분변미생물이식 연구의 임상응용

고 흥

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Gut Microbiota
Microbiome

Human Microbiome
- Oral microbiome
- Skin microbiome
- Digestive tract microbiome
- Urinary microbiome
- Fungi
- Bacteria
- Viruses
- Parasites

Genetics
- NOSE: mucus production, antimicrobial chemicals
- MOUTH: assist digestion, ward off pathogens
- LUNGS: lubricate pulmonary tissues
- STOMACH: prevents gastric complications
- COLON: digestion of complex carbohydrates
- SEXUAL ORGANS: maintain pH and H₂O₂ production to kill microbes
- SKIN: fortify immune system, scent production

Environment
Diet
Lifestyle
Hormones
Industry

What is biotechnology?
Vasu Appanna
Microbiome in Gut

Inputs
- Diet
- Feeding pattern
- CR disruption
  - Genetic
  - Jet lag

Changes in microbe-derived mediators
- SCFAs
- Gain or loss of oscillators
- Modified BAs

Host outcomes
- Altered CR expression
  - Liver
  - Intestines
  - Kidney
- Metabolic homeostasis
  - Body weight
  - Glucose metabolism
  - Energy source
  - Gut barrier function
- Changes in BA synthesis
- Altered CR expression
  - Liver
  - Intestines
- Metabolic homeostasis
  - Body weight
  - Lipid, glucose, cholesterol metabolism
  - Energy expenditure
  - Inflammation

Trends in Endocrinology & Metabolism

Frazier K, et al. Trends Endocrinol Metab 2020
Eubiosis and Dysbiosis

**EUBIOSIS**
- Prevalence of non-pathogenic bacteria
- Normal tight junctions
- Result: immune homeostasis

**DYSBIOSIS**
- Alteration of the tight junction with access of pathogens and release of LPS
- Prevalence of pathogenic bacteria

Access of pathogens and release of inflammatory mediators (TNF-α, COX-2, IL6, iNOS, etc.)
- Chronic inflammation and damages (Inflammatory bowel disease, metabolic disease, autoimmune disease, food intolerance, colorectal cancer)

**Tx.**
Firmicutes/Bacteroidetes ratio (F/B ratio)

Gut microbial balance

↑ F/B = Obesity

↓ F/B = IBD

Specific probiotics

Stojanov S, et al. Microorganism 2020
Firmicutes/Bacteroidetes ratio (F/B ratio)

300 healthy population in Phylum level

From Koh’s Lab
Fecal Microbiota Transplantation (FMT)

1. Stool from a screened donor
2. Filtering and processing
3. Storage and administration
4. Upper Delivery: Nasoenteric or gastric tube
   Orally Through Capsules
4. Lower Delivery: Colonoscopy or enema

Donor recruitment:
- Recruitment
- Questionnaires
- Blood and fecal sampling and analyses
- Information
- Follow-up
- Data management

Laboratory processing:
- Cryopreservation
- Processing before application
- Re-test
- Biobank
- Quarantine management

Clinical application:
- Patient selection
- Information
- Application: Colonoscopy or nasojejunal tube delivery
- Follow-up
- Handling of complications

OpemBiome
Gut Microbiota
2017년
1st case
12세 intractable and refractory ulcerative colitis
FMT 2회 (4주 간격)
1st case Gut microbiome composition (Phylum level)

- **Relative abundance**
- **Donor**
- **1st_FMT**
- **2nd_FMT**

- Phylum level distribution in donor samples before and after FMT.
2017년
2nd case
14세 intractable and refractory ulcerative colitis
FMT 2회 (4주 간격)
2nd case Gut microbiome composition (Phylum level)
Severance clinical trials for FMT in IBD
Severance clinical trials for FMT in IBD
Severance clinical trials for FMT in IBD

The purpose

- To find the key gut microbiome or metabolites to treat & control the inflammation of intestine in IBD
- To make the therapeutic product for the patients with IBD to control their inflammation
최근 연구과제

FMT 기반 만성난성질환(궤양성대장염, 비알코올지방간염, 천식, 우울/불안) 극복 선도형 휴먼 마이크로바이옴 치료기술 개발 (책임연구자)

2022~2025(4년), 총연구비 152억원

산업통상자원부
바이오산업기술개발사업 휴먼마이크로바이옴 의약품 제품화 사업
Fecal microbiota transplantation (FMT)

- Dong-jin dynasty in the 4th century in China, Ge Hong, a Chinese medicine doctor, described the use of human fecal suspension by mouth for patients who had food poisoning or severe diarrhea.
Clinical Application and Potential of Fecal Microbiota Transplantation

R E Ooijevaar 1, E M Terveer 2, H W Verspaget 3, E J Kuijper 2, J J Keller 3 4

Keywords
fetal microbiota transplantation, FMT, *Clostridioides/Clostridium difficile* infection, CDI, inflammatory bowel disease, IBD, irritable bowel syndrome, IBS, hepatic encephalopathy


1. **Microbiome modulation** by direct interaction or competition

2. **Quorum sensing** affect microbiome behavior and community composition when a threshold concentration of auto-inducers is met.

3. **Host bile acid metabolism alteration**
   - Cholic acid
   - Deoxycholic acid
   - Chenodeoxycholic acid
   - Lithocholic acids

4. **Host immunity modulation**
   - Reduced ability of macrophages, monocytes, and dendritic cells to present MHCI-dependent bacterial antigens to colonic T cells
   - Increased interleukin (IL-10) production by innate and adaptive immune cells including CD4+ T cells, iNKT cells, and Antigen Presenting Cells (APC)
   - Increased proportion of Foxp3+ regulatory T-cells within mucosa
FDA approves first FMT therapy and issues guidance

What does this mean for GI specialists and other healthcare professionals treating CDI?

