OPTIMIZING HEALTHSPAN:
The Microbiome
& The Gut-Brain Axis

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DISCLOSURES:

• Consultant for Diagnostic Solutions Laboratory

• Also consulted for Viome and Vibrant America
HEALTHSPAN:
Promoting long-term health in the context of aging ...
AGING:

Chronic inflammation plays a major role in aging & age-related diseases

= “Inflamm-aging”
The microbiome, aging & healthspan

2 The gut-brain axis: new insights

3 Toward improving healthspan with microbiome-based approaches
PART I:
The Microbiome, Aging & Healthspan
EVIDENCE

1. Aging and longevity in lab animals and humans

2. Effects of healthspan-promoting approaches
Aged Gut Microbiota Contributes to Systemical Inflammaging after Transfer to Germ-Free Mice.

• Tested whether gut microbiota contribute to age-related inflammation (“inflammaging”) by transferring gut microbes from young & old mice to young germ-free mice

• Gut microbes from old mice, but not young, increased signs of inflammation in recipient mice
A product produced by certain gut microbes, promoted longevity (in nematodes and fruit flies)

The product (colanic acid) had a positive impact on mitochondria and a type of cellular stress response (unfolded protein response)

Appears to promote longevity by promoting resilience
Signatures of early frailty in the gut microbiota.

The gut microbiota of centenarians: Signatures of longevity in the gut microbiota profile.

Gut microbiota changes in the extreme decades of human life: a focus on centenarians.
“Major taxonomic shifts and a consistent decrease in microbial richness and diversity have been reported in people 65 years of age and older and these changes were associated with worsening of health status and frailty. Similar findings were also obtained in mice.”
“The characterization of gut microbiota of centenarians revealed ... an enrichment in some subdominant health-associated groups (e.g., Akkermansia, Bifidobacterium, and Christensenellaceae)”
(Dis)Trust your gut: the gut microbiome in age-related inflammation, health, and disease

Thomas W. Buford

Abstract

Chronic inflammation represents one of the most consistent biologic features of aging. However, the precise etiology of persistent low-grade increases in inflammation remains unclear. Recent evidence suggests that the gut microbiome may play a key role in age-related inflammation. Indeed, several studies have indicated that older adults display an altered composition of the gut microbiota, and early evidence indicates that this dysbiosis is associated with the presence of several key circulating inflammatory analytes. The present review summarizes knowledge on age-related inflammation and discusses how potential relationships with gut dysbiosis may lead to novel treatment strategies in the future.

“The pattern of disease is an expression of the response of man to his total environment (physical, biological, and social); this response is, therefore, determined by anything that affects man himself or his environment.”

– Rene Dubos, 1961
Table 1. Overview of the main effects of a healthy gut microbiota on the physiologic processes involved in healthy, active aging.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Mediators/Mechanisms</th>
<th>Target Cells/Systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suppression of chronic inflammation, modulation of inflamm-aging</td>
<td>Down-regulation of Interleukin-6, Interleukin-8, Interleukin-10, Tumor Necrosis Factor-α</td>
<td>Neutrophils, activated lymphocytes, natural killer cells</td>
</tr>
<tr>
<td>Enhancement of antioxidant activity</td>
<td>Diet-derived polyphenols, ellagitannins, B complex vitamins</td>
<td>All of the host’s cells</td>
</tr>
<tr>
<td>Prevention of insulin resistance</td>
<td>Short-chain fatty acids, conjugated linoleic acid, gut peptides</td>
<td>Adipocytes, myocytes</td>
</tr>
<tr>
<td>Maintenance of gut barrier function</td>
<td>Reduced absorption of lipopolysaccharide and pro-inflammatory bacterial endotoxins</td>
<td>Neutrophils, activated lymphocytes, natural killer cells</td>
</tr>
<tr>
<td>Enhancement of xenobiotic metabolism and detoxification</td>
<td>Reduced absorption of xenobiotics by increased degradation in the gut</td>
<td>All of the host’s cells</td>
</tr>
<tr>
<td>Modulation of host gene expression</td>
<td>Butyrate, other bacterial metabolic products</td>
<td>Skeletal muscle, central nervous system, immune cells</td>
</tr>
</tbody>
</table>

KEY TAKE-HOMES:

