Prebiotics and milk oligosaccharides affect the colonic metabolome and stressor-induced immunomodulation in mice.

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What is Gut-Brain Axis?

- Signaling between GI tract and Central Nervous System
- Role of intestinal microbiome and its metabolites
- Gut-Brain Axis includes the CNS, neuroendocrine and neuroimmune systems, the enteric nervous system and vagus nerve, as well as gut microbiome

*Figure: J. Neurogastroenterology Vol 21, No 2 April 2015*
Multiple reports of stress-induced changes to gut microbiota community composition.

- Social stress/social defeat (mice)

- Prolonged restraint (mice)
  - Bailey et al., 2010, Infection and Immunity, 78: 1509-1519; Galley et al., Gut Microbes, 2014, 5: 748-760.; Galley et al., 201

- Chronic subordinate colony housing (CSC) (mice):
  - Reber et al., 2016, PNAS, 113 (22): E3130-3139

- Tail shock (rats):
  - Thompson et al., 2017, Frontiers in Behavioral Neuroscience,

- Weaning and social housing (rhesus monkey)
  - Amaral et al., 2017, Psychosomatic Medicine, In Press

Prebiotics and milk oligosaccharides can impact the microbiota in stressor-exposed mice
Why Sialyllactose?

Isolated from cow’s milk (natural source)

- Brain sialic acid accretion
- Microbiome changes
- Behavior effects

Sialyllactose is sialic acid bound to lactose.
SL supplementation reduced stress behavior & increased microbiota diversity in mice

3’-SL and 6’-SL Help Maintain Immature Neurons in the Dentate Gyrus of Stressor-Exposed Mice
Objective of the Study:

Determine whether prebiotics and/or milk oligosaccharides can maintain the structure and the function of colonic microbiota in stressor-exposed mice.
Social Disruption Stressor

- Inter-male aggression begins within 10 min
- Aggressor repeatedly defeats resident mice across a 2 hr period
- Repeated on 6 consecutive days

- Induces a Physiological Stress Response
  - Increases in Circulating Corticosterone (HPA Axis activity)
  - Increases in Circulating Catecholamines (SNS Activity)
  - Brain regions associated with fear and anxiety

- Enhances Immune System Activity
  - Increases in plasma cytokines
  - Increases in splenic leukocyte activity

- Impacts the composition of the gut microbiota
  - Beta diversity of the colonic microbiota
Experimental Design

- Male C57BL/6 mice
  1. Control diet (AIN-93G mouse chow)
  2. AIN-93G supplemented with GOS + PDX + SL
  3. AIN-93G supplemented with SL

- Mice were randomly assigned to stressor or non-stress control group

Weeks 1-2
- Control or Experimental Diet
- SDR Stressor
- No-Stress Control

Week 3
- Assess fecal microbiota (16s rRNA gene sequencing)
- Assess colonic metabolome (using LC/MS/MS)
- Assess plasma cytokines and splenic leukocytes
Evident that both stressor exposure and diet impact the *structure* of the microbiota, but do they also impact the *function* of the microbiota?
Question: Are there metabolites that are affected in stressor-exposed mice fed GOS+PDX+SL or fed SL that were not evident in mice fed the control diet?
PUFA’s and endocannabinoids have anti-inflammatory abilities.

Can GOS+PDX+SL and SL prevent stressor-induced immunomodulation?
Conclusions:

Prebiotics and milk oligosaccharides:

1. Change the structure and the function of the microbiota
   - 16s rRNA gene sequencing
   - Metabolomic profiling

2. Have a different effect on stressor-exposed vs. non-stressed control mice.
   - PUFA
   - Endocannabinoids

3. Attenuate some of the effects of social stress on immune system activity.
   - Splenic leukocytes
   - Plasma cytokines

Our study suggests that prebiotics and milk oligosaccharides can support immune system regulation during stressor exposure through effects on the microbiota.
Acknowledgements

Bailey Lab
Dr. Michael Bailey
Dr. Amy Mackos
Dr. Vanessa Varaljay
Dr. Ross Maltz
Dr. Jinyu Xu
Robert (Max) Jaggers
Sydney Fisher
Courtney Backen
Jenny Resiliac

Funded By:

Dr. Brian M. Berg
Thank you!