The microbiome and obesity

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Dietary Modulation of the Microbiome and Cancer Risk

2016 AICR Research Conference – Bethesda, Maryland
Prevalence of “New Age” disorders has increased over the past half century

<table>
<thead>
<tr>
<th>Year</th>
<th>Type 2 Diabetes Prevalence</th>
<th>Obesity Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>No Data</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>2000</td>
<td>&lt;4.5%</td>
<td>10–13.9%</td>
</tr>
<tr>
<td>2010</td>
<td>4.5%–5.9%</td>
<td>&lt;14%</td>
</tr>
<tr>
<td></td>
<td>6.0%–7.4%</td>
<td>14–17.9%</td>
</tr>
<tr>
<td></td>
<td>7.5%–8.9%</td>
<td>18–21.9%</td>
</tr>
<tr>
<td></td>
<td>&gt;9.0%</td>
<td>22.0%–25.9%</td>
</tr>
</tbody>
</table>

Source: Behavioral Risk Factor Surveillance System, CDC
Development of obesity is multi-factorial and complex.
What might be contributing to the increasing prevalence of “Western” disorders?
Diet shapes gut bacteria profiles in humans

- Different dietary intake results in differences in gut bacteria

  - A.) Burkina Faso, Africa
    - Dietary intake, ages 1-6
      - 672.2 – 996.1 kcal/day
        » Protein: 30.9 - 40.2g
        » Fat: 18.9 - 31.2g
        » Carbohydrate: 102.6 – 148.6g
  
  - B.) European Union, Italy
    - Dietary intake, ages 1-6
      - 1068.7 – 1512.7 kcal/day
        » Protein: 41.9 – 66.7g
        » Fat: 56.1 – 73.9g
        » Carbohydrate: 190.0 – 290.0g

FMT from lean donors improves insulin sensitivity in obese subjects

*Improved symptoms of Type II Diabetes and Metabolic syndrome

Lean male donors  
Obese male recipients BMI ≥ 30

Vrieze et al., Gastro. (2012) 143:913-916
Germ-free mice are resistant to diet-induced obesity

Standard environment
+ Microbes

Germ-free environment
- Microbes

Low Fat diet
Lean

High Fat diet
Obese

Low fat or High Fat diet
Lean
Germ-free mice exhibit altered metabolic response to Western diets compared to controls.

Backhed et al, 2004; Backhed et al, 2007
Proposed mechanisms for the role of microbes in diet-induced obesity

Melo Carvalho and Abdalla Saad, Mediators of Inflammation, 2013
Hepatic genes up-regulated in germ-free (GF) vs. conventionalized mice

- Androgen and Estrogen Metabolism
- PXR/RXR Activation
- Methionine Metabolism
- LXR/RXR Activation
- Fatty Acid Metabolism
- Linoleic Acid Metabolism
- Circadian Rhythm Signaling
- Xenobiotic Metabolism Signaling
- Metabolism of Xenobiotics by Cytochrome P450
- Biosynthesis of Steroids
- LPS/IL-1 Mediated Inhibition of RXR Function

Leone, et al., Cell Host & Microbe. 2015
Relationship between circadian clock and nuclear receptors

Leone, et al., Cell Host & Microbe. 2015
Circadian clock networks regulate daily metabolic functions

Circadian clock alterations in some cancers

<table>
<thead>
<tr>
<th></th>
<th>Activators</th>
<th>Repressors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clock KO</td>
<td>Bmal1 KO</td>
</tr>
<tr>
<td>Rhythmic in DD</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Period length</td>
<td>Slightly shorter</td>
<td>Arrhythmic</td>
</tr>
<tr>
<td>Peripheral tissues</td>
<td>Arrhythmic</td>
<td>Arrhythmic</td>
</tr>
<tr>
<td>Body weight</td>
<td>Increased</td>
<td>Reduced</td>
</tr>
</tbody>
</table>

