30-day mortality) in Australian patients treated with FLU or VAN.

Methods. Sera from 86 patients with SAB (24.4% MRSA) were obtained from a clinical study of patients treated with FLU or VAN. All of the patient samples were collected at clinical presentation (day 0 or day 1 of infection) and were treated with FLU or VAN throughout. Patients were classified into either clinical success (CS = 68) or clinical failure (CF = 18), defined as death or prolonged bacteremia >4 days. Patient