Diet, the Gut Microbiome and Cancer

Johanna W. Lampe, PhD, RD
Fred Hutchinson Cancer Research Center,
Seattle, WA
jlampe@fredhutch.org
Dietary Exposures and Cellular Processes Linked to Cancer

Involvement of Microbial Metabolism

- Differentiation
- DNA repair
- Carcinogen metabolism
- Proliferation
- Hormonal regulation
- Apoptosis
- Inflammation
- Immune function

Adapted from WCRF/AICR 2007 Expert Report
Outline

- How does diet affect gut microbial community?
- How does the gut microbiome affect components of diet?
Gut Microbial Metabolism

- Obtain energy and nutrients to live and reproduce
- Microbiome: >100 times as many genes as human genome
- Carry out reactions that human gut enzymes cannot
  - Fermentation
  - Denitrification
  - Sulfate reduction
  - Aromatic fission
  - Hydrolysis/deconjugation

Diagram:
- Food enters the body.
- Human digestion: The indigestibles.
- Bacterial metabolism: The leftovers.
Fermentation of Carbohydrates: Sugars, Dietary Fiber and Resistant Starch

>81 different glycoside hydrolase families

Gill et al, Science, 2006
Microbial Metabolism of Proteins & Amino Acids

- Proteins Peptides
  - hydrolysis
  - Aromatic Amino acids
    - Phenols and indoles
    - α, β elimination
  - Other Amino acids
    - Ammonia NH$_3^+$/NH$_4^-$
    - deamination
    - Amines
    - deamination & fermentation
    - decarboxylation
  - Sulfur Amino acids
    - H$_2$, CO$_2$, CH$_4$
    - Organic acids
    - Sulfur compounds

Adapted from Nyangale et al. J Proteome Res, 2012
Gut Microbiome and Dietary Fats

- Metabolism of lipids
- Bile acid metabolism
  - Primary to secondary bile acids
  - Altered microbial community
  - Changes in signaling to liver

How does diet affect the gut microbiome? Evidence from:

Observational studies
- Globally distinct populations
- Long-term food pattern consumption

Short-term dietary interventions
- Low- vs high-fiber diets
- Animal vs plant food sources
- Macronutrient ratios

Global Population Differences: African-Americans in US vs Native South Africans

Microbiota Change with Diet Switch in African Americans and Native South Africans

- 2-wk feeding study

US AAs fed:
- Fiber: 14→55g/d
- Fat: 35→16%

Native Africans fed:
- Fiber: 66→12g/d
- Fat: 16→52%

Diet Pattern Change and Gut Microbiome: Fat & Fiber and Colorectal Cancer Risk Factors

- High-fiber, low-fat diet changed microbiome:
  - Increased saccharolytic fermentation and butyrate production
  - Decreased secondary bile acid synthesis

- Functional changes in gut microbiota were accompanied by colorectal cancer relevant changes in colonic mucosal proliferation and inflammation

Short-Term Feeding of Plant- and Animal-Based Diets Alters Gut Microbiota

- 10 subjects tracked across plant- and animal-based diet treatments.
- Animal-based diet increased bile-tolerant microorganisms and decreased microbes that metabolize plant polysaccharides.
- Bacterial metabolic gene expression (RNA-seq) tends to cluster by diet.
- Diet doesn’t always overcome inter-individual differences in GMC structure (16S rRNA).

Diet Patterns and Gut Microbiome: Controlled Low and High-Glycemic Load Diets

4-week randomized crossover feeding study in 12 healthy U.S. men and women.

Eucaloric diets with same macronutrient distribution, except:
- Low GL: 55 g fiber
- High GL: 28 g fiber

Discriminant analysis of microbiome distinguishes by diet

Neuhausser et al, J Nutr 2012
Hullar & Lampe, unpublished data, 2016
Multigenerational Effects of Diet on Bacterial Diversity

How does the gut microbiome affect diet?

- Alters exposure to nutrients and bioactives
- Generates new compounds, which:
  - Serve as energy source
  - Regulate metabolism
  - Reduce inflammation
  - Cause oxidative stress
## Bacteria Can Produce New Compounds from Food Components

<table>
<thead>
<tr>
<th>Food Component</th>
<th>Bacterial Metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary fiber</td>
<td>Butyrate and other SCFAs</td>
</tr>
<tr>
<td>Choline</td>
<td>Trimethylamine</td>
</tr>
<tr>
<td>Soy isoflavones</td>
<td>Equol, O-desmethylandolensin</td>
</tr>
<tr>
<td>Plant lignans</td>
<td>Enterodiol, enterolactone</td>
</tr>
<tr>
<td>Ellagitannins</td>
<td>Urolithins A and B</td>
</tr>
<tr>
<td>Anthocyanins</td>
<td>Hippuric acid &amp; small phenolics</td>
</tr>
<tr>
<td>Glucosinolates</td>
<td>Isothiocyanates</td>
</tr>
<tr>
<td>Linoleic Acid</td>
<td>Conjugated linoleic acid</td>
</tr>
</tbody>
</table>
Diet-Microbial Community Interaction Affects Exposure to Dietary Metabolites

- 17 obese men, randomized cross-over design
- 4 weeks of weight-reduction diets:
  - high-protein; med carb
  - high-protein; low-carb
- HPLC diet resulted in decrease in fecal cancer-protective metabolites (butyrate) and increased concentrations of hazardous metabolites (\(N\)-nitroso compounds).