1. Aging and associated diseases and conditions are associated with microbiome imbalances
KEY TAKE-HOMES:

2. Some microbiome features are associated with healthy aging and longevity
MICROBIOME IMBALANCE

- Decreased beneficial microbes
- Increased unfriendly microbes (e.g., pro-inflammatory)
- Imbalance + health consequences = “dysbiosis”
Beneficial Microbes: Examples

CLOSTRIDIA (SCFA producers)
- Faecalibacterium
- Roseburia
- Eubacterium
- Coprococcus
- Butyrivibrio
- Anaerotruncus
- Dorea
- Blautia
- Ruminococcus

OTHERS
- Lactobacilli
- Akkermansia muciniphila
- Bifidobacteria
- Bacilli
- Bacteroides
- E. coli
<table>
<thead>
<tr>
<th>PROTEOBACTERIA</th>
<th>OTHERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. pylori</td>
<td>Ruminococcus gnavus</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>Streptococcus</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>Enterococcus</td>
</tr>
<tr>
<td>Citrobacter</td>
<td>Collinsella aerofaciens</td>
</tr>
<tr>
<td>Proteus</td>
<td>Alistipes</td>
</tr>
<tr>
<td>Serratia</td>
<td>Candida</td>
</tr>
<tr>
<td>Desulfovibrio</td>
<td>Parasites</td>
</tr>
<tr>
<td>Bilophila</td>
<td></td>
</tr>
</tbody>
</table>
DECREASED DIVERSITY

• Lower capacity to perform beneficial functions and produce beneficial products

• Decreased stability and resilience (ability to withstand / recover from disturbances)
Unhealthy Intestinal Lining

Microbiome Imbalance (Dysbiosis)

Immune Imbalance
EVIDENCE

1. Aging and longevity in lab animals and humans

2. Effects of healthspan-promoting approaches
HEALTHSPAN-PROMOTING APPROACHES:

• Calorie restriction & fasting
• Phytochemicals / polyphenols
• Lifespan / healthspan-promoting pharmaceuticals
CALORIE RESTRICTION & FASTING
Structural modulation of gut microbiota in life-long calorie-restricted mice.


Author information

Abstract

Calorie restriction has been regarded as the only experimental regimen that can effectively lengthen lifespan in various animal models, but the actual mechanism remains controversial. The gut microbiota has been shown to have a pivotal role in host health, and its structure is mostly shaped by diet. Here we show that life-long calorie restriction on both high-fat or low-fat diet, but not voluntary exercise, significantly changes the overall structure of the gut microbiota of C57BL/6 J mice. Calorie restriction enriches phylotypes positively correlated with lifespan, for example, the genus Lactobacillus on low-fat diet, and reduces phylotypes negatively correlated with lifespan. These calorie restriction-induced changes in the gut microbiota are concomitant with significantly reduced serum levels of lipopolysaccharide-binding protein, suggesting that animals under calorie restriction can establish a structurally balanced architecture of gut microbiota that may exert a health benefit to the host via reduction of antigen load from the gut.
Fasting the Microbiota to Improve Metabolism?

Joel T. Haas1,2,3 and Bart Staels1,2,3,4,*

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2INSERM UMR 1011, 59000 Lille, France
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http://dx.doi.org/10.1016/j.cmet.2017.09.013

While intermittent or periodic fasting provides a variety of favorable health benefits, the molecular mediators of these effects are poorly understood. In this issue of Cell Metabolism, Li and colleagues (2017) highlight the role of gut microbiota in mediating benefits of intermittent fasting through activation of adipose tissue beiing.

In recent years, enormous efforts have been invested in the development of therapies to combat the growing obesity epidemic. It is common knowledge that reducing energy intake and increasing energy expenditure are the two main strategies to control obesity. However, these approaches can lead to adverse consequences such as muscle atrophy, protein wasting, and even death in mice. While several studies already demonstrated the metabolic benefits of EODF in rodents and humans, this is the first to identify beiing as a potential mediator of these effects.

In response to fasting (Badman et al., 2007; Inagaki et al., 2007), still demonstrated EODF-induced beiing. What, then, causes EODF-induced beiing? The authors found marked alterations in the gut microbiota following EODF in mice.
Predominant gut Lactobacillus murinus strain mediates anti-inflammatory effects in calorie-restricted mice.

Abstract

**Background:** Calorie restriction (CR), which has a potent anti-inflammatory effect, has been demonstrated to induce dramatic changes in the gut microbiota. Whether the modulated gut microbiota contributes to the attenuation of inflammation during CR is unknown, as are the members of the microbial community that may be key mediators of this process.

