Gut Microbiota: A Key Regulator of Brain and Metabolic Function

Dr. Cristina Torres Fuentes & Prof. John F. Cryan

APC Microbiome Institute, University College Cork, Cork, Ireland

University of Applied Sciences

February 9, 2017, Fribourg, Switzerland
APC Microbiome Institute, Cork, Ireland

Prof. John Cryan and Prof. Ted Dinan

Dr. Harriet Schellekens

Prof. Catherine Stanton
The Gut Microbiota

Unique composition to each individual

150 times more genes than in the human genome

Human genome
23,000 genes

Human microbiome
1,000,000+ genes

Are We Really Vastly Outnumbered? Revisiting the Ratio of Bacterial to Host Cells in Humans

Ron Sandler, 1 Shai Fuchs, 2, 3, * and Ron Milo 1, *  
1 Department of Plant and Environmental Sciences, Weizmann Institute of Science, Rehovot 7610001, Israel
2 Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 7610001, Israel
* Present address: Department of Pediatric Endocrinology and Metabolism, The Hospital for Sick Children, Toronto, ON M5G 1X8, Canada
* Correspondence: shai.fuchs@skidb.ca (S.F.), ron.milo@weizmann.ac.il (R.M.)

http://dx.doi.org/10.1096/cell.2016.01.013

It is often presented as common knowledge that, in the human body, bacteria outnumber human cells by a ratio of at least 10:1. Revisiting the question, we find that the ratio is much closer to 1:1.
Targeting the gut microbiota
Gut microbiota development

Dominguez-Bello et al., 2010: Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci USA. 2010;107[26]:11973

Ottman et al., 2012

Ottronia et al., 2012
Gut microbiota and brain function

Is there a connexion between the gut and the brain? Who is in control?
The Language of Gut-Brain Axis

“Follow your instincts. That’s where true wisdom manifests itself.”
KUSHANDWIZDOM
OPRAH

“Between gut instincts, gut feelings and gut reactions my abs get a great workout.”
ANDERSON

GUT FEELING

IDiomLAND.COM

GUT FEELINGS
GERD GIGERENZER

GUT INSTINCT IS YOUR GREATEST CRITIC
LYNN A. ROBINSON

trust your gut

HOW THE POWER OF INTUITION CAN GROW YOUR BUSINESS

Butterflies in My Stomach and Other School Hazards
by Serge Bloch

http://apc.ucc.ie
The Brain-Gut Axis

Basic Functions
- Motility
- Secretion
- Permeability
- Mucosal immunity

Complex Functions
- Visceral Pain
- Autonomic Nervous System
- Hunger/satiety
- Mood/Emotion
- Cognition

HPA axis

Enteric Nervous system

Vagus Nerve

Immune system

Dietary Permeability

Basic Functions

Complex Functions

Stress

Mood/Emotion
Ingestion of *Lactobacillus* strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve

Javier A. Bravo\(^{a,1}\), Paul Forsythe\(^{b,c,1}\), Marianne V. Chew\(^{b}\), Emily Escaravage\(^{b}\), Hélène M. Savignac\(^{a,d}\), Timothy G. Dinan\(^{a,e}\), John Bienenstock\(^{b,1,2}\), and John F. Cryan\(^{a,d,3,2}\)

\(^{a}\)Laboratory of NeuroGastroenterology, Alimentary Pharmabiotic Centre, \(^{b}\)School of Pharmacy, and Departments of \(^{c}\)Psychiatry and \(^{d}\)Anatomy, University College Cork, Cork, Ireland; \(^{e}\)The McMaster Brain–Body Institute, St. Joseph’s Healthcare, Hamilton, ON, Canada L8N 4A6, and Departments of \(^{f}\)Medicine and \(^{g}\)Pathology and Molecular Medicine, McMaster University, Hamilton, ON, Canada L8S 4L8

**Probiotics**
- *Lactobacillus rhamnosus* JB1
- *Bifidobacteria Longum* 1704

**Prebiotic**
- GOS/FOS

- **Reduced Anxiety**
- **Antidepressant-like Behaviour**
- **Enhanced Cognition**
- **Reduced Stress Response**

Bravo et al., PNAS Sept 2011;
Savignac et al Behav. Brain Res 2015
Burokas et al., Unpublished
The Brain-Gut Axis

Exaggerated stress response

Germ-Free

Sociability deficit

Brain development alterations

BLA hyperactivation and hippocampal hypoactivation

Sudo et al., J. Physiol, 2004
O’Mahony et al., Biol. Psychiatry, 2009
Bravo et al., PNAS, 2011

Sociability deficit

Three-chambered sociability test

Sociability

Mouse Empty

Conventional Germ free

Social Cognition

Novel Familiar

Conventional Germ free

Desbonnet et al., Mol Psychiatry, 2014


Hoban et al, Transl Psychiatry, 2016
Gut microbiota and Metabolic function

How the gut microbiota influence the metabolic function?
Microbiota-driven mechanisms of metabolism and appetite regulation

