Gut Microbiota in Human Metabolic Health and Disease

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MacMillan Group Meeting
March 16th, 2021
Gut Microbiome is Important for Human Health

Considerable part of the environmental influence on human health and disease risk may be mediated or modified by microbial communities.

And many others.....

Outline

Overview of Gut Microbiome

Microbial Metabolites and Metabolic Health
- BCAAs
- Imidazole Propionate
- SCFAs

Gut Microbiome and Metabolic Disease
- Obesity
- Cardiovascular Disease

Interventions
- Diet
- Drugs and Pre/Pro/Postbiotics
- Bioengineered Commensals
- Fecal Microbiota Transplantation
Microbe vs. Microbiome vs. Microbiota

**Microbe (or microorganism)** = Organism which is too small to be seen by the naked eye

Viruses
Algae
Bacteria
Protozoa
Fungi

**Microbiota**
The microorganisms found within a specific environment

**Microbiome**
Collection of genomes from all microorganisms in an environment

Gut Microbiota

Microorganisms found in the gut (mouth to anus)

Human Microbiota

Microbes on a human comprise about 1–3% of body mass

Pedersen, O.; Fan, Y. Nat. Rev. Microbiol. 2021, 19, 55
What does the Gut Microbiota do?

Aids Metabolism
- *e.g.* digestion, synthesis of essential vitamins

Protection
- *First line of defence against pathogens*

Regulation of Immune System
- *e.g.* via SCFAs

A healthy gut microbiome is essential for human health

Germ-free (GF) animals (*no microbes*) have multiple abnormalities

Colonization with gut microbiota partially resolves abnormalities

Gut Microbiota Metabolism

For their own energy supply, gut microbiota ferment energy-yielding nutrients

Food Source → Specific Bacteria → Metabolite

5–10% of energy needs come from these fermented nutrients

Metabolite can lead to biological effect in host

Pedersen, O.; Fan, Y. Nat. Rev. Microbiol. 2021, 19, 55
Key Takeaway: **Gut microbiota metabolism leads to microbial metabolites which affect the host**
What does a Healthy Gut Microbiome look like?

- **High taxa diversity**
  
  (# and evenness of species)

- **High microbial gene richness**
  
  (number of unique genes)

**Stable microbiome functional cores**

Genes encoding glycosaminoglycan degradation, production of SCFAs, biosynthesis of essential amino acids and vitamins

Huge variation between individuals - *No golden standard*

Environment Alters the Gut Microbiota

Environment and Diet

- Antibiotics
- Saturated Lipids
- Dietary Fiber
- Pollution
- Cholesterol

Change in composition of microbiota

Change in metabolites

- Me
- Me
- O
- NH₂

e.g. insulin sensitivity, inflammation, appetite, behaviour, immunomodulatory activity

Health Impact

Pedersen, O.; Fan, Y. Nat. Rev. Microbiol. 2021, 19, 55
Gut Dysbiosis

Disturbance to gut microbiota homeostasis due to an *imbalance in microbiota, changes in their metabolic activity or changes in their local distribution*.

**Trigger**

- Beneficial bacteria
  - Healthy functions

**Out-of-Balance Gut Microbiome**

- Pro-inflammatory bacteria
  - Unhealthy functions

**Gut Dysbiosis**

Pedersen, O.; Fan, Y. Nat. Rev. Microbiol. 2021, 19, 55
Gut dysbiosis has been associated with many diseases although causation proved for few of them.
Gut Dysbiosis and Metabolic Health

Metabolic Health

Have an overall metabolism that is linked to derivable life quality and longevity

Metabolic Disease

Inflammation

Insulin Sensitivity

Energy Homeostasis

Hormone Secretion

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Intestinal microbial products affect host energy homeostasis, body adiposity, glucose tolerance, insulin sensitivity, inflammation and endocrine regulation.