**Results:** Here, we report that a unique *Lactobacillus*-predominated microbial community was rapidly attained in mice within 2 weeks of CR, which decreased the levels of circulating microbial antigens and systemic inflammatory markers such as tumour necrosis factor alpha (TNF-α). *Lactobacillus murinus* CR147, an isolate in the most abundant operational taxonomic unit (OTU) enriched by CR, downregulated interleukin-8 production in TNF-α-stimulated Caco-2 cells and significantly increased the lifespan and the brood size of the nematode *Caenorhabditis elegans*. In gnotobiotic mice colonized with the gut microbiota from old mice, this strain decreased their intestinal permeability and serum endotoxin load, consequently attenuating the inflammation induced by the old microbiota.

**Conclusions:** Our study demonstrated that a strain of *Lactobacillus murinus* was promoted in CR mice and causatively contributed to the attenuation of ageing-associated inflammation.

**Keywords:** Calorie restriction, Gut microbiota, Chronic inflammation, Lifespan, *Lactobacillus murinus*
Caloric restriction promotes rapid expansion and long-lasting increase of Lactobacillus in the rat fecal microbiota.

Increased gut microbiota diversity and abundance of Faecalibacterium prausnitzii and Akkermansia after fasting: a pilot study.

Fasting the Microbiota to Improve Metabolism?
Antiobesity molecular mechanisms of action: Resveratrol and pterostilbene.

Pan MH\textsuperscript{1,2,3,4}, Wu JC\textsuperscript{5}, Ho CT\textsuperscript{6}, Lai CS\textsuperscript{7}.

Author information

Abstract

Obesity is a current global epidemic that has led to a marked increase in metabolic diseases. However, its treatment remains a challenge. Obesity is a multifactorial disease, which involves the dysfunction of neuropeptides, hormones, and inflammatory adipokines from the brain, gut, and adipose tissue. An understanding of the mechanisms and signal interactions in the crosstalk between organs and tissue in the coordination of whole-body energy metabolism would be helpful to provide therapeutic and putative approaches to the treatment and prevention of obesity and related complications. Resveratrol and pterostilbene are well-known stilbenes that provide various potential benefits to human health. In particular, their potential anti-obesity effects have been proven in numerous cell culture and animal studies. Both compounds act to regulate energy intake, adipocyte life cycle and function, white adipose tissue (WAT) inflammation, energy expenditure, and gut microbiota by targeting multiple molecules and signaling pathways as an intervention for obesity. Although the efficacy of both compounds in humans requires further investigation with respect to their oral bioavailability, promising scientific findings have highlighted their potential as candidates for the treatment of obesity and the improvement of obesity-related metabolic diseases.
Effect of resveratrol and pterostilbene on aging and longevity.

Cardiovascular and Antiobesity Effects of Resveratrol Mediated through the Gut Microbiota.

Improved Glucose Homeostasis in Obese Mice Treated With Resveratrol Is Associated With Alterations in the Gut Microbiome.

Pterostilbene-induced changes in gut microbiota composition in relation to obesity.
Thousands of therapeutically active plant-derived compounds are widely present in berries, fruits, nuts, and beverages like tea and wine. The bioactivity and bioavailability of these compounds, which are typically glycosylated, are altered by microbial bioconversions in the human gut.
Lactobacillus acidophilus Metabolizes Dietary Plant Glucosides and Externalizes Their Bioactive Phytochemicals.

“These findings highlight the role of human gut L. acidophilus and select lactobacilli in the bioconversion of glyco-conjugated phytochemicals, which is likely to have an important impact on the HGM [human gut microbiome] and human host.”
Small intestine lumen

Lactobacillus acidophilus NCFM

GLYCOLYSIS

β-(1,6)-diglucoside phytochemicals

β-glucoside phytochemicals

Mucus
Epithelial cells

Mucin binding proteins

Epithelial cell adhesion

Absorption

Microbiota interactions

Further metabolism

Microbiota composition alteration

INCREASED BIOACTIVITY

Antimicrobial

Antioxidants

Anti-inflammatory

Neuroprotective

Chemopreventive

Anti-estrogenic

Anti-cancer

Toxicity

Cardioprotective
TAKE-HOMES:

1. The microbiome is critical for conversion of most phytochemicals/polyphenols into their bioactive forms
TAKE-HOMES:

2. Individual differences in the ability of the microbiome to covert polyphenols affects the bioactivity of any given polyphenol ("responders & non-responders")
“... polyphenols modulate the composition of the gut microbial community mostly through the inhibition of pathogenic bacteria and the stimulation of beneficial bacteria. In the latter, they may act as a prebiotic metabolite and enrich the beneficial bacteria ...”
Prescription Drugs
“The apparent reductions in all-cause mortality and diseases of ageing associated with metformin use suggest that metformin could be extending life and healthspans by acting as a geroprotective agent.”
Metformin alters the gut microbiome of individuals with treatment-naive type 2 diabetes, contributing to the therapeutic effects of the drug

Hao Wu1,12, Eduardo Esteve2–4,12, Valentina Tremaroli1, Muhammad Tanweer Khan1, Robert Caesar1, Louise Mannerås-Holm1, Marcus Ståhlman1, Lisa M Olsson1, Matteo Serino5, Mercè Planas-Fèlix6, Gemma Xifra2–4, Josep M Mercader6, David Torrents6,7, Rémy Burcelin8,9, Wifredo Ricart2–4, Rosie Perkins1, José Manuel Fernández-Real2–4 & Fredrik Bäckhed1,10,11

Metformin is widely used in the treatment of type 2 diabetes (T2D), but its mechanism of action is poorly defined. Recent evidence implicates the gut microbiota as a site of metformin action. In a double-blind study, we randomized individuals with treatment-naive T2D to placebo or metformin for 4 months and showed that metformin had strong effects on the gut microbiome. These results were verified in a subset of the placebo group that switched to metformin 6 months after the start of the trial. Transfer of fecal samples (obtained before and 4 months after treatment) from metformin-treated donors to germ-free mice showed that glucose tolerance was improved in mice that received metformin-altered microbiota. By directly investigating metformin–microbiota interactions in a gut simulator, we showed that metformin affected pathways with common biological functions in species from two different phyla, and many of the metformin-regulated genes in these species encoded metalloproteins or metal transporters. Our findings provide support for the notion that altered gut microbiota mediates some of metformin’s antidiabetic effects.
Transient rapamycin treatment can increase lifespan and healthspan in middle-aged mice.

Bitto A¹, Ito TK¹, Pineda VV¹, LeTexier NJ¹, Huang HZ¹, Sutlief E¹, Tung H¹, Vizzini N¹, Chen B¹, Smith K¹, Meza D¹, Yajima M², Beyer RP³, Kerr KE⁴, Davis DJ⁵, Gillespie CH⁵, Snyder JM⁶, Treuting PM⁶, Kaeberlein M¹.

Author information

Abstract
The FDA approved drug rapamycin increases lifespan in rodents and delays age-related dysfunction in rodents and humans. Nevertheless, important questions remain regarding the optimal dose, duration, and mechanisms of action in the context of healthy aging. Here we show that 3 months of rapamycin treatment is sufficient to increase life expectancy by up to 60% and improve measures of healthspan in middle-aged mice. This transient treatment is also associated with a remodeling of the microbiome, including dramatically increased prevalence of segmented filamentous bacteria in the small intestine. We also define a dose in female mice that does not extend lifespan, but is associated with a striking shift in cancer prevalence toward aggressive hematopoietic cancers and away from non-hematopoietic malignancies. These data suggest that a short-term rapamycin treatment late in life has persistent effects that can robustly delay aging, influence cancer prevalence, and modulate the microbiome.
KEY TAKE-HOMES:

1. Healthspan-promoting approaches may be mediated (at least in part) by the microbiome
2. These approaches tend to increase diversity and beneficial microbes (e.g., Lactobacilli, Akkermansia), and decrease unfriendly microbes.
1. The microbiome, aging & healthspan
2. The gut-brain axis: new insights
3. Toward improving healthspan with microbiome-based approaches
The gut is a major sensory organ.
Huge epithelial surface area

70% of immune system

Largest endocrine organ

100 trillion microbes

200-500 million neurons in ENS
How is info relayed between gut & brain?
The Enteric Network: Interactions between the Immune and Nervous Systems of the Gut

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\textsuperscript{1}Division of Biology & Biological Engineering, California Institute of Technology, Pasadena, CA 91125, USA
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http://dx.doi.org/10.1016/j.immun.2017.05.011

