Alterations in Patterns of Gene Expression and Perturbed Pathways in the Gut-Brain Axis Are Associated With Chemotherapy-Induced Nausea

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SUPPORTIVE CARE MAKES EXCELLENT CANCER CARE POSSIBLE

Conflict of Interest Disclosure

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This study has no real or apparent conflicts of interest to report.

Background

- Chemotherapy-induced nausea (CIN) occurs in 30% to 60% oncology patients
- Current antiemetic interventions are not efficacious
- Current hypothesized mechanisms that underlie CIN have limited support
- Understanding the underlying mechanisms will lead to the development of more targeted interventions

Study Aim

To evaluate for differentially expressed genes and perturbed pathways associated with the gut-brain axis across two independent samples of oncology patients who did and did not experience CIN

Experimental Design

- **Oncology patients (n=709) completed questionnaires** that obtained information on demographic and clinical characteristics in the week prior to their second or third cycle of CTX
- **CIN occurrence was assessed** using the Memorial Symptom Assessment Scale
- Gene expression analyses was performed using **RNA-sequencing (sample 1, n=357) and Microarray (sample 2, n=352)** methodologies
- **Fisher's combined probability method** was used to determine genes that were significantly differentially expressed and pathways that were significantly perturbed between the two nausea groups across both samples

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Results

- CIN was reported by 63.6% of the patients in sample 1 and by 48.9% of the patients in sample 2
- Using Fisher's combined probability method, **703 genes were significantly DE** at a strict FDR of 5% under the Benjamini-Hochberg (BH) procedure
- Using Fisher's combined probability method, **37 pathways were significantly perturbed** using a strict FWER of 1% under the Bonferroni method

MAJOR FINDING

Nine perturbed pathways were involved in mechanisms associated with

- **Mucosal Inflammation**
- **Disruption of Gut Microbiome**

Mucosal Inflammation

Pathway ID	Name	Adjusted pGlobal*
hsa04060	Cytokine-cytokine receptor interaction	0.00084
hsa04062	Chemokine signaling pathway	0.00084
hsa04010	Mitogen activated protein kinase signaling pathway	0.00306
hsa04064	Nuclear factor κB signaling pathway	0.00982

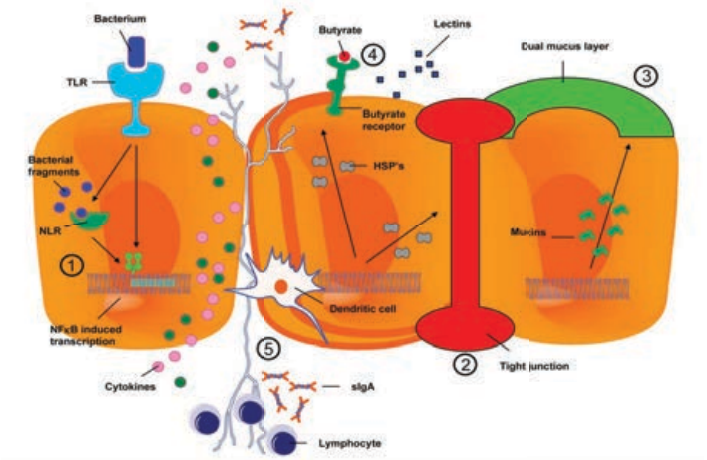
*FWER of 1% under the Bonferroni method

Disruption of the Gut Microbiome

Pathway ID	Name	Adjusted pGlobal*
hsa03320	Peroxisome-proliferation-activated receptor signaling pathway	0.00084
hsa04530	Tight junction	0.00084
hsa04659	Interleukin-17 producing helper T cells differentiation pathway	0.00516
hsa04612	Antigen processing and presentation	0.00652
hsa04672	Intestinal immune network for immunoglobulin A production	0.00917
hsa04064	Nuclear factor κB signaling pathway	0.00982

