Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients.


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Introduction of the Crohn disease

- inflammatory bowel disease (IBD)
- autoimmune disease
- affect any part of the gastrointestinal tract
- in western country, 1/1000 population get the disease

The exact cause of Crohn disease is still unknown!
The common sites involved in Crohn disease

Ileal
Ileocolic
Colonic
Symptoms

- Diarrhea
- Blood in your stool
- Ulcer
- At risk of malnutrition
- Reduced appetite and loss weight
- Also increases the risk of cancer in the area of inflammation...
Treatments and drugs

Actually, there is no cure for Crohn disease.

- Anti-inflammatory drugs
- Immune system suppressor
- Antibiotics
- Others: anti-diarrheals, pain relievers...
- Surgery
Some possible theories for the disease

1) Persistent pathogenic infection
2) Dysbiosis
3) Defective mucosal barrier function
4) Defective microbial clearance
5) Aberrant immunoregulation

The exact cause of Crohn disease is still unknown!
Some important factors of the disease

- Genes: **CARD15**
- Environment: smoking
- Immune system
- Microbes imbalance

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chromosome (human)</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn's disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CARD15</td>
<td>16</td>
<td>NFκB activation and/or regulation, killing of intracellular pathogens, Paneth-cell function, α-defensin production</td>
</tr>
<tr>
<td>SLC22A4 &amp; SLC22A5</td>
<td>5</td>
<td>Organic cation, carnitine transporters, possibly transport xenobiotic substances</td>
</tr>
<tr>
<td>DLG5</td>
<td>10</td>
<td>Epithelial scaffolding protein</td>
</tr>
<tr>
<td>PPARγ</td>
<td>3</td>
<td>Intracellular inhibitor of NFκB and cellular activation</td>
</tr>
</tbody>
</table>
The possible pathways for patients to get the Crohn disease

- Normal gut
  - Environmental trigger (infection, NSAID)
  - Tolerance controlled inflammation

- Acute injury
  - Luminal bacteria
  - Regulation, repair or clearance

- Complete healing
  - Tolerance

- Genetically susceptible host
  - Chronic inflammation

- Crohn disease
Gut flora in human body

- normally live in the digestive tract of animals
- has about ten times number of microorganism than human cell in the intestines
- some bacterium are thought to be capable of causing disease by causing infection or increasing cancer risk for the host
The functions of gut flora

A

- Duodenum
  - $10^2$–$10^3$ cfu/ml
- Colon
  - $10^{11}$–$10^{12}$ cfu/ml
- Jejunum/ileum
  - $10^4$–$10^7$ cfu/ml

B

| Anerobic genera  | Aerobic genera  |
|------------------|-----------------
| Bifidobacterium  | Escherichia     |
| Clostridium      | Enterococcus   |
| Bacteroides      | Streptococcus  |
| Eubacterium      | Klebsiella     |

**Protective functions**
- Pathogen displacement
- Nutrient competition
- Receptor competition
- Production of anti-microbial factors e.g., bacteriocins, lactic acids

**Structural functions**
- Barrier fortification
- Induction of IgA
- Apical tightening of tight junctions

**Metabolic functions**
- Control IEC differentiation and proliferation
- Metabolize dietary endogenous epithelial-derived carcinogens
- Synthesize vitamins e.g., biotin, folate

- Commensal bacteria
- IgA
- Short-chain fatty acids
- Mg$^{2+}$, Ca$^{2+}$, Fe$^{2+}$
- Vitamin K, Biotin, Folate
- Ion absorption
- Salvage of energy
In the previous study, compare the differences between normal people and patients’ microbial distribution in faecal samples using 16S rRNA microarray.
Framework

Is the disease related to specific **bacteria**?

What is the role of the bacteria in inflammatory response?

Which **portion** of the bacteria is functional?

Can the specific molecule **counterbalance** the dysbiosis in colitis mice?

Is it possible to use the bacteria to **reduce the mortality of colitis mice**?
Is the disease related to specific bacteria?

Compare the *F. prausnitzii* distribution of recurrence and non-recurrence patients

A lower proportion of *F. prausnitzii* on resected ileal Crohn mucosa is associated with endoscopic recurrence.

