Next Level Functional Nutrition™

2019 Hot-Topics Webinar Series

Restorative Strategies for Gut Dysfunctions in Chronic Illness

Hosted by Susan Allen-Evenson RDN, CCN, FMN

Presented by Kiran Krishnan, Microbiologist

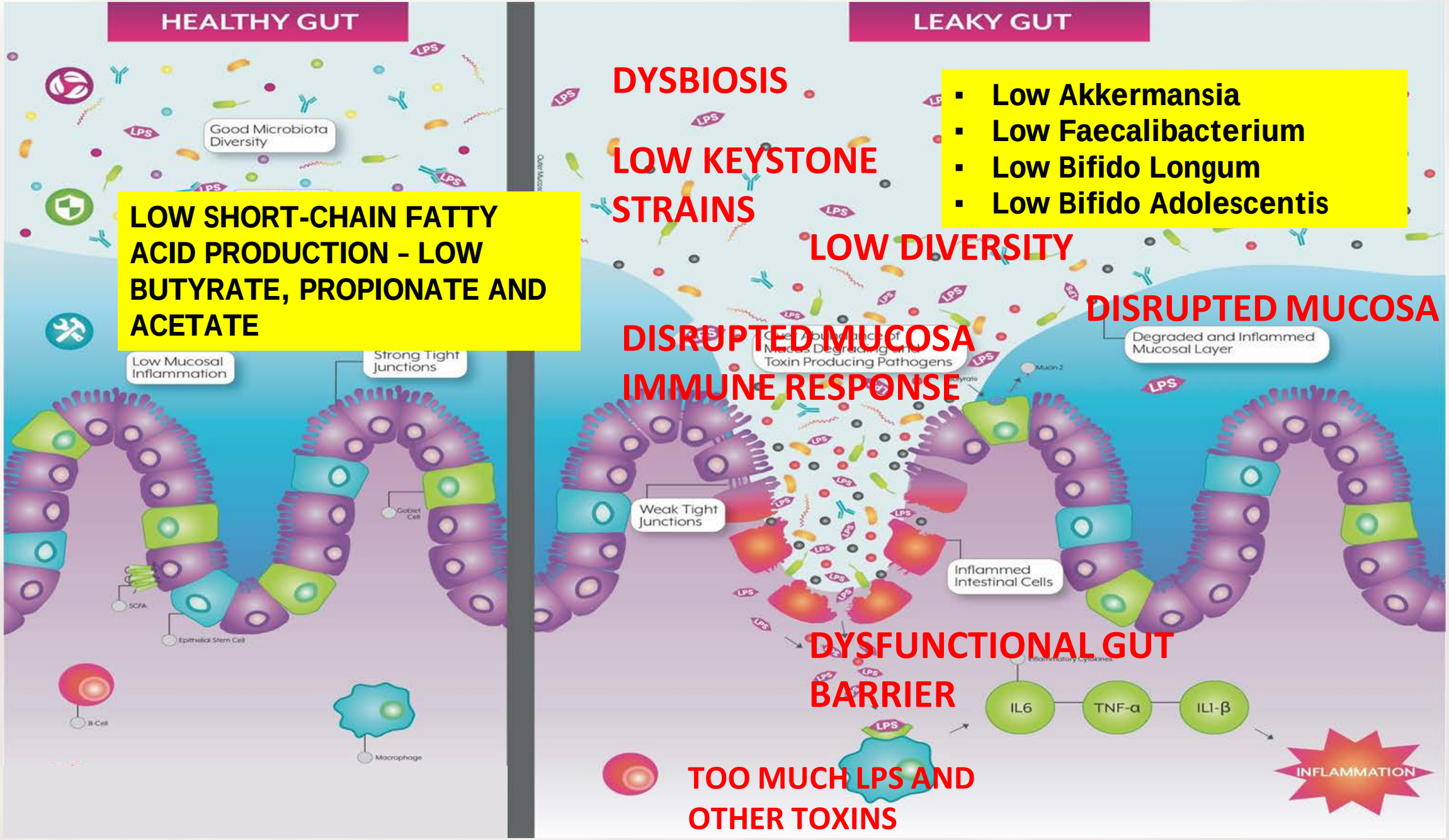
Kiran Krishnan

- Kiran Krishnan is a Research Microbiologist and has been involved in the dietary supplement and nutrition market for the past 18 years. He comes from a strict research background having spent several years with hands-on R&D in the fields of molecular medicine and microbiology at the University of Iowa. Kiran established a Clinical Research Organization where he designed and conducted dozens of human clinical trials in human nutrition. Kiran is also a co-founder and partner in Nu Science Trading, LLC.; a nutritional technology development and research company. Kiran is also a co-founder and Chief Scientific Officer at Microbiome Labs. In his career, he has developed over 50 private label nutritional products for small to large brands in the global market. He is a frequent lecturer on the Human Microbiome at Medical and Nutrition Conferences. He conducts a very popular Microbiome Series educational Webinar, is an expert guest on National and Satellite radio, has appeared in several international documentaries and has been a guest speaker on several International Health Summits as a microbiome expert. He is currently involved in 10 novel human clinical trials on probiotics and the human microbiome. Kiran is also on the Scientific Advisory Board or a Science Advisor for 7 other companies in the industry.
- **Professional Disclosure:** Kiran Krishnan is the Chief Science Officer of Microbiome Labs