Dietary fibres

- Phosphatidylcholine and L-carnitine

- Amino acids

- Bile acids

Firmicutes/
Bacteroidetes

Specific bacteria

Short Chain Fatty Acids

e.g LPS, N-acyl amides, ClpB, MECO-1

TMA

Branched Chain Amino Acids

Secondary Bile Acids

Pedersen, O.; Fan, Y. Nat. Rev. Microbiol. 2021, 19, 55
Microbial Metabolites affect Metabolic Health

Pedersen, O.; Fan, Y. Nat. Rev. Microbiol. 2021, 19, 55
Microbial Metabolites affect Metabolic Health

Pedersen, O.; Fan, Y. Nat. Rev. Microbiol. 2021, 19, 55
Amino Acid Derived Metabolites Linked in Insulin Resistance

Amino acid-derived microbial metabolites play a role in insulin resistance

Specific Bacteria

BCAAs

Indole and derivatives

Imidazole Propionate

Amino acid-derived microbial metabolites play a role in insulin resistance

Pedersen, O.; Fan, Y. Nat. Rev. Microbiol. 2021, 19, 55
Case Study: BCAAs and Insulin Sensitivity

Elevated circulating concentration of the BCAAs *leucine, isoleucine and valine* are a strong biomarker for insulin resistance

![Chemical structures of leucine, isoleucine, and valine]

**Table:**

<table>
<thead>
<tr>
<th>Model</th>
<th>Isoleucine</th>
<th>Leucine</th>
<th>Valine</th>
<th>Tyrosine</th>
<th>Phenylalanine</th>
<th>Isoleucine, tyrosine and phenylalanine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Models adjusting for age, sex, BMI and fasting glucose (n = 378)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Metabolite as continuous variable</td>
<td></td>
<td></td>
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<tr>
<td>Per s.d.</td>
<td>1.70 (1.27–2.28)</td>
<td>1.62 (1.20–2.17)</td>
<td>1.57 (1.17–2.09)</td>
<td>1.85 (1.35–2.55)</td>
<td>2.02 (1.40–2.92)</td>
<td>2.42 (1.66–3.54)</td>
</tr>
<tr>
<td><em>P</em></td>
<td>0.0004</td>
<td>0.001</td>
<td>0.002</td>
<td>0.0001</td>
<td>0.0002</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Metabolite as categorical variable</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>First quartile</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>Second quartile</td>
<td>1.11 (0.58–2.10)</td>
<td>2.40 (1.24–4.68)</td>
<td>1.49 (0.75–2.94)</td>
<td>1.89 (0.94–3.81)</td>
<td>1.39 (0.74–2.59)</td>
<td>3.48 (1.68–7.23)</td>
</tr>
<tr>
<td>Third quartile</td>
<td>2.14 (1.07–4.27)</td>
<td>3.15 (1.46–6.84)</td>
<td>2.15 (1.05–4.42)</td>
<td>3.26 (1.56–6.84)</td>
<td>2.12 (1.04–4.32)</td>
<td>2.82 (1.25–6.34)</td>
</tr>
<tr>
<td>Fourth quartile</td>
<td>3.14 (1.51–6.55)</td>
<td>3.66 (1.61–8.29)</td>
<td>3.14 (1.43–6.86)</td>
<td>2.82 (1.25–6.34)</td>
<td>2.28 (1.00–5.20)</td>
<td>5.99 (2.34–15.34)</td>
</tr>
<tr>
<td><em>P</em> for trend</td>
<td>0.001</td>
<td>0.004</td>
<td>0.003</td>
<td>0.010</td>
<td>0.035</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

**Untargeted metabolomics finds that BCAAs are associated with insulin resistance**

Case Study: BCAAs and Insulin Sensitivity

Measure the microbiome of the patients

Plugged the gut microbiome (genes) into KEGG database to investigate metabolic potential of these metabolites

**Functional modules correlated with insulin resistance include enzymes for BCAA biosynthesis**

Case Study: BCAAs and Insulin Sensitivity

To determine responsible species for these functional modules, rerun the KEGG analysis omitting genes for a single species each time.