Interactions between the nervous and immune systems enable the gut to respond to the variety of dietary products that it absorbs, the broad spectrum of pathogens that it encounters, and the diverse microbiome that it harbors. The enteric nervous system (ENS) senses and reacts to the dynamic ecosystem of the gastrointestinal (GI) tract by translating chemical cues from the environment into neuronal impulses that propagate throughout the gut and into other organs in the body, including the central nervous system (CNS). This review will describe the current understanding of the anatomy and physiology of the GI tract by focusing on the ENS and the mucosal immune system. We highlight emerging literature that the ENS is essential for important aspects of microbe-induced immune responses in the gut. Although most basic and applied research in neuroscience has focused on the brain, the proximity of the ENS to the immune system and its interface with the external environment suggest that novel paradigms for nervous system function await discovery.
Microbiota Signaling Pathways that Influence Neurologic Disease.

**Neural:** Efferent nerves, acetylcholine

**Endocrine:** HPA axis, PYY

**Neural:** Vagal nerve & neurotransmitters

**Endocrine:** HPA axis, PYY

**Immune:** Microbial antigens & metabolites

**Central Nervous System**
- Stress responses
- Anxiety
- Pain responses
- Satiety and feeding
- Microglia homeostasis
- Neuroinflammation

**Intestine**
- Motility, secretion, and permeability
- Synthesis of PYY
- 5-HT production by enterochromaffin cells
- Enteric neuron signals via the vagal nerve

**Microbiota**
- SCFA production
- Tryptophan & indole metabolism
- Neurotoxins
- Neutransmitters
- LPS, peptidoglycan, and polysaccharide A

**Mediators of and Responses to Gut-Microbiota-CNS Two-Way Communication**
Circular muscle

Submucosal plexus

Blood vessel

Mucosa

Epithelial cells

Immune cells

EEC

Neuropod

Lumen

Bacteria

J Clin Invest. 2015;125(3):918–925
TAKE-HOMES

1. Gut senses the environment (food, microbiome, pathogens) in numerous ways and relays info to the brain
TAKE-HOMES

2. The brain responds to the input from the gut in many ways, including regulating gut function and microbiome balance.
Implications of gut-brain imbalances?
“Recent investigations suggest that gut microbiota affects brain activity through the microbiota-gut-brain axis under both physiological and pathological disease conditions like Parkinson's disease.”
“The trigger that causes blood brain barrier leakage, immune cell activation and inflammation, and ultimately neuroinflammation in the central nervous system is believed to be due to the chronic low-grade inflammation in the gut.”
Altered Gut Microbiota in a Mouse Model of Alzheimer's Disease.

Gut microbiome alterations in Alzheimer's disease.

Neuroinflammation, Gut Microbiome, and Alzheimer's Disease.

The role of microbial amyloid in neurodegeneration.
Parkinson’s disease:
- α-synuclein aggregation
- (Neuro)inflammation
- Microglia activation

Alzheimer’s disease:
- β-amyloid deposition
Gut microbiota changes in the extreme decades of human life: a focus on centenarians.

**Brain**
- Delayed onset/absence of cognitive impairment
- No neurodegenerative diseases (AD, PD)
- Low levels of anxiety and depression

**Effect of Tryptophan, Serotonin and Kynurenine pathway (?)**

**Gut**
- Abundance of genes involved in the tryptophan metabolism
- Increase of GM biodiversity
- Increase of *Christensenellaceae/Akkermansia*
- Rearrangement of *Clostridium Cluster IV* (SCFAs producers)

**Blood**
- Reduction of tryptophan levels
- Increase of IL-6 and IL-8 levels
- Specific signature of glycerophospholipids and sphingolipids
- Decreased of 9-HODE and 9-oxo-HODE levels

**Urine**
- Increased urinary excretion of gut derived PCS and PAG
**Brain**
- Delayed onset/absence of cognitive impairment
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**Urine**
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1. The microbiome, aging & healthspan

2. The gut-brain axis: new insights

3. Toward improving healthspan with microbiome-based approaches
1. Identifying microbiome imbalances (patterns)
2. General approaches for correcting general imbalances
3. Specific approaches for correcting individual imbalances
Microbiome Testing

- Numerous options
- Clinical and direct-to-consumer (DTC)
- Clinical: pathogens, GI health markers
- DTC: general microbiome makeup / balance
GOAL: Identifying microbes (composition) and/or their functions (genes or gene expression)

Gene (DNA)-based tests: mostly composition, some provide gene info (potential functions)