<table>
<thead>
<tr>
<th></th>
<th>M</th>
<th>HPMC</th>
<th>HPLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein, %</td>
<td>13</td>
<td>28</td>
<td>29</td>
</tr>
<tr>
<td>Fat, %</td>
<td>37</td>
<td>37</td>
<td>66</td>
</tr>
<tr>
<td>Carb, %</td>
<td>50</td>
<td>35</td>
<td>5</td>
</tr>
<tr>
<td>NSP, g</td>
<td>22</td>
<td>9</td>
<td>13</td>
</tr>
</tbody>
</table>

a,b,c significantly different p<0.001

Choline Metabolism, TMAO, and Cancer?

- Shared risk factors with atherosclerosis:
  - Oxidative stress
  - Inflammation
  - Insulin resistance

- TMAO and aggressive prostate cancer in ATBC:
  - OR: 1.36 (1.02–1.81), p=0.039

- Choline metabolites and colorectal cancer in WHI:
  - OR: 1.65 (1.17-2.34)

Mondul et al. *Int J Cancer*, 2015
Bae et al, *Cancer Res*, 2014
Anthocyanin Metabolism by Gut Microbes

- Higher consumption of high-anthocyanin foods inversely associated with risk of hypertension and CVD mortality.
- Low bioavailability of parent compounds.
- Microbial hydrolysis of glucosides and ring cleavage yield range of small phenolics detected in serum and urine.

Metabolic Phenotypes: Microbial Production of Equol and ODMA From Soy Isoflavone Daidzein

- Daidzein
- Dihydroadaidzein
- Cis/Trans-isoflavan-4-ol
- O-Desmethylangolensin
- Equol

80-90% of individuals produce O-Desmethylangolensin

20-60% of individuals produce Equol
Daidzein-Metabolizing Phenotypes and Cardiovascular Risk among 595 Chinese Postmenopausal Women

- Equol producers, compared to nonproducers, had:
  - Higher fat-free mass
  - Lower systolic and diastolic blood pressure
  - Lower serum triglyceride, hs-CRP and FFA

- O-DMA producers, compared to nonproducers, had:
  - Lower BMI and %body fat
  - Lower total cholesterol

- Habitual soy isoflavone intake had little relation to CVD risk factors in either metabolizing phenotype.

Obese Adults More Likely to be ODMA-Nonproducer Phenotype

<table>
<thead>
<tr>
<th></th>
<th>18 to &lt;25 kg/m²</th>
<th>25 to 29.9 kg/m²</th>
<th>30+ kg/m²</th>
<th>P-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>ODMA producers n (%)</td>
<td>142 (59.9)</td>
<td>71 (30.0)</td>
<td>24 (10.1)</td>
<td></td>
</tr>
<tr>
<td>ODMA nonproducers</td>
<td>29 (48.3)</td>
<td>17 (28.3)</td>
<td>14 (23.3)</td>
<td></td>
</tr>
<tr>
<td>OR*</td>
<td>REF</td>
<td>1.0 (0.5, 2.1)</td>
<td>2.8 (1.2, 6.2)</td>
<td>0.032</td>
</tr>
<tr>
<td>Equol producers n (%)</td>
<td>77 (62.1)</td>
<td>32 (25.8)</td>
<td>15 (12.1)</td>
<td></td>
</tr>
<tr>
<td>Equol nonproducers</td>
<td>94 (54.3)</td>
<td>56 (32.4)</td>
<td>23 (13.3)</td>
<td></td>
</tr>
<tr>
<td>OR*</td>
<td>REF</td>
<td>1.3 (0.7, 2.2)</td>
<td>1.1 (0.5, 2.2)</td>
<td>0.629</td>
</tr>
</tbody>
</table>

*n=297; adjusted for age (in years), race, and gender and menopausal status.
Enterolignan Production by Gut Bacteria

**LEGEND:**
1. O-deglycosylation
2. O-demethylation
3. dehydrogenation
4. dehydroxylation

- Secoisolariciresinol Diglucoside
- Secoisolariciresinol
- Enterolactone (ENL)
- Enterodiol (END)

2,3-bis(3,4-dihydroxybenzyl)butyrolactone
Gut Microbial Diversity Differs by Tertiles of Urinary Enterolactone Excretion

Hullar et al, *CEBP*, 2015
Gut Microbiome Associated with Urinary Enterolactone (ENL) Excretion

- GMC composition is significantly different between high and low ENL excreters (MRPP, p<0.0005).
- Association remains significant with adjustment for fiber intake and adiposity.
- Low ENL clusters together

Hullar et al, CEBP, 2015
Phylogenetic Distribution of Microbiome in High-ENL Excreters

- Unique genera high ENL excreters
- Distributed across Phyla
Summary

- Diet can change the gut microbiome and its impact on the host.
  - Is it the microbe itself or a consortia of microbes?
  - Is it the metabolites produced by microbes?
  - Or the combination of both?

- Availability of nutrients or bioactive substances important for health can be influenced by gut microbiota.

- Metabolic phenotypes integrate diet and microbial action.

- Better understanding the impact of the bacterial metabolites on regulatory pathways may help guide future diet and cancer prevention strategies.