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

Komal Singh RN, MS, PhD
Post-Doctoral Fellow
School of Nursing, University of California San Francisco
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.
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

*FWER of 1% under the Bonferroni method*

<table>
<thead>
<tr>
<th>Pathway ID</th>
<th>Name</th>
<th>Adjusted pGlobal*</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsa04060</td>
<td>Cytokine-cytokine receptor interaction</td>
<td>0.00084</td>
</tr>
<tr>
<td>hsa04062</td>
<td>Chemokine signaling pathway</td>
<td>0.00084</td>
</tr>
<tr>
<td>hsa04010</td>
<td>Mitogen activated protein kinase signaling pathway</td>
<td>0.00306</td>
</tr>
<tr>
<td>hsa04064</td>
<td>Nuclear factor κB signaling pathway</td>
<td>0.00982</td>
</tr>
</tbody>
</table>
## Disruption of the Gut Microbiome

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

*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

The Multinational Association of Supportive Care in Cancer · Annual Meeting 2019 · www.mascc.org/meeting
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
Gut-Brain Axis

- 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
Gut-Brain Axis

- 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
Acknowledgements

• This study was supported by a grant from the National Cancer Institute (NCI, CA134900)

Funding for Doctoral Training
• National Institute of Nursing Research
  – T32 NR007088
• American Cancer Society Doctoral Degree Scholarship in Cancer Nursing
• El Camino Hospital Auxiliary Scholarship
• Nursing Alumni Association Scholarship

Funding for Postdoctoral Training
• National Institute of Nursing Research
  – T32 NR016920
Acknowledgements

- Christine Miaskowski
- Kord Kober
- Steve Paul
- Bruce Cooper
- Judy Mastick
- Grace Mausisa
- Melissa Mazor
- Kay Bolla
- Anatol Sucher
- Sandra Weiss
- Elena Flowers
- Anand Dhruva
- UCSF PN iSMRG
- Patient participants