Gene expression-based tests: active microbes and their functions (actual functions)
Diversity
Balance
Avoid or reduce major disruptions to microbiome when possible (antibiotics, gut infections, diet)

- Gut healing /anti-inflammatory diet & protocols
- Emphasize the 4Ps: plants, prebiotics, probiotics, phytonutrients (polyphenols)
- Emphasize specific nutrients that influence specific microbial & mucosal factors
Emphasize the 4P’s

Probiotics & fermented foods

Plant foods
(variety, whole, organic)

Prebiotics / fiber

Phytochemicals / polyphenols
“Enrichment of the HFD with inulin, but not cellulose, resulted in the restoration of the gut bacteria that are beneficial to the host–microbiota relationship, and a boost to the intestinal defences.”
Improving healthspan via changes in gut microbiota and fermentation.

Keenan MJ¹, Marco ML², Ingram DK³, Martin RJ⁴.

Author information

Abstract
Dietary resistant starch impact on intestinal microbiome and improving healthspan is the topic of this review. In the elderly population, dietary fiber intake is lower than recommended. Dietary resistant starch as a source of fiber produces a profound change in gut microbiota and fermentation in animal models of aging. Dietary resistant starch has the potential for improving healthspan in the elderly through multiple mechanisms as follows: (1) enhancing gut microbiota profile and production of short-chain fatty acids, (2) improving gut barrier function, (3) increasing gut peptides that are important in glucose homeostasis and lipid metabolism, and (4) mimicking many of the effects of caloric restriction including upregulation of genes involved in xenobiotic metabolism.
Phytochemicals / Polyphenols
Avoiding or minimizing disruptors

Dietary variety and rotation (types and quantity)

• Whole organic vegetables, herbs, spices, bitters, fruits, other plants as tolerated

• Prebiotics, phytonutrients (e.g., curcumin), probiotics & fermented foods (wide range of each)

• Intermittent fasting and avoiding snacking
Microbiome Disruptors
• Processed & poor-quality foods (additives, low fiber, low polyphenol)

• Poor digestion & absorption**

• Antibiotics and other drugs & chemicals

• Gut & systemic infections

• Excessive stress, poor sleep
Optimize digestion (secretion & motility)

“Rest and digest”
PROMOTE RESILIENCE
promote capacity of the microbiome to tolerate disruptions

PROMOTE RECOVERY
promote optimal recovery of the microbiome after a disruption
Addressing Big Disruptions

- Follow general recommendations, emphasizing diversity, vitamins A & D
- Probiotics: S. boulardii + broad-spectrum probiotic
- Polyphenols: curcumin, quercetin, berry extracts, green tea extract, ginger, clove, cinnamon, herbs
- Antimicrobials if warranted
- STRICT adherence for minimum 30 days
Case Study: Dave

- 40s, busy professional, recreational athlete
- 1-year Hx of fatigue & GI symptoms (bloating, mild diarrhea, abdominal discomfort)
- Frequent international travel (symptoms began after a specific trip abroad)

