Gestational gut microbial remodeling is impaired in a rat model of preeclampsia superimposed on chronic hypertension

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Introduction

- Preeclampsia, a hypertensive disorder of pregnancy, is a leading cause of maternal and fetal morbidity.
- It affects 2-8% of all pregnancies, and its pathophysiology is not fully understood.
- Recent studies in preeclamptic patients have suggested a role for the gut microbiome (GM) in the disease.
- In addition, emerging evidence from both human and animal studies have reported that short-chain fatty acids (SCFAs) and other gut-derived metabolites such as lactate may modulate blood pressure .
- We have previously characterized the Dahl salt sensitive rat (Dahl S), a known genetic model of hypertension and kidney disease, as a spontaneous model of preeclampsia superimposed on chronic hypertension.

Hypothesis

We hypothesized that preexisting chronic hypertension impairs maternal gut microbial remodeling contributing to the development of superimposed preeclampsia.

Protocol

- Female Sprague Dawley (SD) and Dahl S (SS/jr) rats were maintained in conventional caging in the same room and on the same diet (Teklad 7034, 0.3% NaCl). Half of the rats of each strain were mated to have pregnant and virgin groups (n=7-9/group).
- Fecal samples were collected at baseline (BL), early (D6), mid (D13), late pregnancy (D20) and one-week postpartum (D28) to assess gut microbiome composition via 16S rRNA gene sequencing.
- Differential abundance analysis of α-diversity was assessed by the Shannon diversity index.
- We used principal coordinates analysis (PCoA) to assess between-subject diversity (β-diversity) in microbial community composition based on a distance matrix of microbial abundance (Bray-Curtis).
- Linear discriminate analysis effect size (LEfSe) analysis was performed to identify the taxa characterizing the differences among groups.
- PICRUSt (phylogenetic investigation of communities by reconstruction of unobserved states) was used to predict functional potential.

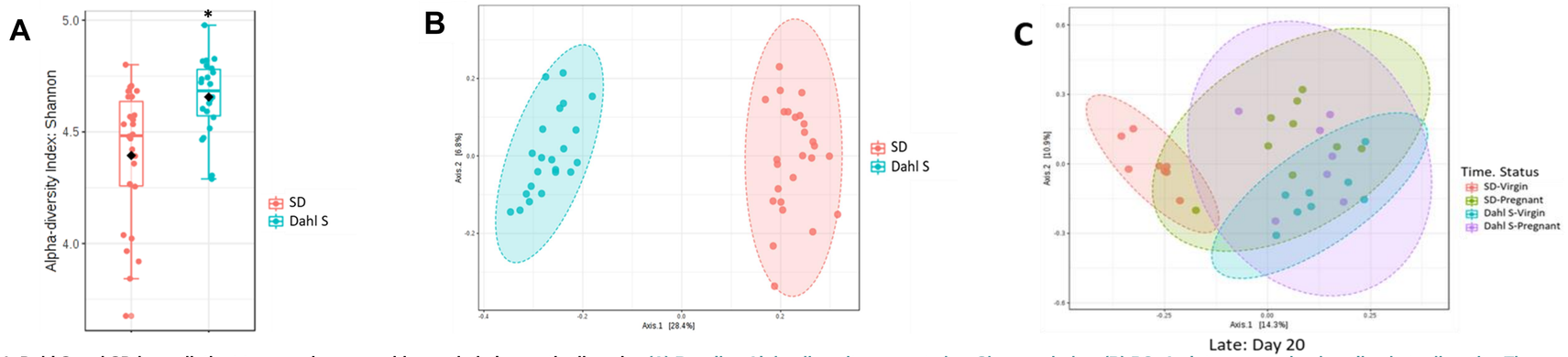

Figure 1. Dahl S and SD have distinct taxonomic composition and phylogenetic diversity. (A) Baseline Alpha diversity presented as Shannon index. (B) PCoA plot representing baseline beta-diversity. The distance between the two clusters indicates that the microbial population is significantly distinct between strains. (C) Changes in the beta-diversity during pregnancy, PCoA plots representing β-diversity during late pregnancy, day 20. Each dot represents an individual rat.