Torres-Fuentes et al., submitted to The Lancet Gastroenterology & Hepatology
Gut microbiota and Metabolic function

- **Alteration of microbiota** → increased adiposity and influences metabolic processes in peripheral organs:
  - Brain satiety control
  - Metabolism of lipids
  - Intestinal permeability alteration
  - Alteration of the capacity to harvest energy

**Gram-negative bacteria** → particularly Bacteroidetes

**Gram-positive bacteria** → particularly Firmicutes (which include Lactobacillus) and the class *Erysipelotrichi*.

The gut microbiota as an environmental factor that regulates fat storage

Fredrik Bäckhed*, Hao Ding††, Ting Wang†, Lora V. Hooper†**, Gou Young Koh††, Andras Nagy†***, Clay F. Semenkovich†††, and Jeffrey I. Gordon*†@@

*Center for Genome Sciences and Departments of †Molecular Biology and Pharmacology, ‡Genetics, and †††Medicine, Cell Biology, and Physiology, Washington University School of Medicine, St. Louis, MO 63110; †Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto, ON, Canada MSG 1X5; ‡Biomedical Center, Department of Biological Sciences, Korea Advanced Institute of Science and Technology, Daejeon, 305-701, Republic of Korea; and †††Department of Medical Genetics and Microbiology, University of Toronto, Toronto, ON, Canada M5S 1A8

Contributed by Jeffrey I. Gordon, September 24, 2004

Germ Free

60% increase in total body fat
2.3-fold increase in hepatic triglycerides
Dramatic increase in Insulin Resistance

40% less total body fat
caloric intake 29% higher
An obesity-associated gut microbiome with increased capacity for energy harvest

Peter J. Turnbaugh¹, Ruth E. Ley¹, Michael A. Mahowald¹, Vincent Magrini², Elaine R. Mardis¹,² & Jeffrey I. Gordon¹

The worldwide obesity epidemic is stimulating efforts to identify host and environmental factors that affect energy balance. Comparisons of the distal gut microbiota of genetically obese mice and their lean littermates, as well as those of obese and lean human volunteers have revealed that obesity is associated with changes in the relative abundance of the two dominant bacterial divisions, the Bacteroidetes and the Firmicutes. Here we demonstrate through metagenomic and biochemical analyses that these changes affect the metabolic potential of the mouse gut microbiota. Our results indicate that the obese microbiome has an increased capacity to harvest energy from the diet. Furthermore, this trait is transmissible: colonization of germ-free mice with an ‘obese microbiota’ results in a significantly greater increase in total body fat than colonization with a ‘lean microbiota’. These results identify the gut microbiota as an additional contributing factor to the pathophysiology of obesity.

©2006 Nature Publishing Group

Gut microbiota of obese individuals is more efficient at extracting energy from a given diet than the microbiota of lean individuals.

dramatic increase in body fat within 10–14 days
Gut microbiota and Metabolic function

Gut Microbiota from Twins Discordant for Obesity Modulate Metabolism in Mice

Ridaura et al., Sciences, 2013

Figures by Walker and Parkhill, Sciences, 2013
Bariatric surgery and Gut Microbiota

Conserved Shifts in the Gut Microbiota Due to Gastric Bypass Reduce Host Weight and Adiposity

Alice P. Liou\textsuperscript{1}, Melissa Paziuk\textsuperscript{1}, Jesus-Mario Luevano Jr.\textsuperscript{2}, Sriram Machineni\textsuperscript{1}, Peter J. Turnbaugh\textsuperscript{2,\textdagger}, and Lee M. Kaplan\textsuperscript{1,\textdagger}

\textbf{Gammaproteobacteria} and \textbf{Verrucomicrobia} (\textit{Akkermansia})

\textbf{Firmicutes}

Mice that underwent bariatric surgery

\textbf{Germ-free}

\textbf{weight loss and decreased fat mass}

\textit{Figure from Torres-Fuentes et al., submitted to The Lancet Gastroenterology & Hepatology}
Gut microbiota and brain function

Can we modulate the gut-brain axis?

Therapeutic potential?
Modulating the Gut Microbiota: Dietary interventions

Elie Metchnikoff (1845-1916)
Nobel Prize 1908

"live microorganisms which, when administered in adequate amounts, confer a health benefit on the host"

PROBIOTICS
PREBIOTICS
Non-digestible fibre
Psychobiotics

The Prolongation of Life: Optimistic Studies
Elie Metchnikoff
Pre/Pro-biotics and Obesity

Tissue inflammation and metabolic endotoxemia

- B. animalis (B420) (Burcelin, R. et al., 2011; Danisco SA patent)
- A. muciniphila (Everard, A. et al., 2013)
- Oligofructose (Everard et al 2014)

Abdominal adiposity and body weight

- L. gasseri (LG2055) (Kadooka, Y. et al., 2010/2011)
- L. gasseri (BNR17) (Kang, JH. et al., 2010)
- B. breve (B3) (Kondo, S. et al., 2010)
- L. rhamnosus (PL60) (Lee H.Y. et al., 2006)
- Oligofructose (Parnell et al., 2009)
- Inulin-type fructans (Dewulf et al, 2011)