Yu and Weaver, 2011
## Circadian clock alterations in some cancers

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Gene</th>
<th>Modification</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic and familiar breast tumors</td>
<td><em>Per1, Per2</em></td>
<td>Decreased expression</td>
<td>Winter et al., 2007</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td><em>Per1, Per2, Cry1</em></td>
<td>CPG methylation</td>
<td>Shih et al., 2006</td>
</tr>
<tr>
<td>Colon cancer</td>
<td><em>Per2</em></td>
<td>Downregulation</td>
<td>Faustino et al., 2008; Wood PA, et al., 2009</td>
</tr>
<tr>
<td>Non-Hodgkins lymphoma</td>
<td><em>Bmal1</em></td>
<td>CPG hypermethylation</td>
<td>Taniguchi et al., 2009</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td><em>Bmal1</em></td>
<td>Decreased expression</td>
<td>Jung-Hynes et al., 2010</td>
</tr>
</tbody>
</table>

Adapted from Savvidis and Koutsilieris. 2012
Hypothesis

Diet-induced gut microbiota provide critical inputs that regulate circadian gene networks, affecting metabolic outcome.

• Do GF mice exhibit altered circadian gene expression patterns on low fat (regular chow) and high fat diets?

• Do gut microbes exhibit diurnal patterns, and are these patterns altered under high-fat feeding conditions?

• If so, how are these patterns regulated?
Germ-free mice are resistant to high fat (HF) diet-induced obesity

Body weight

Caloric consumption

Leone, et al., Cell Host & Microbe. 2015

\( n = 17 \) or \( 18 \) age-matched, individually housed male mice/trt group

***\( p<0.001; \) **\( p<0.01; \) *\( p<0.05 \)
Germ-free mice exhibit altered central and peripheral circadian gene expression

Leone, et al., Cell Host & Microbe. 2015

\( n = 2 \) or \( 3 \) mice/time point/trt group; Zeitgeber (ZT) 0 = lights on, 6am; ZT12 = lights off, 6pm
High fat diet elicits shifts in gut microbial membership

PCoA: PC1 versus PC2

PC1 – 56.2%

PC2 – 13.9%

HF

RC

HF

RC

Zeitgeber Time (ZT)

= ZT 2

= ZT 6

= ZT 10

= ZT 14

= ZT 18

= ZT 22

Leone, et al., Cell Host & Microbe. 2015

n = 2 or 3 mice/time point/trt group; Zeitgeber (ZT) 0 = lights on, 6am; ZT12 = lights off, 6pm
High fat diet alters diurnal oscillations of specific 16S rRNA operational taxonomic units (OTUs)

Leone, et al., Cell Host & Microbe. 2015

n = 2 or 3 mice/time point/trt group; Zeitgeber (ZT) 0 = lights on, 6am; ZT12 = lights off, 6pm
High fat diet alters diurnal oscillations of gut microbiota function

Leone, et al., Cell Host & Microbe. 2015

$n = 2$ or $3$ mice/time point/trt group; Zeitgeber (ZT) 0 = lights on, 6am; ZT12 = lights off, 6pm
High fat diet impacts diurnal patterns of known microbially-produced metabolites

Leone, et al., Cell Host & Microbe. 2015

$n = 2$ or $3$ mice/time point/trt group; Zeitgeber (ZT) $0 =$ lights on, 6am; ZT12 = lights off, 6pm
Microbial metabolites elicit a direct impact on hepatic circadian gene expression in vitro

Leone, et al., Cell Host & Microbe. 2015
Butyrate elicits a direct impact on hepatic circadian gene expression in vivo

Leone, et al., Cell Host & Microbe. 2015
Timed butyrate delivery restores liver circadian gene expression and reduces adipose tissue in high fat fed mice

Leone, et al., unpublished data

$n = 4$ mice/trt group
Gut microbes sense dietary cues that translate into outputs that maintain circadian networks.

**Dietary intake**
- When
- How much
- What

**Gut microbiota**
- Microbial Oscillations
- Metabolome

**Circadian Networks**
- Shift work
- Sleep apnea
- Jet lag

- Microbial signals

**Examples**
- High fat diet

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Image source: THE UNIVERSITY OF CHICAGO BIOLOGICAL SCIENCES
High-fat diet induced gut microbiota lack outputs that are required for maintenance of circadian networks.
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Sunrise from the Knapp Center for Biomedical Discovery after a long circadian study

The microbiome and obesity 27