P. copri and B. Vulgatus largely drive the association between insulin resistance and BCAA biosynthetic modules.

Case Study: BCAAs and Insulin Sensitivity

Microbial functional analysis additionally recognized depletion of genes encoding for bacterial BCAA uptake (and their associated bacterial species)

Increased BCAA pool
**Case Study: BCAAs and Insulin Sensitivity**

*Increased BCAA levels in mice* following fecal transplantation from insulin-resistant individuals.

1. Take fecal sample from IR patient
2. Feed fecal sample to mouse

*P. copri*

*Reduced insulin sensitivity and increased levels of BCAA when mice fed P. copri*

Case Study: Imidazole Propionate and Insulin Resistance

Imidazole propionate has been shown to impair insulin signaling

Perform untargeted metabolomics on plasma of patients with and without T2D

Find four AA-derived metabolites in higher concentrations in T2D patients

Only imidazole propionate is present in higher concentrations

To focus on microbial metabolites only, repeat metabolomics on germ-free and conventional mice

Koh, A. et al. Cell 2018, 175, 947
Case Study: Imidazole Propionate and Insulin Resistance

Put histidine in an *in vitro* gut simulator, *see IP only with T2D microbes*.

Suggests *type 2 diabetes-associated microbiota shunts urocanate to a lesser-known pathway to produce imidazole propionate*.

Histidine → Urocanate → Imidazole Propionate (IP)

Glutamate

Cis-Urocanate

Koh, A. et al. *Cell* 2018, 175, 947
Case Study: Imidazole Propionate and Insulin Resistance

Imidazole propionate worsened glucose intolerance and insulin signaling

Overexpression of the mTORC1-mediated insulin signaling pathway was found in liver tissue of T2D individuals

Show that IP inhibits insulin signalling through mTOR (rapamycin inhibits this effect)

Koh, A. et al. Cell 2018, 175, 947
Microbial Metabolites affect Metabolic Health

Pedersen, O.; Fan, Y. Nat. Rev. Microbiol. 2021, 19, 55
SCFAs and Energy Homeostasis and Body Adiposity

Short Chain Fatty Acids

Monocarboxylic acids with six or fewer carbon atoms produced by the microbiota upon fermentation of indigestible polysaccharides

Dietary fibres

Firmicutes/
Bacteroidetes

Acetate

Propionate

Butyrate

Short chain fatty acids have effects on satiety, energy harvest, glucose homeostasis, fat storage and inflammation

Pedersen, O.; Fan, Y. Nat. Rev. Microbiol. 2021, 19, 55
**Case Study: SCFAs and Energy Homeostasis and Body Adiposity**

Mice treated with butyrate precursor drug (tributyrin) are protected from diet-induced obesity and insulin resistance

