Intestinal Microbiota and Circadian Rhythms

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Outline

• Microbiota and its importance for health and disease states
• What are circadian rhythms? - What are the causes and consequences of disruption of the circadian clock?
• Circadian rhythms and microbiota interaction
Composition & Luminal Concentrations of Dominant Microbial Species in the GI Tract

Microbiota Effects on Physiology

**Metabolism**
- Energy expenditure \(\downarrow\)
- Nutrient accessibility \(\uparrow\)
- Short-chain fatty acids \(\uparrow\)
- Adiposity \(\uparrow\)

**Behaviour**
- Synaptic connectivity \(\downarrow\)
- Anxiety \(\uparrow\)
- Pain perception \(\uparrow\)

**Intestinal function**
- GALT maturation \(\uparrow\)
- Tissue regeneration \(\uparrow\)
- Gut motility \(\uparrow\)
- Permeability \(\uparrow\)

**Intestinal vessel formation**
- TF glycosylation \(\downarrow\)
- Thrombin cleavage \(\downarrow\)
- PAR1 activation \(\downarrow\)
- TF phosphorylation \(\downarrow\)
- ANG1 expression \(\downarrow\)
- Vascularization

**Bone homeostasis**
- \(T_{\mu}17\) cells \(\uparrow\)
- TNF in colon and bone \(\uparrow\)
- Osteoclastogenesis \(\uparrow\)
- Bone mass

*Nature Reviews Microbiology* 11, 2013
Microbiome-Host Interactions

Epigenetics, Diet, Life Style, Stress, Aging, Xenobiotics, (drugs, antimicrobial agents, pollutants) and Idiopathic factors

Dysbiotic gut microbiota

Altered microbe host interactions

Pathogen

Mutualistic microbiota

Inflammatory

Metabolic

Neurological

Pathological

Tumorigenesis

Diseases

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Microbiota and Disease

Liver Disease

Imbalanced microbiota

Neurodegenerative diseases

IBD, IBS & CRC

Gastric diseases

Metabolic diseases

Journal of Cellular Physiology 11 FEB 2016 DOI: 10.1002/jcp.25284
Influences on the Intestinal Microbiota

Nature Reviews Microbiology

11, 2013
Clustering of Gut Microbial Taxa into Enterotypes is Associated with Long-Term Diet

G D Wu et al. Science 2011;334:105-108
Diet Drives the Gut Microbiota

De Filippo C et al. PNAS. 2010;107:14691.
Sleep Deprived, Circadian Misaligned
Outline

• Microbiota and its importance for health and disease states
• What are circadian rhythms? What are the causes and consequences of disruption of the circadian clock?
• Circadian rhythms and microbiota interaction
What are Circadian Rhythms?

- A circadian rhythm is any biological process that displays an endogenous, entrainable, oscillation of ~24h
  - *Endogenous*: self-sustained
  - *Entrainable*: adjust to cues in the environment
  - *Circadian* comes from the Latin words *circa* ("around") and *diēs* ("day")
What are Circadian Rhythms?

• Allow an organism to prepare for predictable changes in the environment
  – Light:dark cycles
  – Food availability
  – Physical demands

• Regulate nearly everything!

What are Circadian Rhythms?

- Highest testosterone secretion: 09:00
- Bowel movement likely: 08:30
- Melatonin secretion stops: 07:30
- Sharpest rise in blood pressure: 06:45
- Lowest body temperature: 04:30
- Deepest sleep: 02:00
- Noon: 12:00
- High alertness: 10:00
- 14:30: Best coordination
- 15:30: Fastest reaction time
- Greatest cardiovascular efficiency and muscle strength: 17:00
- 18:00
- 18:30: Highest blood pressure
- 19:00: Highest body temperature
- 21:00: Melatonin secretion starts
- 22:30: Bowel movements suppressed

 Eyesfornews.com
The Molecular Circadian Clock

- Rhythms are driven by a molecular circadian clock via a negative feedback loop

What Sets the Circadian Clock?