<table>
<thead>
<tr>
<th></th>
<th><em>F. prausnitzii</em></th>
<th><em>C. coccoides</em></th>
<th><em>Firmicutes</em></th>
<th><em>Bacteroidetes</em></th>
<th><em>Bifidobacterium</em></th>
<th><em>Enterobacteria</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MAM at time of surgery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endoscopic recurrence group</td>
<td>0.2 ± 0.2*</td>
<td>15.1 ± 3.4</td>
<td>15.4 ± 6.3</td>
<td>31.6 ± 12.2</td>
<td>3.6 ± 2.7</td>
<td>12.5 ± 8.0</td>
</tr>
<tr>
<td>No endoscopic recurrence group</td>
<td>3.3 ± 1.7*</td>
<td>16.3 ± 8.3</td>
<td>19.5 ± 8.5</td>
<td>32.0 ± 11.0</td>
<td>4.5 ± 2.4</td>
<td>1.5 ± 0.9</td>
</tr>
<tr>
<td><strong>MAM at 6 months</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Endoscopic recurrence group</td>
<td>0.1 ± 0.1</td>
<td>14.6 ± 5.7</td>
<td>14.8 ± 5.7*§</td>
<td>31.3 ± 8.8</td>
<td>1.0 ± 0.7</td>
<td>9.3 ± 3.1</td>
</tr>
<tr>
<td>No endoscopic recurrence group</td>
<td>5.2 ± 3.8</td>
<td>30.0 ± 4.9</td>
<td>35.2 ± 5.0*§</td>
<td>50.3 ± 4.5</td>
<td>2.3 ± 1.2</td>
<td>3.5 ± 2.6</td>
</tr>
</tbody>
</table>
peripheral blood mononuclear cell (PBMC)
**F. prausnitzii** shows anti-inflammatory effects on peripheral blood mononuclear cell (PBMC)

**What is the role of the bacteria in inflammatory response?**

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Crohn’s disease</th>
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</thead>
<tbody>
<tr>
<td><strong>Innate immune response</strong></td>
<td></td>
</tr>
<tr>
<td>IL-1β</td>
<td>↑</td>
</tr>
<tr>
<td>TNF</td>
<td>↑↑</td>
</tr>
<tr>
<td>IL-6</td>
<td>↑</td>
</tr>
<tr>
<td>IL-8a</td>
<td>↑</td>
</tr>
<tr>
<td>IL-12</td>
<td>↑</td>
</tr>
<tr>
<td>IL-18</td>
<td>↑</td>
</tr>
<tr>
<td>IL-29</td>
<td>↑</td>
</tr>
<tr>
<td>IL-27</td>
<td>↑</td>
</tr>
<tr>
<td><strong>T-cell response</strong></td>
<td></td>
</tr>
<tr>
<td>IFN-γ</td>
<td>↑</td>
</tr>
<tr>
<td>IL-5</td>
<td>N</td>
</tr>
<tr>
<td>IL-13</td>
<td>N</td>
</tr>
<tr>
<td>IL-17</td>
<td>↑</td>
</tr>
<tr>
<td>IL-21</td>
<td>↑</td>
</tr>
</tbody>
</table>

Proinflammatory cytokines: IL12, IFN-γ
Anti-inflammatory cytokine: IL10

*used to distinguish between strains exhibiting inflammatory regulation property*
Which portion shows anti-inflammatory effect?
**F. prausnitzii** supernatant abolishes NF-κB activation in Caco-2 reporter cell line

Supernatant of *F. prausnitzii*, have the anti-inflammation property.

The influence on NF-κB activation was tested by the SEAP reporter system.
Using TNBS-induce mice to mimic the symptom of Crohn disease in human

Inject TNBS

TNBS = 2,4,6-trinitrobenzene sulfonic acid

Colitis mice
*F. prausnitzii* exhibits anti-inflammatory effects on TNBS-induced colitis mice

Proinflammatory cytokines: IL12, TNF α
Antiflammatory cytokine: IL10

Living *F. prausnitzii* or its supernatant result in an attenuation of colitis with reduced weight loss.
Can the specific molecular counterbalance the dysbiosis in colitis mice?

**F. prausnitzii** and its supernatant tend to counterbalance the TNBS-induced dysbiosis in colitic mice.

Treatment with either *F. prausnitzii* or its supernatant tended to counterbalance the dysbiosis observed in colitis control mice for bacteria: *C. leptum, C. coccoides, Bacteroides*, and *F. prausnitzii.*
F. prausnitzii and its supernatant can act by a gut-independent route

In the groups treated with live F. prausnitzii or its supernatant, the mortality rate was dramatically decreased.

Is it possible to used the bacteria to reduce the mortality of colitis mice?
Summary

Is the disease related to specific bacteria?

What is the role of the bacteria in inflammatory response?

Which portion of the bacteria is functional?

Can the specific molecular counterbalance the dysbiosis in colitic mice?

Is it possible to use the bacteria to reduce the mortality of colitic mice?

Use *F. prausnitzii* as a probiotic to counterbalance dysbiosis is a promising strategy in Crohn disease treatment!
Thanks for your attention

and special thanks for my advisor
professor Yang