TOTAL GUT RESTORATION

RECONDITION | REINFORCE | REBUILD

KIRAN KRISHNAN


HEALTHY GUT
LEAKY GUT
Good Microbiota Diversity
LOW SHORT-CHAIN FATTY ACID PRODUCTION – LOW BUTYRATE, PROPIONATE AND ACETATE
Low Mucosal Inflammation
Strong Tight Junctions
Goblet Cell
SCFA
Epithelial Stem Cell
B-Cell
Macrophage
DYSBIOSIS
LOW KEYSTONE STRAINS
Low Akkermansia
Low Faecalibacterium
Low Bifido Longum
Low Bifido Adolescentis
LOW DIVERSITY
DISRUPTED MUCOSA
IMMUNE RESPONSE
Toxin Producing Pathogens
DISRUPTED MUCOSA
Degraded and Inflammed Mucosal Layer
Mucin 2
Weak Tight Junctions
Inflammed Intestinal Cells
DYSFUNCTIONAL GUT BARRIER
IL6
TNF-α
IL1-β
INFLAMMATION
TOO MUCH LPS AND OTHER TOXINS
LPS

Review

Beneficial modulation of the gut microbiota

Calum J. Walsh [a,b], Caitriona M. Guinane [a], Paul W. O'Toole [b,c], Paul D. Cotter [a,c,*]

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ABSTRACT

The human gut microbiota comprises approximately 100 trillion microbial cells and has a significant effect on many aspects of human physiology including metabolism, nutrient absorption and immune function. Disruption of this population has been implicated in many conditions and diseases, including examples such as obesity, inflammatory bowel disease and colorectal cancer that are highlighted in this review. A logical extension of these observations suggests that the manipulation of the gut microbiota can be employed to prevent or treat these conditions. Thus, here we highlight a variety of options, including the use of changes in diet (including the use of prebiotics), antimicrobial-based intervention, probiotics and faecal microbiota transplantation, and discuss their relative merits with respect to modulating the intestinal community in a beneficial way.

DYSBIOSIS

1. Introduction

Humans are now thought of as "superorganisms" on the basis of the genetic potential encoded within our resident microbial populations in addition to our own genome. It has been suggested that our microbiota develops with us and alters its own composition and gene expression in response to changing environmental conditions [1]. The largest and most varied of the human-associated microbial communities exists in the gastrointestinal (GI) tract.

The gut microbial population is made up of approximately 1000 the host. The functions and pathways encoded in the core microbiome are thought to confer the greatest benefit to the host and are probably essential for the correct functioning of the gut. Some well-studied benefits include protection against potential pathogens, digestion of polysaccharides, production of essential vitamins, stimulation of angiogenesis, regulation of fat storage and modulation of the host's immune system [5]. Recent studies have also shown that the gut microbiota influences the gut-brain axis and shapes stress-related symptoms such as anxiety and pain tolerance [6].

"The disruption of gut microbiota has been implicated in many conditions and diseases, including **obesity, inflammatory bowel disease, irritable bowel syndrome, type 2 diabetes, and colorectal cancer**."

"As we gain a deeper understanding of the specific relationships between the gut microbiota and disease, we expose potential therapeutic targets. **Intelligent modulation** of the intestinal community is a topic that had gained considerable interest and has the possibility to be extremely beneficial for human health."

REVIEW

The gut microbiota and inflammatory bowel disease

Katsuyoshi Matsuoka · Takanori Kanai

LOW DIVERSITY

Received: 4 August 2014 / Accepted: 2 October 2014 / Published online: 25 November 2014

Abstract Inflammatory bowel disease (IBD) is a chronic and relapsing inflammatory disorder of the gut. Although the precise cause of IBD remains unknown, the most accepted hypothesis of IBD pathogenesis to date is that an aberrant immune response against the gut microbiota is triggered by environmental factors in a genetically susceptible host. The advancement of next-generation sequencing technology has enabled identification of various alterations of the gut microbiota composition in IBD. While some results related to dysbiosis in IBD are different between studies owing to variations of sample type, method of investigation, patient profiles, and medication, the most consistent observation in IBD is reduced bacterial diversity, a decrease of Firmicutes, and an increase of Proteobacteria. It has not yet been established how dysbiosis contributes to intestinal inflammation. Many of the known IBD susceptibility genes are associated with recognition and processing of bacteria, which is consistent with a role of the gut microbiota

Introduction

Inflammatory bowel disease (IBD) is a disorder characterized by chronic and relapsing intestinal inflammation and is mainly defined as either ulcerative colitis (UC) or Crohn's disease (CD). Although the cause of IBD remains unknown, genetic background is considered to be involved in the pathophysiology of IBD because a number of disease susceptibility genes have been identified. The rapid increase in the incidence of IBD, however, cannot be explained by genetic factors alone, and environmental factors must also be essential to its development.