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>Tb</th>
<th>HFD</th>
<th>HFD + Tb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides, mg/dl</td>
<td>43.2 ± 2.6</td>
<td>45.3 ± 3.7</td>
<td>56.7 ± 3.8*#</td>
<td>50.4 ± 4.5</td>
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<tr>
<td>Cholesterol, mg/dl</td>
<td>132.2 ± 6.8</td>
<td>129.8 ± 4.8</td>
<td>183.0 ± 8.3*#</td>
<td>161.2 ± 6.8</td>
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<tr>
<td>LDL cholesterol, mg/dl</td>
<td>67.5 ± 5.5</td>
<td>63.6 ± 6.1</td>
<td>111.3 ± 6.4**#</td>
<td>97.1 ± 9.4</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
<td>63.3 ± 3.7</td>
<td>58.1 ± 2.1</td>
<td>62.1 ± 3.8</td>
<td>58.2 ± 3.1</td>
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<tr>
<td>NEFA, mM</td>
<td>0.30 ± 0.03</td>
<td>0.32 ± 0.03</td>
<td>0.45 ± 0.05**#</td>
<td>0.27 ± 0.03</td>
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<tr>
<td>AST, U/ml</td>
<td>111.8 ± 15.9</td>
<td>114.3 ± 9.9</td>
<td>103.8 ± 15.0</td>
<td>103.9 ± 18.1</td>
</tr>
<tr>
<td>ALT, U/ml</td>
<td>30.2 ± 10.0</td>
<td>36.3 ± 9.2</td>
<td>34.0 ± 6.5</td>
<td>29.9 ± 4.4</td>
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<tr>
<td>Leptin, pg/ml</td>
<td>4.061 ± 744</td>
<td>6.512 ± 786</td>
<td>20.944 ± 2145**#</td>
<td>15.642 ± 1.178**#</td>
</tr>
<tr>
<td>Resistin, pg/ml</td>
<td>3.788 ± 391</td>
<td>3.950 ± 333</td>
<td>7.871 ± 593**#</td>
<td>6.024 ± 447**#</td>
</tr>
<tr>
<td>Fasting glucose, mM</td>
<td>9.48 ± 0.40</td>
<td>8.86 ± 0.34</td>
<td>10.86 ± 0.35**#</td>
<td>9.48 ± 0.35</td>
</tr>
<tr>
<td>Insulin, ng/ml</td>
<td>0.37 ± 0.04</td>
<td>0.47 ± 0.07</td>
<td>1.01 ± 0.08**#</td>
<td>0.75 ± 0.09**#</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>21.92 ± 3.58</td>
<td>26.84 ± 3.85</td>
<td>75.70 ± 5.80**#</td>
<td>45.77 ± 6.31</td>
</tr>
</tbody>
</table>

Case Study: SCFAs and Leptin

SCFAs are linked to leptin, an anorexigenic hormone that suppresses food intake.

Unexpectedly find that acetic acid (solvent) during ligand screening for human GPR41 receptor can bind to GPR41.

Case Study: SCFAs and Leptin

Found that GPR41 mRNA is expressed in white (WAT) but not brown adipose tissue (BAT)

As leptin production is much higher in white adipose tissue, looked at effect of SCFAs on leptin

**Case Study: SCFAs and Leptin**

Using a luciferase assay, find that SCFAs stimulate leptin production in Ob-Luc cells.

Increased luciferase activity with propionic acid in cells overexpressing GPR41.

**Oral administration of propionate increases circulating leptin levels in vivo**

Case Study: SCFAs and Energy Homeostasis and Body Adiposity

Look for DNA segments that are deleted from bacteria in some individuals or present in a variable number of copies in others.

Look for associations between these structural variations.

Structural variations in *Anaerostipes Hadrus* genome shows inverse relationship with body weight, waist circumference and BMI.

Case Study: SCFAs and Energy Homeostasis and Body Adiposity

These structural variations encode metabolic modules for metabolizing 3-hydrobutanoyl-CoA to butyrate.

Potential mechanistic link between these metabolic pathways and host health.

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Weight of Germ-Free Mice vs. Conventional Mice

Germ-free mice (no microbes) can eat 30% more calories than conventional mice and not gain weight

Microbiota are important for obesity and weight gain

Coates, M. E. *Laboratory Animals* 1975, 9, 275
Composition of the Microbiome differs between Obese and Lean Individuals

The composition of the microbiome differs between obese and lean individuals in humans.

At the species level, levels of multiple gut microbiota change between obese and lean individuals.


