Global Health & Infectious Disease
Trainee Oral Symposium
March 27, 2014

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PRESENTERS
Leticia Monin, MSc
Graduate student, Department of Richard King Mellon Foundation, University of Pittsburgh, Pittsburgh and Department of Molecular Microbiology, Washington University in St. Louis

Title: Helminth Antigen-Driven Impairment of Th1 Responses in Tuberculosis

Authors & Affiliations:
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Abstract:
Mycobacterium tuberculosis (Mtb) infects 13 of the world's population. Although most Mtb-infected people have asymptomatic latent tuberculosis (TB), they have a 10% lifetime risk of developing active TB. Interferon-γ-secreting CD4+ Th1 cells are instrumental in anti-Mtb immunity. Although CD4+ T cell loss during HIV infection augments TB reactivation, the factors leading to active TB in immunocompetent individuals remain elusive. Helminth infections elicit host Th2 responses and are co-endemic with Mtb infection. Several human studies suggest that helminth co-infection underlies increases in TB reactivation. Here, we determined whether an antigenic preparation of Schistosoma mansoni (SEA) modulates Mtb-specific Th responses. We report that SEA inhibits IFN-γ secretion by lung CD4+ T cells from Mtb-infected mice. Further, RNAseq analysis revealed down-regulation of Th1-related genes in SEA-treated Th cells. Using a mouse model of Mtb infection, we found that Mtb-infected, SEA-treated mice exhibited decreased Th1 responses. Accordingly, these mice had increased lung bacterial burden. Together, we show that parasitic antigens limit Mtb immunity, supporting the use of deworming to prevent TB reactivation in helminth-infected populations.

Natalie Spillman, PhD
Postdoctoral Fellow, Department of Molecular Microbiology, Washington University School of Medicine, St. Louis

Title: Exported Epoxide Hydrolases of Plasmodium Falciparum: Possible Role in Modulation of Host Vasoregulation

Authors & Affiliations:
Natalie J. Spillman1 and Daniel E. Goldberg1; 1Howard Hughes Medical Institute, Washington University School of Medicine

Abstract:
Hundreds of proteins are exported from the malaria parasite into its host erythrocyte. We are investigating two ‘hypothetical’ proteins of the α,β-hydrolase fold family that share sequence similarity with epoxide hydrolases (EHS)-enzymes that catalyze the hydrolysis of bioactive epoxides to less-active 1,2-diols. Both exported proteins are active EHS, as when recombinantly expressed can hydrolyze reporter epoxide substrates and physiologically relevant erythrocyte
lipid signaling epoxides, the epoxyeicosatrienoic acids (EETs). EETs function as vasoregulators, promoting vasodilation in the microvasculature, as well as inhibiting the display of surface adhesion ligands on endothelial cells lining the blood vessels. We hypothesize that expression of an exported EH decreases the concentration of EETs in infected erythrocytes and that, as a result, there is a reduction in the amount of EETs released into the circulation. The resultant disruption of vascular function leads to favorable conditions for parasite binding and sequestration in the microvasculature.

Deepa Srikanta, PhD
Postdoctoral Fellow, Department of Molecular Microbiology, Washington University School of Medicine in St. Louis

Title: Insights into Host: Cryptococcal Interactions

Authors & Affiliations:
Deepa Srikanta, Matthew Williams, & Tamara L. Doering, Department of Molecular Microbiology, Washington University School of Medicine, St. Louis

Abstract:
*Cryptococcus neoformans*, the causative agent of cryptococcosis, is an opportunistic fungal pathogen which kills over 600,000 individuals annually. Infection is through inhalation of the fungal particles and subsequent interaction with host macrophages. *Cryptococcus neoformans* has multiple, virulence factors, several of which help it to evade the host immune system. Despite extensive research on cryptococcal pathogenesis, host genes involved in the initial uptake and subsequent stages of infection are woefully understudied. We performed a high-throughput imaging screen where we exposed fungal cells to RNAi-treated host cells and evaluated uptake. Follow-up studies of two kinases in primary cells complemented the results of our initial screen and studies in knockout mice show reduced fungal dissemination. Studies are under way to determine the mechanism of action by which these proteins influence cryptococcal disease. Our exciting findings will shed light on host aspects of cryptococcal pathogenesis and potentially other host:microbe interactions as well.

Jingxian Cai, MPH
Graduate Student, Department of Biostatistics, Jiann-Ping Hsu College of Public Health, Georgia Southern University, Statesboro, GA

Title: Chinese Social Media Reaction to News About 39 Notifiable Infectious Diseases

Authors & Affiliations:
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Abstract:
Background: Weibo, a Chinese microblogging service similar to Twitter, plays an important role in health communication in China. Methods: Weibo data had been collected through 2012 and posts that carried keywords on the 39 infectious diseases that are notifiable in mainland China were selected. We manually read and described the Weibo posts on days when these posts peaked in number. Results: We categorized the Weibo posts into four types, namely reactions to routine health promotion messages or specific health promotion events, reactions to news about disease outbreaks or cases, reactions to movies, books or other media that mention diseases and social interaction of Weibo users that mention diseases in their conversation. Conclusion: Weibo users’ attention to the diseases was higher during specific
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health promotion events or disease outbreaks than on regular days. Social interactions that mentioned infectious diseases suggested that social media could potentially be useful tools in health communication.