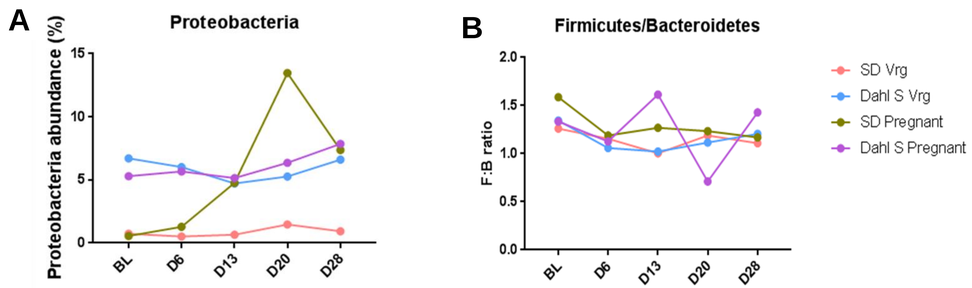

Figure 2. Dahl S rats display dysbiosis. (A) Percent Proteobacteria phylum abundance. (B) Firmicutes to Bacteroidetes ratio.

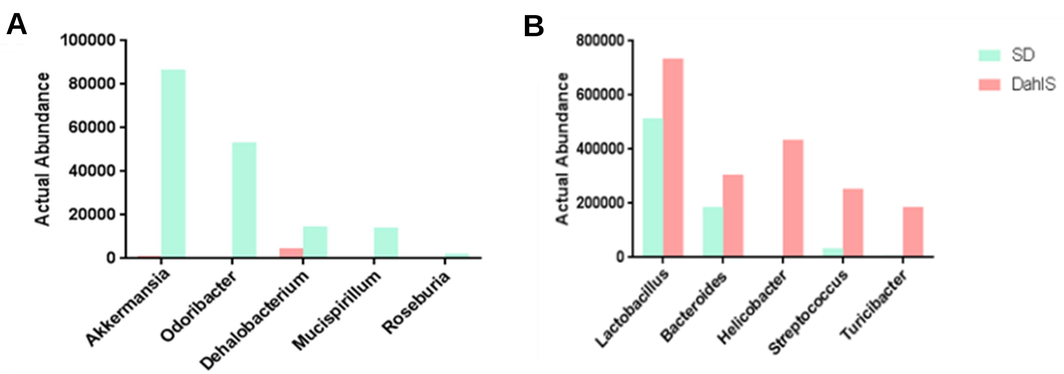

Figure 3. LEfSe results representing the differentially abundant genera between Dahl S and SD at baseline. (A) Genera of good bacteria are significantly more abundant in SD. (D) Genera of pathogenic bacteria are significantly more abundant in Dahl S.

Table: Metabolic pathways associated with SCFAs

Pathway name	Butanoate metabolism	Propanoate metabolism
SD	32 (0.43)	29 (0.57)
Dahl S	33 (0.01)*	31 (0.01)*

Number of gene hits (p-value), *p<0.05

Conclusions and Future Directions

- The female Dahl S rat exhibits gut dysbiosis outside of pregnancy
- SD rats showed a pregnancy specific increase in Proteobacteria, the Dahl S had no changes in this phylum during pregnancy.
- The SD β-diversity diverged upon pregnancy whereas virgin and pregnant Dahl S remained overlapped.
- The normotensive SD is enriched with beneficial bacteria, and Dahl S enriched with those associated with disease.
- Butanoate and propanoate metabolic pathways may be dysregulated.

Altogether, these data suggest that superimposed preeclampsia may be associated with impaired pregnancy-specific GM changes and dysregulation in SCFA production.

Future studies will investigate the therapeutic potential of supplementation of beneficial SCFAs for the treatment of PE in this model.

Acknowledgements

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