INFECTIOUS DISEASE

Abstracts 44 – 52

Moderators: Ronald Gibbs, MD; Geeta Swamy, MD

44 A comprehensive metagenomic catalogue of microbiota across body sites in primates: a high fat maternal diet alters the offspring microbiome to 1 year of age

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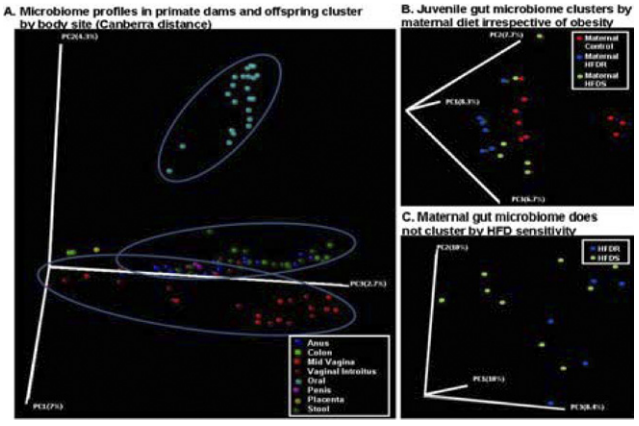
OBJECTIVE: Microbiota are present from at least a time of birth, with up to 10-fold the number of organisms (the "microbiome") and a collective genome (the "metagenome") which exceeds ours by >100-fold. An altered gut microbiome has been described in association with obesity and other disease states. However, how and when these altered microbiota communities take up residence are under explored. We reasoned that our well-characterized primate model of maternal obesity would be an ideal means to decipher the relative contribution of maternal diet, obesity, and microbiota on the developmental microbiome.

STUDY DESIGN: Age and weight-matched dams were placed on control (13%) or HF (35%) diets. Over the study interval, distinct maternal cohorts emerged: obese HF diet sensitive [HFS], obesity-resistant [HFR], and lean [CTR]. 161 comprehensive body site samples (placenta, oral, GI, fecal, GU) from these dams and their offspring (fetal and 1yr) were deep sequenced (16S V5V3 rRNA gDNA; 454FLXTitanium). Data were QC filtered and exhaustively analyzed (OTU, genera; Canberra) using our custom supervised learning and QIIME pipelines.

RESULTS: Extensive computational analysis was performed on 596 megabytes of generated metagenomic data (>1.8 million filtered reads of 494nt). We observed significant clustering of maternal and offspring (fetal and 1yr) OTU predominately by body site (panel A; >3285 OTU genera). Of noted interest, at 1yr of age the core gut microbiome is defined by a HF maternal diet and irrespective of obesity nor postwean diet (B). Using limited discriminate sets, we were able to classify offspring microbiome profiles by maternal diet (RandomForrest, 91.5% success). The maternal gut microbiome does not cluster by HFD (C).

CONCLUSION: Employing state of the art metagenomics, we demonstrate that core body site microbiomes are conserved across primate species. Moreover, HF maternal diet (not obesity nor postnatal diet) establishes a perturbed microbiome in the offspring. These data suggest that the maternal diet profoundly influences the offspring microbiome and may thus serve to arbitrate later in life obesity.



45 Inflammation-induced preterm birth (II-PTB): prenatal IL1β blockade prevents neonatal brain injury in a region specific manner but not preterm birth

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OBJECTIVE: II-PTB results in a spectrum of adverse neurobehavioral disorders. Using a murine model of II-PTB, we have demonstrated a marked elevation of IL1β in the fetal brain and fetal neuronal injury. As IL1β is a key mediator in pathogenesis of many neuroinflammatory disorders, we hypothesized that maternal pretreatment with IL1β antagonist (Kineret; ILA) would prevent neonatal brain injury associated with II-PTB.

STUDY DESIGN: A mouse model of II-PTB was used. ILA was injected IP at 10 mg/kg into CD-1 dams 30min prior to IU injections of lipopolysaccharide (LPS) or normal saline (NS). There were 3 groups: 1) IP NS+IU NS (control; n=10 dams); 2) IP NS+IU LPS (LPS; n=20 dams); 3)IP ILA+IU LPS (ILA; n=13 dams). Rates of PTB, neonatal morbidity and mortality, growth and neurological development were evaluated. Gene expression was evaluated in the neonatal brain (NB) at PND5 in a brain region specific manner using QPCR. We assessed neuronal and neurobehavioral specific markers: nNOS, NMDAR1, synaptobrevin, synaptophysin, synaptogyrin, doublecourtin, reelin and neurexin; markers of astrocytes GFAP and oligodendrocytes PLP1. Specific protein changes were assessed with Western blot (WB). For QPCR and WB, 3-5 litters/group (with 3 NB per litter) were compared.

RESULTS: ILA was not able to prevent II-PTB ($p>0.05$). Postnatal growth in ILA group was not different from control ($p>0.05$). Pretreatment with ILA resulted in postnatal levels of neuronal and neurobehavioral markers in cortex comparable to those of control ($p>0.05$). However, cerebellar levels of reelin, neurexin, NMDAR1, synaptobrevin and nNOS in NB remained to be elevated as compared to control ($p<0.05$).

CONCLUSION: Maternally administered ILA, prior to intrauterine inflammation, appears to prevent neonatal brain injury in a region specific manner. The results indicate that fetal brain injury in II-PTB occurs by different mechanisms in fetal cortex and cerebellum. More-