Valerie O'Brien, BS
Department of Molecular Microbiology, Washington University in St. Louis

Title: Molecular Insights Into Recurrent Urinary Tract Infection: Elucidating the Pathogenesis of Acute Cystitis in the Non-Naive Host

Authors & Affiliations:
Valerie P. O'Brien¹, Thomas J. Hannan³, Drew J. Schwartz¹, Amanda L. Lewis¹, Scott J. Hultgren¹; ¹Department of Molecular Microbiology and Center for Women’s Infectious Disease Research, Washington University School of Medicine ²Department of Pathology and Immunology, Washington University School of Medicine

Abstract:
Urinary tract infections (UTI) are among the most common infectious diseases and are highly recurrent. This, coupled with the global rise of multi-drug resistant uropathogens, indicates the urgent need for new therapeutics, such as a UTI vaccine. We recently developed a mouse model of recurrent UTI that is useful for investigating the molecular mechanisms of recurrence and for testing novel therapeutics. Here our objective was to use this mouse model to investigate how host adaptations affect susceptibility to recurrent UTI. We found that a history of UTI lowers the bacterial requirement for virulence during a recurrent episode, allowing less virulent uropathogens to establish chronic bladder infections. We also found that vaccination with the type 1 pilus adhesin FimH protects mice against recurrent UTI. These findings may help explain the globally high rates of recurrent UTI and provide a strategy for therapeutic intervention.

Joshua Geltz, MS
Department of Medical Microbiology, Immunology, Cell Biology, Southern Illinois University School of Medicine, Springfield, IL

Title: Vaccine-Induced Protection Against HSV-2 is Mediated by a Polyclonal Immune Response Towards Many Viral Proteins

Authors & Affiliations:
Joshua J. Geltz and William P. Halford  Department of Medical Microbiology, Immunology, Cell Biology, Southern Illinois University School of Medicine, Springfield, IL

Abstract:
A billion people worldwide are carriers of herpes simplex virus type-2 (HSV-2), and many suffer with recurrent genital herpes. For the past 30 years, HSV-2 glycoprotein D (gD) subunit vaccines have been repeatedly advanced to clinical trials and have repeatedly failed to protect vaccine recipients from contracting genital herpes. Our lab has developed a live-attenuated HSV-2 vaccine (0ΔNLS) which is 100-times more effective as a HSV-2 vaccine in animal models than a gD subunit vaccine. (PLoS ONE 6(3): e17748). The goal of the current study was to explore why the live HSV-2 0ΔNLS vaccine was 100-times more effective. Using a combination of Western blot analysis and immunoprecipitation-mass spectrometry, we have positively identified several of the dominant antigens of the live HSV-2 0ΔNLS vaccine. Intriguingly, the two most dominant antigens were intracellular HSV-2 proteins, UL29 and UL39, neither of which have ever been considered for use in a HSV-2 vaccine.
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Pardeep Kumar, PhD
Postdoc Research Associate, Department of Internal Medicine - Infectious Diseases, Washington University in St. Louis

Title: Enterotoxigenic Escherichia coli Soluble EtpA Adhesin Serves as a Novel Molecular Bridge Between Bacterial Flagella and Intestinal Mucins

Authors & Affiliations:
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Abstract:
EtpA, a novel adhesin secreted by enterotoxigenic Escherichia coli (ETEC) bridges conserved regions of flagellin molecules exposed at the tips of flagella with the epithelial surface. Since intestinal epithelium is protected by a mucosal surface abundant in heavily glycosylated proteins, we tested recombinant EtpA (rEtpA) binding to human glycans. Glycan array screening revealed rEtpA binding to rare ‘GlcNAc α1-4Gal1-R’ glycans present on gastrointestinal mucins. Using molecular interaction and fluorescence microscopy studies, we showed that rEtpA interacts with the major glyco-calyx mucin MUC3 as well as MUC2, the major gel-forming mucin in the intestinal lumen. Removal of MUC2 from LS174T cell monolayers reduced ETEC adherence. Likewise, siRNA-mediated depletion of MUC3 in target epithelial cells impaired rEtpA binding, reduced bacterial adhesion, and effective toxin delivery. These data suggest that EtpA plays a unique role in ETEC adherence by acting as a molecular bridge between flagella and host intestinal mucins.

Mark Charbonneau, BS
Graduate Student, Department of Pathology, Washington University in St Louis

Title: Milk Oligosaccharide Supplementation Improves Growth in a Gnotobiotic Mouse Model of Undernutrition

Authors & Affiliations:
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Abstract:
Undernutrition represents the leading cause of childhood mortality worldwide and is a global health challenge. While the underlying causes of undernutrition are not fully understood, it is not attributable to food insecurity alone. Studies in human populations and gnotobiotic mice indicate that the gut microbiota plays an important role in disease pathogenesis. We have developed a gnotobiotic mouse model of undernutrition utilizing young mice harboring a defined bacterial community, isolated from and representing the majority of the diversity present in a stunted Malawian infant. Combining an undernourished Malawian bacterial community and nutritionally deplete diet stunts body weight and lean mass gain that is restored by isocaloric dietary supplementation with milk oligosaccharides (MO). Further, this MO-dependent growth increase is dependent on the gut microbiota and independent of an enteric pathogen, Salmonella enterica. Finally, we find that MO alter the distal gut metabolic profile, bacterial abundance, and the bacterial transcriptome in vivo.