*FWER of 1% under the Bonferroni method

Mucosal Inflammation and Disruption of the Gut Microbiome



CTX-induced alterations of the gut microbiome can increase mucosal inflammation by

- Influencing the production and release of immunoglobulin A (IgA)
- Regulating signaling cascades that mediate inflammatory responses
- Disorganization of tight junctions

Van Vilet et al., Plos Review, 2010 and Artis, D., Nature Reviews| Immunology, 2008

Conclusions

- Persistent CIN remains a significant clinical problem
- First study to report differentially expressed genes and perturbed pathways were associated with **two novel mechanisms** (i.e., mucosal inflammation and disruption of gut microbiome) and occurrence of CIN
- While additional research is warranted to evaluate complex mechanisms that underlie CIN, our study **provides insights into why unrelieved CIN remains a significant clinical problem**

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Gut-Brain Axis

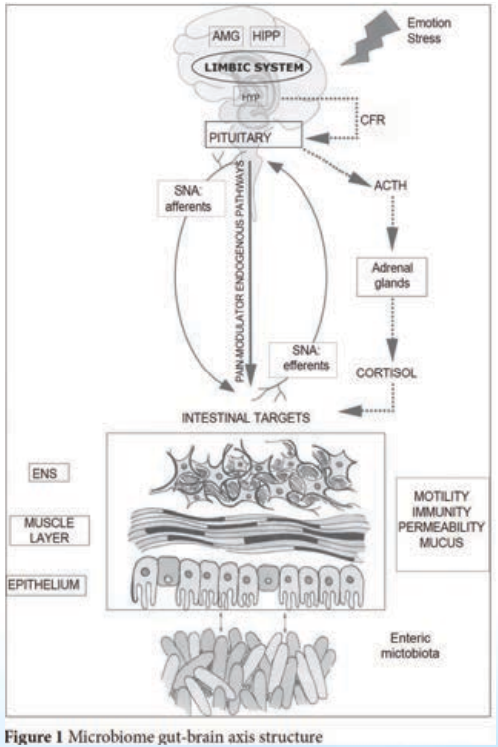

Figure 1 Microbiome gut-brain axis structure

- GBA comprises bidirectional communication between the brain and intestinal functions
- Gut microbiome influences these interactions
- Principal mechanisms of bidirectional communication include:
  - Mucosal immune regulation
  - Protection of intestinal barrier and tight junction integrity
  - Alterations of intestinal permeability

Carabotti et al., Annals of Gastroenterology, 2015

Gut-Brain Axis

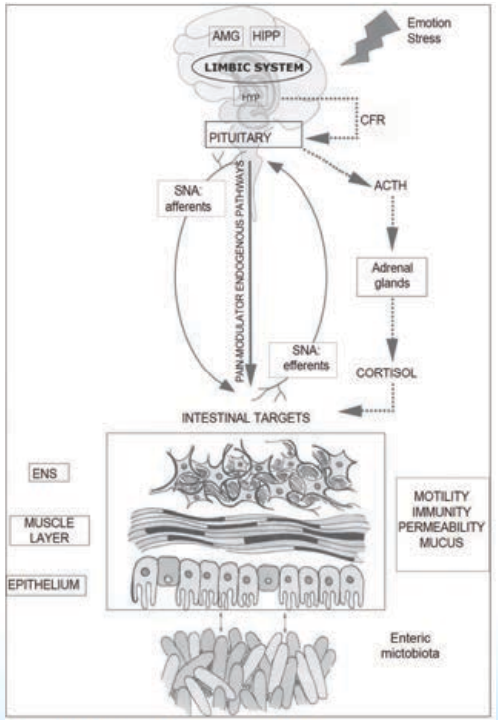

Figure 1 Microbiome gut-brain axis structure

- **Mucosal inflammation** and **Disruption of gut microbiome** by CTX can alter the function of the GBA
- This alteration in the GBA may be an underlying mechanism associated with the occurrence of CIN

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Carabotti et al., Annals of Gastroenterology, 2015

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