The involvement of the gut microbiota in the pathophysiology of IBD has recently been highlighted. Several lines of evidence suggest an essential role of the gut microbiota in intestinal inflammation. (1) In murine models of IBD such as IL-10-deficient mice and the $CD45Rb^{high}$ transfer model, where transferred naïve helper T cells cause microbiota-dependent intestinal inflam-

"While some results related to dysbiosis in IBD are different between studies owing to variations of sample type, method of investigation, patient profiles, and medication, **the most consistent observation in IBD is reduced bacterial diversity**, a decrease of Firmicutes, and an increase of Proteobacteria."

"A number of trials have shown that **therapies correcting dysbiosis**, including fecal microbiota transplantation and probiotics, **are promising in IBD**."

KEYSTONE STRAINS – A. MUCINIPHILA

frontiers in Microbiology

MINI REVIEW
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doi: 10.3389/fmicb.2017.01765

Next-Generation Beneficial Microbes: The Case of *Akkermansia muciniphila*

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Metabolic disorders associated with obesity and cardiometabolic disorders are worldwide epidemic. Among the different environmental factors, the gut microbiota is now considered as a key player interfering with energy metabolism and host susceptibility to several non-communicable diseases. Among the next-generation beneficial microbes that have been identified, *Akkermansia muciniphila* is a promising candidate. Indeed, *A. muciniphila* is inversely associated with obesity, diabetes, cardiometabolic diseases and low-grade inflammation. Besides the numerous correlations observed, a large body of evidence has demonstrated the causal beneficial impact of this bacterium in a variety of preclinical models. Translating these exciting observations to human would be the next logic step and it now appears that several obstacles that would prevent the use of *A. muciniphila* administration in humans have been overcome. Moreover, several lines of evidence indicate that pasteurization of *A. muciniphila* not only increases its stability but more importantly increases its efficacy.

OPEN ACCESS

Edited by:
Rebeca Martín,
INRA Centre Jouy-en-Josas, France

"*A. muciniphila* is **inversely associated with obesity, diabetes, cardiometabolic diseases and low-grade inflammation**."

"Nowadays, *A. muciniphila* is widely considered as a novel potential candidate to **improve metabolic disorders associated with obesity, diabetes, liver diseases and cardiometabolic disorders**. Indeed, its administration has been shown to **profoundly reduce the development of such diseases**."

Review Article

Association between *Faecalibacterium prausnitzii* Reduction and Inflammatory Bowel Disease: A Meta-Analysis and Systematic Review of the Literature

Yuan Cao, Jun Shen, and Zhi Hua Ran

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Background. Laboratory data suggests a reduction of *Faecalibacterium prausnitzii* (*F. prausnitzii*) is confirmed both in fecal samples in inflammatory bowel disease (IBD) patients. Numerous observational studies have suspected dysbiosis, an imbalance between protective and harmful bacteria to be relevant to the etiology and pathogenesis of IBD. *Methods*. Medline, EMBASE, Pubmed, and others. were searched by 2 independent reviewers. Of 48 abstracts reviewed, 11 studies met our inclusion criteria (subject $N = 1180$). Meta-analysis was performed with Review Manager 5.2. *Results*. The bacterial count of *F. prausnitzii* in IBD patients was significantly lower (6.7888 ± 1.8875) log10 CFU/g feces than healthy controls (7.5791 ± 1.5812) log10 CFU/g feces; $P < 0.0001$. The Standardization Mean Difference of *F. prausnitzii* in IBD patients was −0.94 (95% confidence interval [CI]: −1.07−−0.80). Subgroup analyses revealed a trend toward a greater effect for CD (SMD: −1.13, 95% CI: −1.32−−0.94) when compared to UC (SMD: −0.78, 95% CI: −0.97−−0.60). *Conclusions*. The abundance of *F. prausnitzii* was decreased in IBD patients compared with healthy controls. Furthermore, the reduction of *F. prausnitzii* and misbalance of the intestinal microbiota are particularly higher in CD patients with ileal involvement.

KEYSTONE STRAINS – F.PRAUSNITZII

"The abundance of *F. prausnitzii* was **decreased in IBD patients** compared with healthy controls."

"In summary, our meta-analysis and systematic review suggest a possible **protective benefit of *F. prausnitzii* against the development of IBD**. Therefore, further treatment such as **probiotics or prebiotics to increase the levels of *F. prausnitzii*** in IBD are lead to attempts."

