Intestinal *Blautia* regulates gastrointestinal toxicity in cancer patients receiving standard dose chemotherapy

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Conflict of interest

Hannah Wardill, PhD

Has no real or apparent conflicts of interest to report.
The microbiome: a new risk prediction tool for gastrointestinal toxicity?
The microbiome: a new risk prediction tool?

- Microbiome is **unique and individualized**
The microbiome: a new risk prediction tool?

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• Microbiome is uniquely position to **modulate cancer treatment efficacy and toxicity** due to influence on:
  
  • Drug metabolism
  • Mucosal immunology / barrier integrity / inflammation
  • Tolerance / immunogenic cell death
The microbiome: a new risk prediction tool?

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- Microbiome is uniquely position to **modulate cancer treatment efficacy and toxicity** due to influence on:
  - Drug metabolism
  - Mucosal immunology / barrier integrity / inflammation
  - Tolerance / immunogenic cell death
- Unlike human genome, the **microbiome is highly plastic** enabling risk modification and fine tuning of treatment outcomes
Retrospective cohort investigation

• Archival fecal samples from N=12 patients undergoing standard dose 5-FU based chemotherapy for CRC and breast cancer
Retrospective cohort investigation

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• Patients donated N=2 stool samples: samples:
  • 1 X before chemotherapy cycle
  • 1 X day 5 (peak diarrhea)
Retrospective cohort investigation

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• Toxicity was assessed using NCI CTCAE v5.0;
  • Toxic = G3+ diarrhea
  • Non-toxic = G0/G1 diarrhea
5-FU based chemotherapy disrupts microbial diversity and composition

Figure 1: Species diversity (Shannon’s index) pre- and post-chemotherapy in toxic and non-toxic patients.
5-FU based chemotherapy disrupts microbial diversity and composition

Figure 2: Significantly affected bacterial species in toxic and non-toxic individuals.
Toxic and non-toxic patients have distinct microbial signatures before chemotherapy.

Figure 3: Principle component analysis of pre-treatment microbiome composition.
Toxic and non-toxic patients have distinct microbial signatures before chemotherapy

Figure 4: Microbial composition (genera level) in toxic and non-toxic individuals
Toxic and non-toxic patients have distinct microbial signatures before chemotherapy.

Figure 4: Microbial composition (genera level) in toxic and non-toxic individuals.

Figure 5: Relative abundance of Blautia in toxic and non-toxic individual.
**Blautia correlates with toxicity outcome**

- Microbial composition aligning with PC considered protective
- Correlated species with PC2
Blautia correlates with toxicity outcome

- Microbial composition aligning with PC considered protective
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<table>
<thead>
<tr>
<th></th>
<th>Collinsella aerofaciens</th>
<th>Streptococ. Thermophil.</th>
<th>Blautia luti</th>
<th>Ruminococcus lactaris</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correlation coefficient</td>
<td>-0.839***</td>
<td>-0.593**</td>
<td>0.744**</td>
<td>0.616**</td>
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</tbody>
</table>
What is driving this phenomenon?
**Blautia luti in vitro activity**

- Isolated *blautia luti* from fresh human faeces (healthy individual)
- Cultured anaerobically in YCFAG, isolated supernatant via centrifugation
- Investigated impact of *blautia luti* supernatant (B-SPN) on:
  - Colonic epithelial proliferation (xCELLigence system)
  - Epithelial barrier function (trans-epithelial electrical resistance)
Conclusions

• 5-FU based chemotherapy causes microbial dysbiosis reflected by a decrease in species diversity, a loss of butyrate-producing commensals and an increase in opportunistic pathogens

• Pre-treatment microbial composition critical in determining outcomes

• Blautia genera associated with favourable toxicity outcomes

• Restoration of **blautia genera may be important in protecting against gastrointestinal toxicity**, via:
  • Promotion of epithelial restitution
  • Restoration of the intestinal barrier
  • Stimulation of commensal expansion
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