Transfer of Obese Mouse Microbiota

Lean or obese mouse

Germ-free (GF) mouse (no microbes)

Colonization with obese mouse microbes over lean mouse leads to significant increase in body fat%

Compare GF mice colonized with lean or obese microbes

Effect of Fecal Transplant

Took fecal samples from lean and obese twin

Colonized GF mice with these microbiota by fecal transplantation

Increased total body and fat mass were transmissible

Cohousing lean and obese mice prevents increased adiposity (mice are coprophagics - feces eating)

Ridaura, V. K. et al. Science 2013, 341, 1241214
Obesity is associated with a Decreased Capacity for Unidirectional Conjugation

Microbiota from stool samples of obese and lean individuals

Extract and sequence DNA

Compare DNA with database

Identify genes, pathways and relative frequencies in sample

Obesity associated with decreased capacity for transfer of genetic material between bacteria and reduction in superoxide reductase

Intestinal oxidative stress

Thingholm, L. B. et al. Cell Host Microbe 2019, 26, 252
Cardiovascular Disease

Changes in gut microbiota structure and function in those with symptomatic atherosclerosis

Enrichment in genus *Collinsella* and depletion of *Roseburia* and *Eubacterium*

Fecal microbiota transplantation from hypertensive patients to GF mice leads to elevated blood pressure

TMAO and Cardiovascular Disease

Blood plasma from controls and CVD patients

LC/MS analysis to define analyses associated with cardiac risk

Applying acceptability criteria gave 18 analytes

3 of the 18 analytes showed significant correlations between one another

TMAO

Choline

Betaine

TMAO and Cardiovascular Disease

Foods rich in the lipid phosphatidylcholine (e.g. eggs, red meat, fish) thought to be major dietary sources of choline. Proposed that intestinal microflora have a role in TMAO formation from dietary free choline.

$\text{PC-rich food} \xrightarrow{\text{via TMA}} \text{Phosphatidylcholine} \xrightarrow{\text{Choline}} \text{TMAO}$

$\Delta \text{Concentration (µM)}$

$0 \ 0 \ 0 \ 0 \ 0 \ 2 \ 4$

$\text{Time (h)}$

$\Delta \text{Concentration (µM)}$

$0 \ 0 \ 0 \ 0 \ 0 \ 1.6 \ 3.2$

$\text{Time (h)}$

$\text{Betaine} \ x \ 
\text{Choline} \ x \ 
\text{TMAO} \ x$

$\text{Mouse fed } d^9\text{-choline}$

$\text{Antibiotics}$

$\text{No } d^9\text{-TMAO}$

Plasma levels of choline, TMAO and betaine were associated with atherosclerosis risk in humans.

**Atherosclerosis-prone mouse fed TMAO or choline**

- **Promoted atherosclerosis (x3!)**

**Mouse pretreated with antibiotics**

- **No effect on atherosclerosis**

**TMAO and Cardiovascular Disease**

Role of TMAO in promoting atherosclerosis is controversial

However, *TMAO has been shown to be an excellent biomarker for predisease*

Choline-rich diet led to *plaque instability* in prone mice *but not atherosclerosis*

*TMAO aggravates atherogenesis in prone individuals primarily though plaque instability*
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Interventions

Untargeted

Exercise

Diet

Fecal Microbiota Transplant

Pro/pre/post biotics

General improvement in microbial composition and function

Targeted

Phage Therapy

CRISPR Cas9

Bioengineered Commensals

Drugs targeting metabolism

Specific modification in metabolism-related gut microbiota

Pedersen, O.; Fan, Y. Nat. Rev. Microbiol. 2021, 19, 55
Diet

Diets high in saturated or monounsaturated fat negatively influence the microbiota whereas diets high in polyunsaturated fat are neutral.

High polysaccharide diets are beneficial and lead to:

- altered gut microbiota with increased faecal, serum of urine concentrations of SCFAs
- weight loss
- improvements of cytokine and metabolome profiles

**Diet**

- **Diet high in vegetable fibers**
  - (low in animal fat/protein)
  - Indigestable polysaccharides
  - Fermented by beneficial bacteria
  - Short chain fatty acids (SCFAs)
  - Beneficial effects to host

- **Diet high in animal fat/protein**
  - (low in vegetable fibers)
  - No fermentable polysaccharides, microbes switch to *amino acids*
  - Fermented by harmful bacteria
  - Acidic products => increase in pH
  - Causes leakage of molecules into blood, triggering inflammation and IR

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Pre-, pro- and postbiotics deliver microorganisms or substrates that provide health benefit to host.