PERSPECTIVES

INFLAMMATION

Intestinal barriers protect against disease

Leaky cell-cell junctions contribute to inflammatory and autoimmune diseases

By **Sandra Citi**

All body surfaces and cavities are lined by layers of epithelial cells, which are connected by cell-cell junctions. These junctions serve three main purposes: adhesion, to maintain tissue integrity; creation of a barrier, to control the passage of ions, water, molecules, cells, and pathogens across epithelial layers; and signaling, to receive and transmit cues that affect cell behavior and tissue function. The barrier function is crucial to maintaining tissue homeostasis. Breaking or even slightly perturbing epithelial barriers can lead to serious pathological consequences, including infection and inflammation (*1*–*3*). The intestinal epithelial barrier is constantly being challenged by the gut microbiome, and is leaky in patients with inflammatory bowel disease (IBD) (*1, 3, 4*). Three studies now characterize how gut epithelial barrier dysfunction is involved in IBD, autoimmune disease, and systemic infection, respectively. On page 1161 of this issue, Mohanan *et al.* (*5*) describe how inactivation of the IBD susceptibility gene, *C1orf106* (chromosome 1 open reading frame 106), leads to decreased intestinal barrier function, thereby promoting intestinal sue. The tight junction (TJ), which contains claudins, occludin, and tricellulin as the main transmembrane proteins, is the most apical junction along the lateral surface, and is directly responsible for barrier function (*8, 9*). The *zonula adhaerens* (ZA), localized immediately below TJs between adjoining epithelial cells, is an adhesive junction composed of cadherin and nectin transmembrane adhesion molecules connected to the actin cytoskeleton. It regulates barrier function indirectly, because it is required for TJ formation, and because the contractility of the perijunctional actomyosin ring associated with its cytoplasmic surface modulates TJ function (*1*) (see the figure). The TJ barrier is made up of polymeric strands of proteins of the claudin family, which form tiny paracellular "pores" that either allow or block the passage of selected ions (*8, 10, 11*). Claudins are held in place by a cytoplasmic network of scaffolding molecules, linked to actin filaments (*12*). Thus, permeability of epithelial layers to ions and water depends on the specific expression of one or more of the 27 claudin isoforms, which varies within and between tissues, and is modulated by many different physiological and pathological cues, including inflammatory cytokines (*1–3, 8, 11*).

Larger solutes permeate across the barrier through the "leak" pathway, which is thought to result from temporary discontinuities within TJ polymeric claudin strands, mediated by occludin and tricellulin, and by the contraction of the actomyosin cytoskeleton (*1, 2, 12*). Another mechanism of barrier regulation is endocytic internalization of junctional protein components, which can drive constitutive physiological remodeling of cell-cell junctions, as well as pathological weakening of the barrier (*13*). Both TJs and ZAs are signaling hubs, recruiting and regulating proteins with different roles, including regulators of the actin cytoskeleton, gene expression, and response to growth factors and pathogens (*14*). Unrestricted passage of pathogens and cells across epithelial layers occurs when the integrity of cell-cell junctions is severely disrupted. Thus, diverse pathological states can ultimately affect barrier function, epithelial integrity, and tissue repair by acting on one or a combination of protein targets that are involved in the diverse functions of cell-cell junctions.

EPITHELIAL BARRIER

"Three studies now characterize how **gut epithelial barrier dysfunction is involved in IBD, autoimmune disease, and systemic infection**."

"Pathogenic bacteria can induce intestinal barrier defects and translocate to lymph nodes and liver, **triggering systemic autoimmune disease**, such as systemic lupus erythematosus (SLE)."

The gut-brain barrier in major depression: Intestinal mucosal dysfunction with an increased translocation of LPS from gram negative enterobacteria (leaky gut) plays a role in the inflammatory pathophysiology of depression

MUCOSAL DYSFUNCTION

ORIGINAL AR

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Submitted: 2008-01-06 *Accepted: 2008-01-27* *Published online: 2008-02-22*

Key words: **major depression; chronic fatigue syndrome; inflammation; enterobacteria; leaky gut; gut permeability; cytokines; LPS; oxidative stress**

Neuroendocrinol Lett 2008; **29**(1):117–124 **PMID:** 18283240 NEL290108A12

Abstract

There is now evidence that major depression (MDD) is accompanied by an activation of the inflammatory response system (IRS) and that pro-inflammatory cytokines and lipopolysacharide (LPS) may induce depressive symptoms.
The aim of the present study was to examine whether an increased gastrointestinal permeability with an increased translocation of LPS from gram negative bacteria

"The results show that **intestinal mucosal dysfunction** characterized by an increased translocation of gram-negative bacteria (leaky gut) **plays a role in the inflammatory pathophysiology of depression**."