Peripheral Clocks

Maury et al., Circ Res 2010
Central & Peripheral Circadian Rhythms Misalignment

Normal Central / Peripheral Rhythms

Central Circadian Clock
Suprachiasmatic nucleus (SCN)

Peripheral Circadian Clocks

Disorganized Central / Peripheral Rhythms (e.g., wrong-time eating)

Central Circadian Clock
Suprachiasmatic nucleus (SCN)

Peripheral Circadian Clocks
Triggers that Disrupt Circadian Rhythms
Social Jet Lag

Till Roenneberg
Artificial Night Sky Brightness due to Light Pollution in North America
A preliminary picture of the growth from 1950 to 2025
Diseases Associated with Shift Work

• Obesity, NASH
• Metabolic Syndrome, Diabetes
• Cancer (breast, prostate, & colon)
• Cardiovascular Disease
• Inflammatory Bowel Disease (IBD)
• Irritable Bowel Syndrome (IBS)
• Alcoholic liver disease

Inflammation
Inflammation

What is the source of “sterile inflammation?”

Intestinal Microbiota
Can Circadian Disruption Disrupt Microbiota Composition or Function?
Fecal Microbiota Analysis in Day Shift and Night Shift Workers

(A) Peptostreptococcaceae
(B) Turicibacteraceae
(C) Clostridiaceae
(D) Pseudomonadaceae

Day Shift Workers

Night Shift Workers

PCA PC1: 53.8% Variance
PCA PC2: 25.13% Variance
Butyrate Production as a Ratio of Total SCFA Production

Day Shift Worker
Night Shift Worker

Butyrate Production as a Ratio of Total SCFA Production

p<0.05

Ratio Butyrate to SCFA

0:00 06:00 12:00 18:00 0:00

0:00 06:00 12:00 18:00 0:00

Time

Day Shift
Night Shift

*
Serum LBP in Day Shift & Night Shift Workers
Plasma IL6 in Day Shift and Night Shift Workers
Microbiota Dysbiosis is Associated with Metabolic Consequences

Thaiss et al, Cell, 159: 514-529, 2014
Monitoring Circadian Rhythms: Behavior
Environmental Disruption Alters the Microbiota Under “Challenging” Conditions

Circadian Rhythms is Conserved Across Multiple Kingdoms

- Rhythms are observed across multiple kingdoms & each (archaea, bacteria, eukarya) has a different molecular clock to coordinate biological functions
Intestinal Microbiota Exhibit Diurnal Oscillations

>15% of bacterial OTUs have diurnal fluctuations!!!

Thaiss et al., Cell, 159: 514-529, 2014
High-Fat Diet Shifts Diurnal Microbial Function and Metabolite Production
Microbiota Diurnal Oscillations are Controlled by Feeding Time

Most cycling OTUs exhibit a phase shift of ~12h with different feeding times.
Don’t Forget About the Bacteria!

- Intestinal microbiota have circadian rhythms! And they are critical for optimal functioning of the intestinal epithelium (intestinal barrier function)

**Homeostasis in Intestinal Epithelium Is Orchestrated by the Circadian Clock and Microbiota Cues Transduced by TLRs**

Atish Mukherji, Ahmad Kobiita, Tao Ye, and Pierre Chambon.
Transkingdom Control of Microbiota Diurnal Oscillations Promotes Metabolic Homeostasis

Christoph A. Thaiss,1 David Zeevi,2 Maayan Levy,1 Gili Zilberman-Schapira,1 Jotham Suez,1 Anouk C. Tengeler,1 Lior Abramson,1 Meirav N. Katz,1,3 Tal Korem,2 Niv Zmora,3,4,5 Yael Kuperman,6 Inbal Biton,6 Shlomit Gilad,7 Alon Harmelin,6 Hagit Shapiro,1 Zamir Halpern,3,5 Eran Segal,2 and Eran Elinav1,*

Thaiss et al, Cell, 159: 514-529, 2014
Statue Returns to Italy

After a two-year visit to the United States, Michelangelo’s David is returning to Italy…..
His Proud Sponsors in the U.S. were:
Dysbiosis is an “imbalance in the structure and/or function of the microbiota that leads to disruption of host-microorganism homeostasis”
Microbiota and Bioinformatics Collaboration Team

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AA020216: Brain-Gut Interactions in Alcohol-Induced Gut Leakiness
AA023417: Role of Alcohol and Circadian Disruption in Inflammation & Colon Cancer
AA019966: Circadian Desynchrony in Alcohol Induced Gut Leakiness