Regional variation in the gut microbiome and its implications for colorectal cancer screening

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Key facts about the gut microbiome

- $10^{14}$ microbes residing in the human gut, with >2,000 unique species.
- Higher inter-individual variation than intra-individual variation.
- Function more conserved than taxonomy – *functional redundancy*.
- Microbiome structure established by around age 3 years.
- Environment dominates over host genetics in shaping the microbiome.
- Diet can rapidly change the gut microbiome, but the core patterns and functions are shaped by long-term diet/lifestyle – *regional variation*.

Almeida A. Nature. 2019
Olsson LM. Cell Host Microbe. 2022
Wu GD. Science. 2011
Regional variation of the gut microbiome

31 Malawians, 35 Amerindians, 136 US residents

7,009 subjects from 14 districts in 1 province in China


He Y. Nat Med. 2018
Regional variation limits applications of healthy gut microbiome reference ranges and disease models

Yan He¹,²,³,⁴, Wei Wu²,³,⁴, Hui-Min Zheng¹,²,³,⁴, Pan Li¹,²,³,⁴, Daniel McDonald⁵, Hua-Fang Sheng⁶, Mu-Xuan Chen⁷, Zi-Hui Chen⁸, Gui-Yuan Ji⁹, Zhong-Dai-Xi Zheng⁹, Prabhakar Mujagond³, Xiao-Jiao Chen¹, Zu-Hua Rong¹,², Peng Chen⁶, Li-Yi Lyu⁰, Xian Wang⁰, Chong-Bin Wu², Nan Yu¹, Yan-Jun Xu², Jia Yin², Jeroen Raes²,³,⁴, Rob Knight⁵,⁶,⁷, Wen-Jun Ma⁶ and Hong-Wei Zhou¹,²,³,⁴

Prediction accuracy for metabolic syndrome

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Variations. Microbiota-based metabolic disease models developed in one location failed when used elsewhere, suggesting that such models cannot be extrapolated. Interpolated models performed much better, especially in diseases with obvious microbiota-related characteristics. Interpolation efficiency decreased as geographic scale increased, indicating a need to build localized baseline and disease models to predict metabolic risks.
Mechanisms and clinical implications for the link b/t gut microbiota and CRC

- Prediction
  - Screening tool
- Chemoprevention
  - Microbiota modification
  - Combinational approach

**Gut microbiome**

**Local mechanisms**
- Altered host cell proliferation vs. death (*Bacteroides fragilis*)
- Perturbed immune function (*Fusobacterium nucleatum*)
- Altered gut metabolism (Short-chain fatty acid-producing bacteria)

**Systematic mechanisms**
- Host metabolic disturbance
- Systematic immune perturbation
- Enzymatic activity of estrobolome
  - Obesity
  - Inflammation
  - Estrogen

**Clinical outcomes**
- Normal
- Hyperproliferation
- Adenoma
- Carcinoma

Song M. Gastroenterology. 2020
Tilg H, Cancer Cell. 2018
## Microbiome as a screening tool for CRC

<table>
<thead>
<tr>
<th>Study</th>
<th>microbes</th>
<th>Country</th>
<th>AUC for CRC</th>
<th>AUC for adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zeller, 2014</td>
<td>4 species (2 <em>Fusobacterium</em> species, <em>Porphyromonas asaccharolytica</em>, <em>Peptostreptococcus stomatis</em>)</td>
<td>France</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>Zackular, 2014*</td>
<td>5 OTUs (<em>Clostridiales</em>, <em>Clostridium</em>, <em>Lachnospiraceae</em>, <em>Bacteroides</em>)</td>
<td>USA</td>
<td>0.80 (0.69-0.91)*</td>
<td>0.84 (0.74-0.94)*</td>
</tr>
<tr>
<td>Feng, 2015</td>
<td>10 metagenomic groups (<em>Bacteroides massiliensis</em>, <em>Bacteroides xylanisolvens</em>, <em>Bifidobacterium animalis</em>, <em>Paraprevotella clara</em>, <em>Streptococcus mutans</em>, 5 unclassified)</td>
<td>Austria</td>
<td>0.96 (0.88-1.00)</td>
<td>0.60 (0.38-0.82)</td>
</tr>
<tr>
<td>Baxter, 2016</td>
<td>34 OTUs (most belong to <em>Clostridiales</em> order and some to <em>Bacteroides</em>)</td>
<td>USA</td>
<td>0.85</td>
<td>0.67</td>
</tr>
<tr>
<td>Wong, 2017</td>
<td>1 species (<em>F. nucleatum</em>)</td>
<td>China</td>
<td>0.89 (0.80-0.98)</td>
<td>0.58 (0.49-0.67)</td>
</tr>
<tr>
<td>Liang, 2017</td>
<td>4 species (<em>F. nucleatum</em>, <em>Bacteroides clarus</em>, <em>Roseburia intestinalis</em>, <em>Clostridium hathewayi</em>, and one undefined)</td>
<td>China</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>Thomas, 2019</td>
<td>16 species (e.g., <em>Peptostreptococcus stomatis</em>, <em>F. nucleatum</em>, <em>Parvimonas spp.</em>, <em>Porphyromonas asaccharolytica</em>, <em>Gemella morbillorum</em>, <em>Clostridium symbiosum</em> and <em>Parvimonas micra</em>)</td>
<td>Multi</td>
<td>0.81</td>
<td>0.54</td>
</tr>
</tbody>
</table>

*No validation was performed. The AUC was calculated in the training set.
Meta-analysis of fecal metagenomes reveals global microbial signatures that are specific for colorectal cancer


Metagenomic analysis of colorectal cancer datasets identifies cross-cohort microbial diagnostic signatures and a link with choline degradation

The core set of gut microbes associated with CRC is relatively consistent across studies.
Individual microbes consistently associated with CRC

- Using as few as 16 species achieved cross-validation AUC >0.8 for most of the datasets, with little increase in AUC (~2%) from using other species.
- No dataset could accurately discriminate adenomas from controls (average AUC=0.54).
Microbiome improves the accuracy of FIT-based test for adenoma detection

<table>
<thead>
<tr>
<th>Variables</th>
<th>CRC</th>
<th>Adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fn</td>
<td>m3</td>
</tr>
<tr>
<td>AUROC</td>
<td>0.776</td>
<td>0.759</td>
</tr>
</tbody>
</table>

Fn: *Fusobacterium nucleatum*

m3: *Lachnoclostridium sp.*

LR4: Fn+m3+*Bacteroides clarus*

Remains to be validated in other populations

A prospective microbiome study

- Microbiome among Nurses Study (Micro-N): n=20,000
  - To interrogate causes vs. consequences
  - To identify early changes in microbiome during carcinogenesis

U01CA261961: “The Gut Microbiome, Lifestyle, and Colorectal Neoplasia”

Summary

• There is substantial regional variation in the gut microbiome.
• A consistent gut microbial signature has been identified across regions to differentiate CRC from non-CRC.
• Microbial features predict poorly for adenomas but may help improve the accuracy of FIT test.
• Prospective studies are needed to assess the potential of the gut microbiome for early detection of colorectal neoplasia.
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