Gastroesophageal reflux disease—from reflux episodes to mucosal inflammation

Arne Kandulski and Peter Malfertheiner

Abstract | Gastroesophageal reflux disease (GERD) affects 20–30% of the population in Western countries, and is one of the most common clinical problems in daily practice. GERD-associated functional and structural abnormalities are caused by recurrent exposure of the esophagus to acidic and nonacidic refluxate of gastric contents (containing duodenal and intestinal proteases as well as acid and gastric pepsin) from the stomach. Major progress has been made in the understanding of the molecular pathogenesis of GERD-associated mucosal inflammation, suggesting a complex and multifactorial pathogenesis and immune-mediated effects. This Review summarizes the complexity of mucosal pathogenesis, including microscopic changes, mucosal inflammation and GERD-specific molecular mediators, in the context of the clinical features and pathophysiological characteristics of GERD. The abnormal exposure of the esophagus to luminal contents leads to chronic mucosal inflammation that is characterized by the release of IL-8 specifically, as well as other proinflammatory mediators, from the esophageal mucosa. Evidence from animal studies indicates a stepwise inflammatory response by the epithelium, which attracts immune effector cells to infiltrate the mucosa. From bench to bedside, these novel molecular findings might provide new treatment options beyond current acid-suppressive therapy and the principle of inhibition of transient lower esophageal sphincter relaxation.

Kandulski, A. & Malfertheiner, P. *Nat. Rev. Gastroenterol. Hepatol.* **9**, 15–22 (2012); published online 22 November 2011; doi:10.1038/nrgastro.2011.210

MUCOSAL IMMUNE DYSFUNCTION

Introduction

Gastroesophageal reflux disease (GERD) is a chronic disorder that is caused by abnormal reflux with prolonged exposure of the distal esophagus to gastric substantial burden for national health-care systems.[7] The accurate diagnosis of GERD represents a challenge as only 50% of patients with GERD present with

"In the pathophysiology of GERD, abnormal exposure of the esophagus to luminal contents leads to **chronic mucosal inflammation** that is characterized by the release of IL-8 specifically, as well as other proinflammatory mediators, from the esophageal mucosa."

"Hydrogen ions and gastric pepsin exert a corrosive effect on the surface of the esophageal mucosa and degrade junctional proteins, thereby **destroying epithelial barrier function** with the consequent induction of intramucosal inflammation."

AIDS Rev. 2008;10:36-46

Mucosal Immune Dysfunction in AIDS Pathogenesis

Mirko Paiardini[1], Ian Frank[2], Ivona Pandrea[3], Cristian Apetrei[3] and Guido Silvestri[1,4]

[1]Departments of Pathology and Laboratory Medicine and [2]Medicine, University of Pennsylvania, Philadelphia, USA; [3]Tulane National Primate Research Center; [4]Yerkes National Primate Research Center, Emory University, Atlanta, USA

Abstract

The mucosal immune system plays a central role in both the transmission of HIV infection and the pathogenesis of AIDS. Most HIV infections are acquired through mucosal transmission, and quantitative and qualitative defects of mucosal immunity are consistently present in all stages of pathogenic HIV and SIV infections. A series of recent studies has emphasized the role of a rapid, dramatic, and largely irreversible depletion of mucosa-associated lymphoid tissue-based memory CD4⁺CCR5⁺ T-cells as a key determinant of disease progression in HIV-infected individuals and SIV-infected macaques. It has also been proposed that, in order to be effective, an AIDS vaccine should prevent the early depletion of these mucosal CD4⁺ T-cells. However, the observation of depletion of mucosal CD4⁺ T-cells during the primary phase of nonpathogenic SIV infection of natural SIV hosts, such as sooty mangabeys and African green monkeys, suggests that additional pathogenic factors are involved in the AIDS-associated mucosal immune dysfunction. These factors may include: (i) selective depletion of specific CD4⁺ T-cell subsets; (ii) dysfunction of other (non-CD4⁺) immune cells; and (iii) generalized immune activation. Importantly, the mucosal immune dysfunction observed during pathogenic HIV and SIV infection is associated with translocation of microbial products (i.e. lipopolysaccharide) from the intestinal lumen to the systemic circulation where they may be responsible, at least in part, for the chronic immune activation that follows pathogenic HIV and SIV infections. The role of mucosal immunity in AIDS pathogenesis emphasizes the importance of understanding whether and to what extent the HIV-associated depletion of mucosal CD4⁺ T-cells is reversible after prolonged suppression of virus replication with antiretroviral therapy. Further studies of mucosal immunity during primate lentiviral infections will be needed to better understand, and ultimately prevent and treat, the mechanisms underlying the AIDS-associated mucosal immune dysfunction.

