Resistant starch-rich diet attenuates chemotherapy-related neuroinflammation in mice
Courtney Subramaniam 1, 2, Maya Davies 1, 2, Emma Bateman 1, 2, Elise Crane 1, 2, Marc Gladman 1, Hannah Wardill** 1, 2, Joanne Bowen** 1, 2

1) School of Biomedicine, Adelaide Medical School, University of Adelaide, South Australia, Australia
2) Supportive Oncology Research Group, Precision Medicine (Cancer), South Australian Health and Medical Research Institute (SAHMRI), University of Adelaide, South Australia, Australia
** Denotes shared senior authorship

Introduction

• Chemotherapy-induced neuroinflammation is thought to underlie the neuropsychological symptoms associated with chemotherapy1
• These symptoms often cluster with gastrointestinal side effects, which are known to result from the damaging impact of chemotherapy on the gut microbiota2
• The gut microbiota is a critical driver of neuroinflammation in other disease states3
• Despite this, there has been no attempt to ameliorate chemotherapy-induced neuroinflammation using microbiota targeted therapies
• We hypothesise that a high fibre diet may minimise neuroinflammation associated with the chemotherapeutic 5-fluorouracil (5-FU)

Does a high fibre diet promote microbial metabolite production and reduce neuroinflammation in mice treated with 5-FU?

Methods

• 24 female mice (n=6 / group) were treated with 5-FU or vehicle control, with or without a high fibre diet. Tissues were collected as outlined below:

<table>
<thead>
<tr>
<th>Day 0</th>
<th>Day -8</th>
<th>Day 16</th>
<th>Day 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=12 mice received 5FU (N=6 HFi; N=6 ND)</td>
<td>N=12 mice received 5FU (N=6 HFi; N=6 ND)</td>
<td>N=12 mice received 5FU (N=6 HFi; N=6 ND)</td>
<td>N=12 mice received high fibre diet</td>
</tr>
<tr>
<td>Faecal pellets collected N=24 mice</td>
<td>Faecal pellets collected N=24 mice</td>
<td>Faecal pellets collected N=24 mice</td>
<td>Faecal pellets collected N=24 mice</td>
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<td>Tissues collected from N=24 mice</td>
<td>Tissues collected from N=24 mice</td>
<td>Tissues collected from N=24 mice</td>
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• SCFAs quantified using GC-MS and microbiota composition analysed using 16S
• Immunofluorescence staining for glial fibrillary acidic protein (GFAP) was used to assess astrocyte abundance in the brain, as a marker of neuroinflammation

Results

High fibre diet altered faecal microbiota composition and increased caecal propionic acid concentrations

(a) Relative & raw abundance (individual samples)
(b) Relative & raw abundance (grouped samples)
(c) Principal component analysis
(d) Propionic acid
(e) Butyric acid
(f) Acetic acid
(g) Total SCFAs
(h) Differentially abundant microbial families

High fibre diet mitigates the increases to astrocyte staining density induced by 5-FU treatment

(a) CA1
(b) CA3
(c) Dentate gyrus
(d) Prefrontal cortex
(e) Midbrain
(f) Hypothalamus

Conclusions

Propionic acid and microbes differentially abundant with high fibre diet both significantly correlate with astrocyte abundance

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References

Fibre supplementation, and resulting microbial changes, mitigate 5-FU-induced neuroinflammation via propionic acid, warranting further investigation to reveal how these findings can be optimally translated for therapeutic intervention.