Antibiotic perturbation of the murine gut microbiome enhances the adiposity, insulin resistance, and liver disease associated with high-fat diet


Obesity has become pervasive worldwide and is directly correlated to the increasing prevalence of metabolic associated diseases including type 2 diabetes mellitus and nonalcoholic fatty liver disease (NAFLD) (1). The microbiome has gained prominent recognition as key a regulator of metabolism. Alterations in gut flora have been linked to the development of obesity. High-fat diets (HFDs) promote an increase in triglyceride storage in adipose tissue and cause obesity in mice. Additionally, HFDs may alter metabolism of gut bacteria accelerating obesity. Certain bacteria in gut flora including *Bacteroides* species have been identified to be present at increased proportions in obese humans and HFD-fed mice when compared to lean controls and chow-fed mice indicating an association between diet and development of the gut microbiome (2 & 3).

The ubiquitous exposure to antibiotics and the effects of excessive prescription on gut flora populations has garnered interest in the area of metabolism (4). Broad spectrum antibiotics prescribed in infancy from 0 to 23 months of age have been linked to increased rates of childhood obesity (4). To determine the effects of early antibiotic exposure on obesity, insulin resistance, and NAFLD, male and female C57BL/6 mice were placed into two groups: control or sub-therapeutic antibiotic treatment (STAT) beginning at 4 weeks of age. All mice were given a HFD starting at 13 weeks of age until sacrifice at 32 weeks of age. Body composition was quantified every 4 weeks, starting at 4 weeks of age and ending at 28 weeks of age. Fecal samples were collected 2 to 3 times every week from treatment until sacrifice. Genomic DNA was isolated from frozen fecal samples, the 16S rRNA gene V4 region was amplified, and sequenced on an Illumina MiSeq. At sacrifice, fasted serum and livers were collected (5).

Gender differences in metabolic assessments were observed. However, STAT mice displayed insulin resistance and NAFLD when compared to control mice. At 4 weeks the STAT groups started out with a microbiome enriched in *Bifidobacterium, Prevotella*, and S24-7 and the controls were enriched in *Candidatus Arthromitus* and *Firmicutes*. A shift in the microbiome in both the STAT mice and control mice was observed in weeks 4-11. Controls become more *Firmicutes* dominant while the STATs had a bloom in *Proteobacteria*. This includes microbiota age (MAZ scores) that was found to be significantly lower in the STAT mice that developed insulin resistance and NAFLD. This finding was gone at 11, 16, and 30 weeks. Thus, this study identified STAT-specific taxa that are potentially pathogenic and predictive to metabolic disease.

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