(AIDS Rev. 2008;10:36-46)

Corresponding author: Guido Silvestri, gsilvest@mail.med.upenn.edu

MUCOSAL DYSFUNCTION

"Early HIV infection is consistently associated with a rapid, dramatic, and largely irreversible depletion of mucosal CD4+ memory T-cells, particularly those expressing the HIV coreceptor CCR5."

"In conclusion, further studies are needed to solve the complex riddle of how the interaction between primate lentiviruses and the host mucosal immune system leads to the **severe mucosal immune dysfunction associated with progression to AIDS**."

GUT MICROBES
https://doi.org/10.1080/19490976.2018.1494102

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ADDENDUM

Identification of gut microbiome signatures associated with longevity provides a promising modulation target for healthy aging

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ABSTRACT

The world population is aging, which poses a significant burden to the economy and health care system. As people age, so do their gut microbiomes. Age-related changes in gut microbiome have been reported, including decreased microbial diversity and increased Proteobacteria. Recently, we characterized the gut microbiome of a group of long-living (≥ 90 years old) Chinese people. Interestingly, the diversity of their gut microbiome was greater than that of a young adult control group. We also identified several potentially beneficial bacteria enriched in the long-living Chinese group. These results were validated using data from an independent Italian cohort that included a group of long-living individuals. Other recent studies have found similar results. Here, we provide a summary of these discoveries and discuss their implications in healthy aging.

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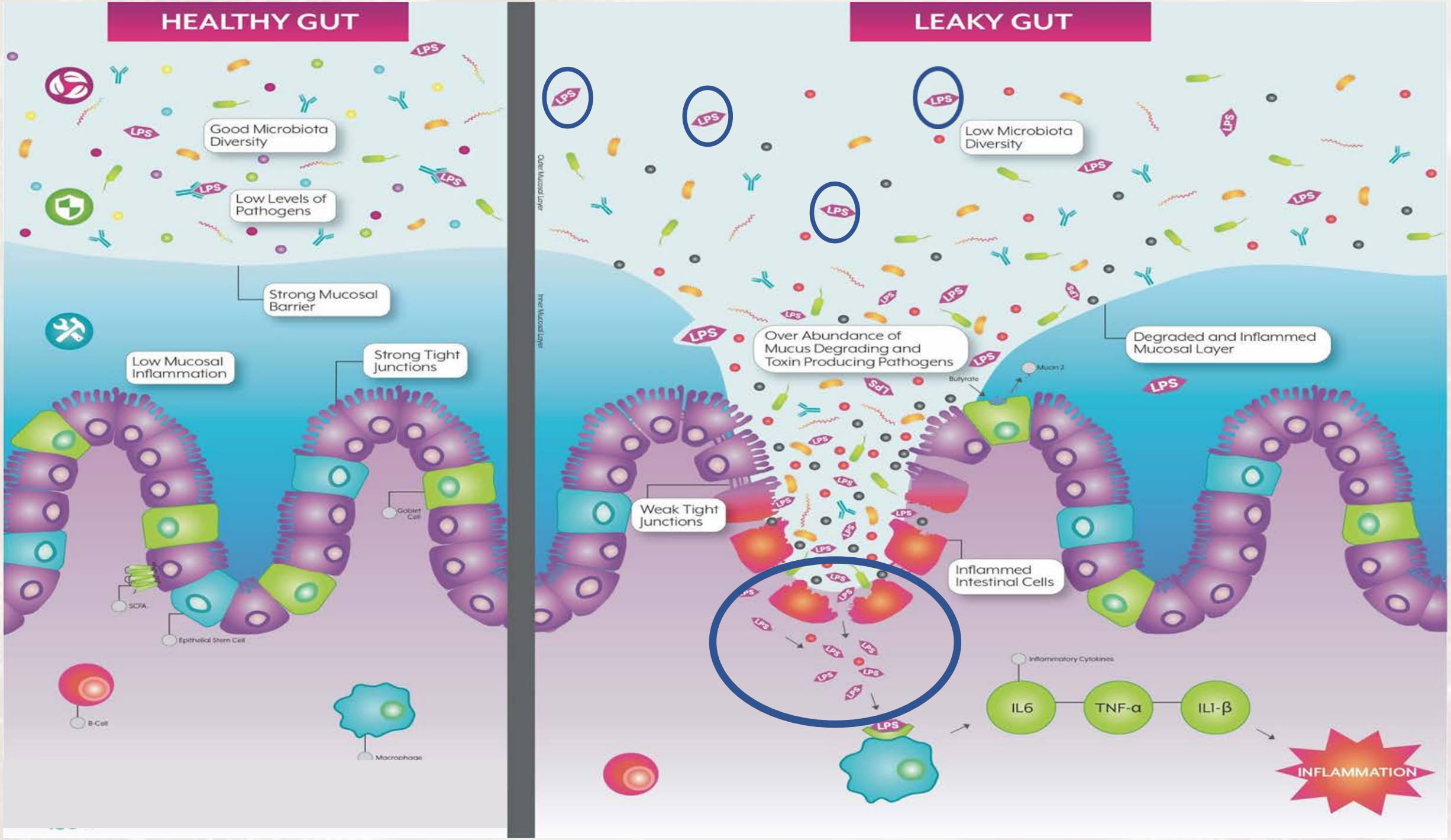
gut microbiota; healthy aging; diversity; beneficial bacteria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Mucin 2
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Inflammed Intestinal Cells
Inflammatory Cytokines
IL6
TNF-α
IL1-β
INFLAMMATION

WHAT IS METABOLIC ENDOTOXEMIA?