Expression of tight junction proteins → Improvement of intestinal barrier function

- B. longum (ATCC 51870) and L. rhamnosus (ATCC 53103) (Sultana, R. et al., 2013)

Fasting glycaemia, insulinemia and triglyceridemia

- Arabinoxylan (Garcia et al 2006)

Appetite by increasing satiety hormones secretion

- VSL#3 probiotic (lactic acid bacteria cocktail) (Yadav, H. et al., 2013)
- inulin-type fructans (Cani et al, 2004)

PREBIOTICS normalize delayed colonic transit in obese mice

*Ex vivo* assay of colonic transit:

Whole colon is placed into an organ bath perfused with pre-warmed to 37°C carbogenated Krebs buffer at 4 mL/min.

**Spontaneous propagation of the artificial pellet (marked with *) along the colon in proximal-to-distal direction:**

Protocol adapted from:

Western populations have depleted diversity from birth through childbearing years & are missing bacterial taxa present in the traditional groups.

Rampelli et al., Cell 2015

Sonnenburg et al., Nature 2016
Modulating the Gut Microbiota: Faecal Microbiota Transplantation

500,000 Americans are affected by C. difficile each year.

30 THOUSAND patients die from C. difficile every year.

1 in 5 patients with C. difficile do not respond to antibiotics.
Behaviour phenotype transfer

NIH Swiss

BALB/c
High anxiety-like behaviour strain

GF

Collins et al., Current Opinion in Microbiology 2013
Gut microbiota and depressive-related behaviour

Healthy

Depressed

Microbiota Composition?

Faecal Microbiota Transplantation

Healthy rat

Rat with depressive-related symptoms (anxiety, anhedonia, inflammation)

Diversity

Kelly, RJ et al. 2016

Illustration adapted from Andrew Rae, NYT
Microbiota-Brain-Gut Axis

**Bioactives**

**STRESS**

**DIET/NUTRITION**

**PROBIOTICS & PREBIOTICS**

**ANTIBIOTICS**

**Intestinal epithelium**

- Microbiota
- Metabolites: SCFA, GABA, SHT neurotransmitters
- Nutrients

**Targets**

**Metabolism**

**Appetite**

**Digestive Health**

**Cognition**

**Mental Health**

**Ageing**

**Schellekens et al.,**

**Blood circulation**

**Vagus nerve**

**HPA axis**

- CRH
- ACTH
- Cortisol

**Ghrelin**

**Leptin, Adiponectin**

**GLP, PYY, CCK**

**Insulin**

**Immun e cells**

**Cytokines**

**Schellekens et al.,** Microbiota-Brain-Gut Axis
Summary

Cryan and Dinan, Nat Rev Neurosci Oct 2012
Dr. Kieran Rea
Dr. Cristina Torres
Dr. Anna Golubeva
Dr. Karen Scott
Dr. Cara Hueston
Dr. Roman Stilling
Dr. John Kelly
Dr. Jahangir Sajjad
Dr. Gerry Moloney
Dr. Andrew Allen
Dr. Paul Kennedy
Dr. Anand Gururajan
Dr. Eoin Sherwin
Dr. Kiran Sandu
Dr. Marcus Boehme
Dr. Gilliard Lach
Dr. Daniela Felice
Dr. Thorsten Becker
Dr. Barbara
Chruscicka
Patrick Fitzgerald
Matteo Pusceddu
Maria Donovan
James O’Leary
Ciaran O’Leime
Livja Morais
Alan Hoban
Clara Seira Oriach
Brunno Rocha
Levone
Veronica Peterson
Rory O’Connor
Anna Connolly
Surabi Theratike
Dalia Kandil
Eileen Curran
Pauline Luczynski,
Ruairi Robertson
Chjara Minuto
Clementine Druelle
Anne-Marie Cusack
Shauna Wallace-Fitzsimmons
Marcel van der Wouw
Karen O’Connor

Prof. Ted Dinan
Prof. Caitriona O’Driscoll
Prof. Fergus Shanahan
Dr. Yvonne Nolan
Prof. Ken O’Halloran
Dr. Ken Nally
Prof Ken O’Halloran
Dr. Niall P. Hyland
Dr. Siobhain O’Mahony
Dr. Brendan Griffin
Dr. Gerard McGlackan
Dr. Olivia O’Leary
Prof Louise Kenny

Prof. Geraldine Boylan
Dr. Gerard O’Keeffe
Dr. Ger Clarke
Dr. Harriet Schellekens
Prof Catherine Stanton
Prof Paul Ross
Dr. Paul Cotter
Prof Paul O’Toole
Prof Colin Hill
John Bienenstock/Paul Forsythe, McMaster University
Dr. Andrew Holmes, NIH, USA
‘The depression started when I realised how much I was spending on yoghurts’
Questions?