**Prebiotics**

Substrate

**Probiotics**

Micro-organisms

**Postbiotics**

Metabolites

(+ microbes sometimes)

Probiotic strains *Lactobacillus*, *Bifidobacterium* and *Saccharomyce* have a long history of safe and effective use.

Clinical indications for multiple diseases (e.g. IBS, *H. pylori*) although more studies needed (no official recommendation).

Pre-, Pro-, Postbiotics

Prebiotic and post studies lag behind probiotic studies, although many promising studies

Oligo-fructose-enriched inulin prebiotics alter the intestinal microbiota and modestly reduce body weight, adiposity and inflammatory markers in obese children

Pasteurized A.muciniphila and its membrane protein Amuic_1100 demonstrated positive effects on markers of human metabolism

Dewulf, E. M. Gut 2013, 62, 1112
Bio-engineered Commensals

Bio-engineered commensals ➔ Genetically modified microbes

Recent promising examples:

E. Coli overexpressing N-acylphosphatidylethanolamine alleviates diet-induced obesity and insulin resistance

L. Gasseri strain engineered to express and secrete GIP-1 increased insulin release and reduced hyperglycemia in diabetic mice

Is delivering genetically modified organisms carrying microbial genes to the human gut acceptable?

Duan, F. F.; Liu, J. H.; March, J. C. Diabetes 2015, 64, 1794
Targeting specific microbial-synthesized metabolites by delivering tailored drugs - an emerging frontier

**TMA inhibition - an early success:**

**DMB, an inhibitor of TMA, inhibited choline diet-enhanced atherosclerosis in mice**

**Function of metabolites is highly context-dependent making therapeutic use challenging**

**Ongoing clinical trials:**

- **DMB**
  - Inhibition of TMA and subsequent inflammation in mice
  - Clinical trial in phase 3

- **TMAO**
  - Inhibition of cholesterol synthesis and atherosclerosis in mice
  - Clinical trial in phase 2

- **SCFAs**
  - Inhibition of inflammation and atherosclerosis in mice
  - Clinical trial in phase 4

- **Ketoconazole**
  - Inhibition of cholesterol synthesis and atherosclerosis in mice
  - Clinical trial in phase 3
Heterologous and Autologous Fecal Microbiota Transplantation

Fecal Microbiota Transplantation

Stool or stool microbiota is transplanted into patient

Autologous = use of own feces from a healthier state
Heterologous = using feces from a healthy donor

For recurrent C. difficile infection, FT is the only true effective treatment!

Heterologous and Autologous Fecal Microbiota Transplantation

Unknown whether heterologous FMT will be an option in preventing or treating more complex diseases

Potential indications examples:
IBD, IBS, Crohn’s, T2D, Obesity, Autoimmune Disorders, Parkinson’s

Multiple challenges for heterologous FMT:

- Immunological compatibility between donor and recipient
- Importance of dieting for stool survival unknown
- Role of bacteriophages/fungi for successful FMT unknown

Autologous FMT would be much less complicated, but feasibility and efficacy unknown

Pedersen, O.; Fan, Y. Nat. Rev. Microbiol. 2021, 19, 55
Conclusions

This research field is still young both in its basic and translational directions

Little of the novel knowledge has been validated or has matured to a stage where it can guide public health or clinical practice

Need to find the hundreds of unknown microbial-derived chemical compounds, and investigate their significance

Incomplete microbial genome databases and lack of functional annotation for most microbial genes makes interpretation of metabolome profiling challenging
Questions?

Gut microbiota in human metabolic health and disease

Figures created with BioRender.com
Case Study: SCFAs and Energy Homeostasis and Body Adiposity

Glucose metabolism more responsive to butyrate supplementation in lean individuals than those with metabolic syndrome

Need more studies testing combinations and different concentrations of SCFAs