Metabolic endotoxemia is essentially an innate immune response that becomes a sub-clinical, persistent, low-grade inflammation because of increased, circulating endotoxins. – Primarily LPS.

- Metabolic endotoxemia is a condition that is estimated to affect approximately 50% of the western population.
- The conditions is characterized by increased serum endotoxin (typically lipopolysaccharide) concentration during the first five hours of the post-prandial period following consumption of a meal.
- Meals that are high in fat and dense in calories seem to impact the condition more so than low fat and low calorie meals.
- This increase in serum endotoxin concentration is followed by elevated inflammation that is marked by measurable increases in interleukin-6, interleukin-1beta, interferon-gamma, triglycerides and post-prandial insulin.
- Chronic metabolic endotoxemia and the associated inflammation has been shown to have significant correlation to increases in the risk of developing a variety of chronic diseases.

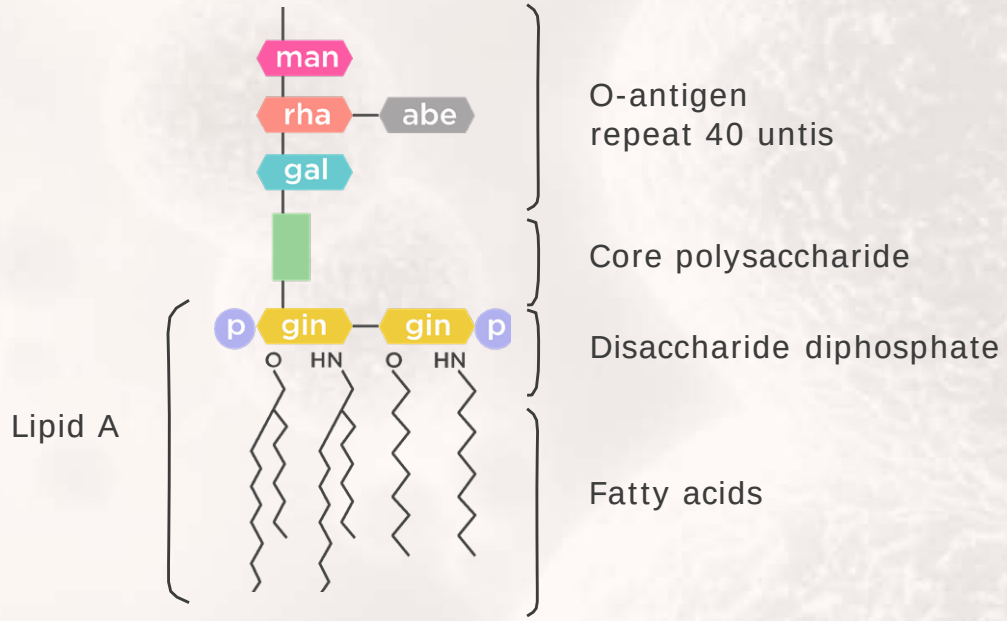
To date, studies support a strong correlation between metabolic endotoxemia (ME) and the increased risk or onset of conditions such as **cardiovascular disease**, **diabetes**, **obesity, hypogonadism, autoimmunity** and even mood disorders such as **anxiety** and **depression.**

WHAT IS ENDOTOXIN?

AKA lipopolysaccharide (LPS)

- Inflammatory immunogens
- Component of gram-negative bacterial outer cell wall
  - Adhesin for colonization of host
  - Diversity of antigenic strains

- Circulates at low-grade levels in healthy individuals
- Toxicity mainly mediated by the lipid-A component