Testing
- Food sensitivity (negative)
- Pathogens & GI markers
<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Result</th>
<th>Expected</th>
</tr>
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<tbody>
<tr>
<td>Bacterial Pathogens</td>
<td></td>
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</tr>
<tr>
<td><strong>Campylobacter</strong></td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>C. difficile, Toxin A</strong></td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>C. difficile, Toxin B</strong></td>
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</tr>
<tr>
<td><strong>E. coli O157</strong></td>
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<tr>
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<td>Negative</td>
</tr>
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<td>Enterotoxigenic <strong>E. coli ST</strong></td>
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</tr>
<tr>
<td>Shiga-like Toxin <strong>E. coli stx1</strong></td>
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<td>Negative</td>
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<tr>
<td>Shiga-like Toxin <strong>E. coli stx2</strong></td>
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<td>Negative</td>
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<tr>
<td><strong>Shigella</strong></td>
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<tr>
<td><strong>Salmonella</strong></td>
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<tr>
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<tr>
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<tr>
<td>Pathogen</td>
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<td>Expected</td>
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<tr>
<td>Viral Pathogens</td>
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<tr>
<td>Adenovirus 40/41</td>
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<td>Negative</td>
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<tr>
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<td>Parasitic Pathogens</td>
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<td>Cryptosporidium</td>
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<tr>
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<tr>
<td>Giardia</td>
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<td>Negative</td>
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<tr>
<td>H. pylori</td>
<td>Range CFU/g</td>
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<tr>
<td><em>Helicobacter pylori</em></td>
<td>&lt;dL</td>
<td>&lt;1.0e3</td>
</tr>
<tr>
<td>Virulence Factor, babA</td>
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<td>Negative</td>
</tr>
<tr>
<td>Virulence Factor, cagA</td>
<td>N/A</td>
<td>Negative</td>
</tr>
<tr>
<td>Virulence Factor, dupA</td>
<td>N/A</td>
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</tr>
<tr>
<td>Virulence Factor, iceA</td>
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<tr>
<td>Virulence Factor, CipA</td>
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<tr>
<td>Virulence Factor, vacA</td>
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</tr>
<tr>
<td>Virulence Factor, virB</td>
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<td>Virulence Factor, virD</td>
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<tr>
<td>Opportunistic Bacteria</td>
<td>Range CFU/g</td>
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<tr>
<td>----------------------------------------------</td>
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<tr>
<td><strong>Potential Autoimmune Triggers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Citrobacter freundii</em></td>
<td>&lt;1.0e4</td>
<td></td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>&lt;7.2e3</td>
<td></td>
</tr>
<tr>
<td><em>Proteus</em> <em>spp.</em></td>
<td>&lt;6.2e3</td>
<td></td>
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<tr>
<td><em>Proteus mirabilis</em></td>
<td>&lt;1.0e3</td>
<td></td>
</tr>
<tr>
<td><strong>Additional Dysbiotic/Overgrowth Bacteria</strong></td>
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</tr>
<tr>
<td><em>Morganella</em> <em>spp.</em></td>
<td>&lt;1.0e3</td>
<td></td>
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<tr>
<td><em>Pseudomonas</em> <em>spp.</em></td>
<td>&lt;2.5e3</td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>&lt;1.0e3</td>
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<tr>
<td><em>Staphylococcus</em> <em>spp.</em></td>
<td>&lt;1.0e4</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus</em> <em>spp.</em></td>
<td>&lt;1.0e3</td>
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<tr>
<td>Parasites</td>
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<tr>
<td>------------------------</td>
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</tr>
<tr>
<td><strong>Protozoa</strong></td>
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<tr>
<td><em>Blastocystis hominis</em></td>
<td>Negative</td>
<td>Negative</td>
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<tr>
<td><em>Dientamoeba fragilis</em></td>
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<tr>
<td><em>Endolimax nana</em></td>
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<tr>
<td><em>Entamoeba coli</em></td>
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<tr>
<td><em>Chilomastix mesnelli</em></td>
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<tr>
<td><em>Cyclospora spp.</em></td>
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<tr>
<td><em>Pentatrichomonas hominis</em></td>
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<td>Negative</td>
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<tr>
<td><strong>Fungi/Yeast</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Candida albicans</em></td>
<td>&lt;dl</td>
<td>&lt;5.0e3</td>
</tr>
<tr>
<td><em>Candida spp.</em></td>
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<td>Negative</td>
</tr>
<tr>
<td><em>Geotrichum spp.</em></td>
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<td>Negative</td>
</tr>
<tr>
<td><em>Microsporidium spp.</em></td>
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<tr>
<td><em>Trichosporon spp.</em></td>
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<tr>
<td>Intestinal Health</td>
<td>Result</td>
<td>Range</td>
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<td>------------------</td>
<td>--------</td>
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<tr>
<td>Digestion</td>
<td></td>
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<tr>
<td>Elastase-1</td>
<td>278</td>
<td>&gt;200 ug/g</td>
</tr>
<tr>
<td>Steatocrit</td>
<td>23</td>
<td>&lt;15 %</td>
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<tr>
<td></td>
<td>High</td>
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</tr>
<tr>
<td>Immune Response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secretary IgA</td>
<td>275</td>
<td>510 - 2010 ug/g</td>
</tr>
<tr>
<td>Anti-gliadin IgA</td>
<td>54</td>
<td>0 - 157 U/L</td>
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<tr>
<td>Inflammation</td>
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<tr>
<td>Calprotectin</td>
<td>578</td>
<td>&lt;50 ug/g</td>
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<td>GI Markers</td>
<td></td>
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<tr>
<td>b-Glucuronidase</td>
<td>2832</td>
<td>&lt;2486 U/mL</td>
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<tr>
<td>Fecal Occult Blood</td>
<td>Negative</td>
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</tbody>
</table>
Approach

