You are what you feed your microbes
**WHAT IS THE MICROBIOME?**

The human body is home to trillions of microbes. The community of microbes living in intimate association with our bodies, and the genes they contain, make up the human microbiome.

**WHERE ARE THEY? WHAT ARE THEY DOING?**

Wherever the human body is exposed to the outside world, there is a microbial community.

Our microbiome helps us extract energy and nutrients from the food we eat, and crowds out or inhibits pathogens.

**WAIT ... WHAT'S A MICROBE?**

A *microbe* is a microscopic organism - this includes viruses, bacteria, and fungi.

Not all microbes make us sick - the microbes in and on our bodies play many essential roles.

**WHO'S THERE?**

Cells in the human body:

- **Red**: fungal
- **Blue**: bacterial
- **Green**: human

**99%**

Microbes contribute an extra 2,000,000 genes to the 20,000 gene human genome.

**2.5lb**

2.5 LBS = WEIGHT of the microbiome

**5:1**

Viruses outnumber bacteria by about 5:1.

**3 PINTS = VOLUME**

3 PINTS = VOLUME of the microbiome
The gut microbiota is a diverse community of microbial species

The composition is affected by:

- age
- health status
- geography
- socioeconomic status
- dietary habits
These communities are extremely variable between people especially in terms of the less abundant organisms. There are stable and less stable individuals.
Spatial structure of microbial communities

A diet containing indigestible carbohydrates affects the mucous layer

When these carbohydrates are missing the community structure is lost

Gut bacteria can produce and modulate functional metabolites

- Digest resistant starch to SCFA that are anti-inflammatory, increase intestinal barrier, decrease intestinal pH
- Produce vitamins K2 and B12 important for bone density and folate metabolism, respectively.
- Produce the neuroactive amino acid GABA and appetite regulating peptides like leptin.
How can the microbiota be a biomarker?

Fermentation products as biomarkers and risk factors for cardiovascular disease
How can the microbiota be a biomarker?

Fermentation products as biomarkers and risk factors for cardiovascular disease
The “classic” view of the colon

- The large intestine (colon) absorbs salt and water; stores and eliminates stool
The “current” view of the colon

• The colonic environment is a crucial determinant of systemic health
  – Short chain fatty acid production (SCFA)
  – Conversion of bioactive substances (e.g. phytoestrogens) to enhance/delay absorption

• Bioactivity of the colon may be a marker of health
  – Total SCFA production and regional differences implicated in cancer, GI disorders (distal colon)
Fermentation products in the colon

- **Carbohydrates**
  - Lactate
  - Biomass
  - Gases (CO2, H2, CH4)
  - SCFA

- **Protein**
  - Amines
  - Phenols
  - Gases (CO2, H2, CH4)
  - Sulfides

- **Others**
  - Ammonia
  - Indoles
  - BCFA
SCFA production in the colon

- SCFA are organic acids with 1-6 carbons
- Principally arise from bacterial fermentation of
  - Carbohydrates: polysaccharide, oligosaccharide
  - Protein: protein, peptide, glycoprotein precursors

\[
\begin{align*}
\text{Acetic acid (acetate)} & \quad 60 \\
\text{Propionic acid (propionate)} & \quad 20 \\
\text{Butyric acid (butyrate)} & \quad 20
\end{align*}
\]
SCFA production in the colon

- Total amount of SCFA in the colon ranges:
  - 70 to 140 mM
  - 20 to 70 mM
SCFA production in the colon

Lignins, Cellulose, Hemicellulose

Pectins, Gums, Hemicelluloses

Beta-glucan, psyllium, glucomannan
SCFA absorption

- Can detect SCFA in feces and serum
- Rapid in the cecum and colon – only 5-10% lost to feces
- Concentration-dependent
  - Via diffusion of protonated SCFA (most)
  - Anion exchange (small amount)
SCFA metabolism

SCFA (Colon)

- Butyrate (70%)
- Acetate (50-70%)
- Propionate

Ceco-colonic epithelium

Liver

Residual acetate

Muscle

Acetate (50-70%) Propionate
SCFA as a biomarker of diet

- Intake of wheat bran or viscous fiber increases total SCFA production, as measured in feces

Fredstrom et al., JPEN, 1994
SCFA as a biomarker of diet

- Molar ratios of SCFA vary somewhat

Fredstrom et al., JPEN, 1994
SCFA as a biomarker of diet

- Different substrates may yield different propionate:acetate ratio

Luo et al., Am J Clin Nutr, 1996
SCFA as a biomarker of diet

- Intake of oat bran increased 14-hour mean serum acetate concentrations by 45% compared with wheat bran

Bridges et al., Am J Clin Nutr, 1992
Acetate is incorporated into cholesterol (precursor for synthesis)

Propionate can reduce incorporation of acetate into cholesterol in rat hepatocytes

Lin et al., Br J Nutr, 1995
In men, but not consistently women, A:P associated with higher cholesterol

Wolever et al., J. Nutr, 1996
Acetate + Propionate

Rectal infusion of propionate with acetate offsets the rise in TC and LDL-C with acetate

Antibiotics and cardiovascular risk

• The host gut microflora may influence cardiovascular risk
• Neomycin and metronidazole lower cholesterol
  – Metronizadole (reduces aerobes)
  – Ciprofloxacin (reduces anaerobes)
Antibiotics and cardiovascular risk

Jenkins et al., Metabolism, 2005
Impact on cardiovascular risk factors

- Bacterial composition may influence cardiovascular risk

Jenkins et al., Metabolism, 2005
Impact on cardiovascular risk factors

- Bacterial composition may influence cardiovascular risk
Impact on cardiovascular risk factors

• Bifidobacteria
  – Associated with secondary bile acid loss
  – May sequester cholesterol in the colon (small effect)
Impact on cardiovascular risk factors

- Bifidobacteria grow better on oligofructose or inulin than other carbohydrates

Wang & Gibson, J Appl Bacteriol, 1993
Considerations for using SCFA as biomarker

• Can be a rapid indicator of changes in fiber intake
• Where do we look?
  – Concentration in serum reflects absorption and production
  – Concentration in feces represents production and excretion
• Relative or absolute amounts?
  – Are the ratios physiologically/clinically significant
• What are longer-term effects?
Declaration

• I have served as an external advisor to the WHO’s Nutrition Guidelines Advisory Committee (2012-present)
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Bonus??
Acetate functions

• Principal SCFA in the colon
• Readily absorbed and transported to the liver
• Acetyl-CoA synthetase catalyzed reaction uses acetate for lipogenesis
• Can be a biomarker of colonic events
Propionate functions

• Formed via fixation of CO2 to succinate
• Formed from lactate and acrylate
• Substrate for hepatic gluconeogenesis
• May inhibit hepatic cholesterol synthesis (in vitro)
• Both a substrate and inhibitor of gluconeogenesis
  – Metabolized to methylmanolyl CoA and succinyl CoA (inhibit pyruvate carboxylase)
  – Enters glycolysis by depleting hepatic citrate
Butyrate functions

- Preferred fuel for colonic epithelial cells
- Regulates cell differentiation and proliferation
- 70-90% metabolized in colonocyte
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Fiber can alter SCFA in 2 ways

• Increasing fecal bulk, shorten transit time
• Increase fermentable substrate
• We can detect markers of increased fiber intake in the blood and feces

Wong, de Souza et al., J Clin Gastroenterol, 2006
Impact of diet on the human intestinal microbiota

Current Opinion in Food Science, Volume 2, 2015, 71–77
the very plasticity that makes the gut microbiota an attractive therapeutic avenue can result in unintentional and maladaptive changes