On Nov. 30, FDA approved the first fecal microbiota therapy for recurrent *Clostridioides difficile* infection (CDI). This approval came days after FDA issued guidance on regulatory requirements for stool banks providing fecal microbiota transplantation (FMT) products. Here is a summary of the regulatory actions and what they mean for GI specialists and our patients with recurrent CDI.

**FDA approves Rebyota®**

FDA approved Rebyota® (Ferring Pharmaceuticals Inc.) for the prevention of recurrence of CDI in patients 18 years of age and older who have completed antibiotic treatment for recurrent CDI.
Improvement in sperm quality and spermatogenesis following faecal microbiota transplantation from alginate oligosaccharide dosed mice.

Rescue of male fertility following faecal microbiota transplantation from alginate oligosaccharide-dosed mice.


Improved MAIT cell functions following fecal microbiota transplantation for metastatic renal cell carcinoma.

Fecal Microbiota Transplantation as an Effective Treatment for Carbapenem-Resistant Klebsiella pneumoniae Infection in a Renal Transplant Patient.
Patients and Methods

Materials and Methods
Stool
Shotgun metagenomics

3 conditions for Prognostic factors
1. Significant cohort difference between R and NR at T0
2. Significant temporal change between T0 and T60
3. Significant separability using the receiver operating characteristic (ROC) curve
### Demographic factors and outcome of FMT

<table>
<thead>
<tr>
<th>Variables (n)</th>
<th>R (4)</th>
<th>NR (6)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>16.82±3.60</td>
<td>31.18±15.02</td>
<td>0.07</td>
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<tr>
<td>Sex, male (%)</td>
<td>2 (50)</td>
<td>5 (83.3)</td>
<td>0.26</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>19.92±1.74</td>
<td>21.71±5.39</td>
<td>0.54</td>
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<tr>
<td>Disease duration (years)</td>
<td>4.34±4.43</td>
<td>6.12±5.31</td>
<td>0.60</td>
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<tr>
<td>Disease extent</td>
<td></td>
<td></td>
<td>0.15</td>
</tr>
<tr>
<td>Pancolitis (%)</td>
<td>25.0 (1)</td>
<td>50.0 (3)</td>
<td></td>
</tr>
<tr>
<td>Left sided (%)</td>
<td>25.0 (1)</td>
<td>50.0 (3)</td>
<td></td>
</tr>
<tr>
<td>Ascending and transverse colon (%)</td>
<td>50.0 (2)</td>
<td>0.0 (0)</td>
<td></td>
</tr>
<tr>
<td>Total Mayo score</td>
<td>9.75±2.22</td>
<td>8.00±2.00</td>
<td>0.23</td>
</tr>
<tr>
<td>Partial Mayo score</td>
<td>7.00±2.16</td>
<td>6.00±1.41</td>
<td>0.40</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
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<tr>
<td>Mesalazine (%)</td>
<td>100.0 (4)</td>
<td>83.3 (5)</td>
<td>0.39</td>
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<tr>
<td>Systemic steroid (%)</td>
<td>0.0 (0)</td>
<td>16.7 (1)</td>
<td>0.39</td>
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<tr>
<td>Azathioprine (%)</td>
<td>75.0 (3)</td>
<td>16.7 (1)</td>
<td>0.07</td>
</tr>
<tr>
<td>Biologics (%)</td>
<td>50.0 (2)</td>
<td>50.0 (2)</td>
<td>1.00</td>
</tr>
<tr>
<td>Budesonide (%)</td>
<td>75.0 (3)</td>
<td>0.0 (0)</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Clinical outcomes after FMT

Severance Hospital FMT Center
Lower Bacteroidetes in responders

UC patients in Remission had lower level of Bacteroidetes before FMT.

Significant separability between R and NR at T0

Repeated Measures ANOVA, test results between groups (***, p<0.001) and between times (  , not significant and  , p<0.05)
Random Forest algorithm of species and genes

13 species candidates
- Unclassified Subdoligranulum sp.
- Coprococcus catus
- Magasphaera micronucliformis
- Bifidobacterium adolescentis
- Eubacterium dolichum
- Parabacteroides distasonis
- Bifidobacterium longum
- Enterococcus raffinosus
- Bacteroides uniformis
- Actinomyces odontolyticus
- Haemophilus parainfluenzae
- Coprococcus catus
- Streptococcus australis

7 gene candidates
- K00005: Glycerol dehydrogenase
- K00132: Acetaldehyde dehydrogenase
- K01223: 6-phospho-beta-glucosidase
- K02809: Sucrose PTS system
- K06610: Inositol transporter
- K15524: Mannosylglycerate hydrolase
- K15588: Putative hydroxymethylpyrimidine transport system substrate-binding protein

p<0.05
Higher level of specific genes in responders

UC patients in Remission had higher level of Glycerol dehydrogenase and Mannosylglycerate hydrolase before FMT.

Repeated Measures ANOVA, test results between groups (***, p<0.001) and between times (  , not significant and   , p<0.05)
Beta diversity of bacterial species and genes
Decision Tree with Bacteroidetes

Classification and regression tree (CART) analysis
Decision Tree with two genes

Classification and regression tree (CART) analysis
Tailored therapy with better outcomes
FMT indication and beyond indication

1. Microbiome modulation by direct interaction or competition

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   - Deoxycholic acid
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   - Increased interleukin (IL-10) production by innate and adaptive immune cells including CD4+ T cells, iNKT cells and Antigen Presenting Cells (APC)
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Thank you for your attention