- Physician-prescribed anti-parasitic for Giardia

- Intensive gut support
  - Digestive enzymes with HCL
  - S. boulardii
  - Broad-spectrum probiotic
  - Zn carnosine
  - L-glutamine
  - Colostrum
  - Vitamins A, D, K
Approach

- Polyphenol & fiber (immune/microbiome balance)
  - SUPPLEMENTS: Curcumin, quercetin, boswellia, ginger, inulin (build up slowly)
  - DIET: Increase herbs, spices, berries
- Strict adherence for minimum 30 days
The Microbione and Personalized Nutrition
Nutrition

Microbiome

Genes & Physiology
Towards utilization of the human genome and microbiome for personalized nutrition.

Bashiardes S¹, Godneva A², Elinav E³, Segal E⁴.

Author information

Abstract
Generalized dietary and lifestyle guidelines have been formulated and published for decades now from a variety of relevant agencies in an attempt to guide people towards healthy choices. As the pandemic rise in metabolic diseases continues to increase, it has become clear that the one-fit-for-all diet approach does not work and that there is a significant variation in inter-individual responses to diet and lifestyle interventions. Recent technological advances have given an unprecedented insight into the sources of this variation, pointing towards our genome and microbiome as potentially and previously under-explored culprits contributing to individually unique dietary responses. Variations in our genome influence the bioavailability and metabolism of nutrients between individuals, while inter-individual compositional variation of commensal gut microbiota leads to different microbe functional potential, metabolite production and metabolism modulation. Quantifying and incorporating these factors into a comprehensive personalized nutrition approach may enable practitioners to rationally incorporate individual nutritional recommendations in combating the metabolic syndrome pandemic.
Responders vs. Nonresponders

- Numerous studies showing individuals respond differently to diets and specific nutrients based on differences in microbiome.

- Converting certain fiber and polyphenols into beneficial products depends upon presence of specific types of microbes.
Akkermansia & Lactobacilli

- **Akkermansia**
  - Cranberries, grape polyphenols, pomegranate, pterostilbene, fasting
  - Prebiotics: FOS

- **Lactobacilli**
  - Pomegranate, red wine polyphenols, curcumin, garlic, apple, cocoa flavonols, fasting / caloric restriction, avoid excess salt intake
  - Prebiotics: FOS, pectin
Bifidobacteria

- Diet / phytonutrients: blueberries (anthocyanins), pomegranate (ellagintannins), apple, red wine polyphenols, coffee, cocoa polyphenols
- Prebiotics: FOS, GOS, XOS, AXOS, inulin, pectin, resistant starch
- Probiotics: Bifidobacteria
- Individuals with FUT-2 SNPs may need additional Bifido support
Protein Fermentation

- Microbial protein breakdown may result in harmful (putrefactive) products if excessive

- Identify cause & address:
  - Excess protein intake
  - Poor protein digestion/absorption
  - Slow motility / constipation
  - Low fiber, resistant starch, phytonutrients
Intermittent metabolic switching, neuroplasticity and brain health.

Mattson MP\textsuperscript{1,2}, Moehl K\textsuperscript{1}, Ghen N\textsuperscript{1}, Schmaedick M\textsuperscript{1}, Cheng A\textsuperscript{1}.

Author information

Abstract
During evolution, individuals whose brains and bodies functioned well in a fasted state were successful in acquiring food, enabling their survival and reproduction. With fasting and extended exercise, liver glycogen stores are depleted and ketones are produced from adipose-cell-derived fatty acids. This metabolic switch in cellular fuel source is accompanied by cellular and molecular adaptations of neural networks in the brain that enhance their functionality and bolster their resistance to stress, injury and disease. Here, we consider how intermittent metabolic switching, repeating cycles of a metabolic challenge that induces ketosis (fasting and/or exercise) followed by a recovery period (eating, resting and sleeping), may optimize brain function and resilience throughout the lifespan, with a focus on the neuronal circuits involved in cognition and mood. Such metabolic switching impacts multiple signalling pathways that promote neuroplasticity and resistance of the brain to injury and disease.
1. The microbiome, aging & healthspan

2. The gut-brain axis: new insights

3. Toward improving healthspan with microbiome-based approaches
THANK YOU!!

Tom Fabian, PhD, CNTP

https://www.facebook.com/TomFabianPhD/

MicrobiomeMastery.com (for practitioners)