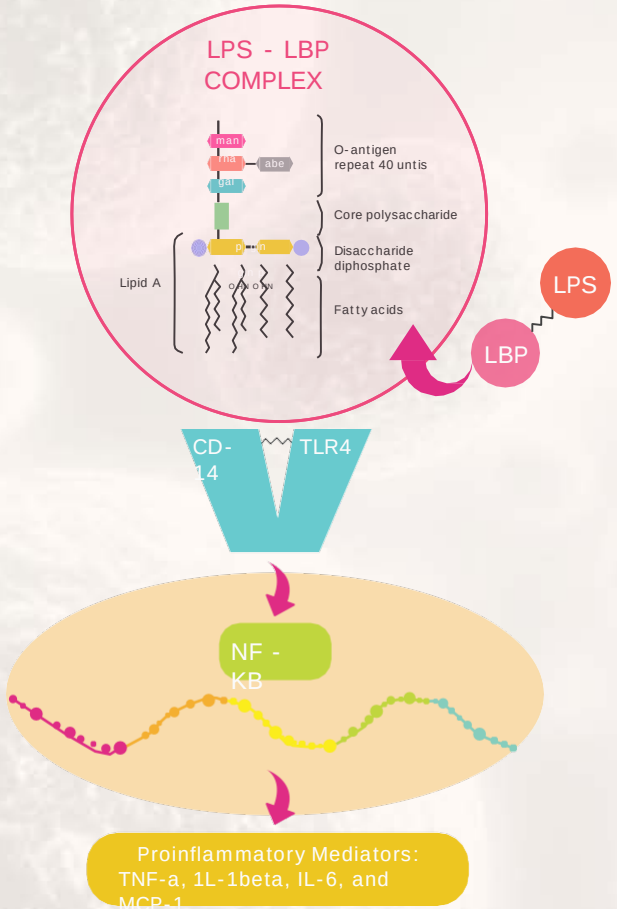


Structure of Lipopolysachharide

http://caltagmedsystems.blogspot.com/2013/05/ uscn-specialist-elisa-kit-manufacturer.html

Erridge, et al. Am J Clin Nutr. 2007;86:1286-1292

IMMUNE ACTIVATION IN METABOLIC ENDOTOXEMIA



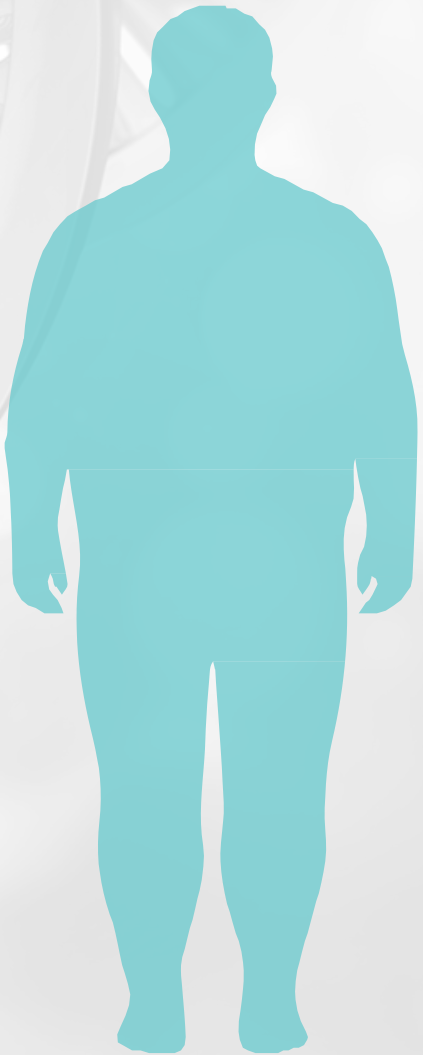
- TLR4 is an important signaling protein in innate immunity and is found on the surfaces of innate immune defense cells like Macrophages and dendritic cells.
- Circulating LPS gets bound by a phospholipid transfer protein called LBP, which carriers LPS to the CD14-TLR complex for examination.
- Once LPS-LBP has bound to the CD14-TLR complex, it initiates an immune cascade that leads to the activation of NFKß
- The activation of NFKß leads to the increased expression of pro-inflammatory mediators TNFα, IL-1beta, IL-6 and MCP-1.
- Innate immune cells that become activated by LPS and subsequently cause the chronic release of pro-inflammatory cytokines, exist in all parts of the body, including the blood-brain barrier.

CLINICAL MANIFESTATIONS OF LPS INDUCED CHRONIC IMMUNE ACTIVATION

METABOLIC ENDOTOXEMIA AND ELEVATED LPS IN DISEASE

THE METABOLIC SYNDROME

- Heart Disease
- Lipid Problems
- Hypertension
- Type 2 Diabetes
- Dementia
- Cancer
- Polysystic Ovarian Syndrome
- Non-Alcoholic Fatty Liver Disease



METABOLIC ENDOTOXEMIA AND ELEVATED LPS IN DISEASE

Metabolic Endotoxemia Initiates Obesity and Insulin Resistance

Patrice D. Cani, Jacques Amar, et al.
Diabetes 2007 Jul; 56(7): 1761-1772. https://doi.org/10.2337/db06-1491

Metabolic endotoxemia directly increases the proliferation of adipocyte precursors at the onset of metabolic diseases through a CD14-dependent mechanism

Elodie Luche, Béatrice Cousin, et al. Mol Metab. 2013 Aug; 2(3): 281–291.

Lipopolysaccharide Causes an Increase in Intestinal Tight Junction Permeability in Vitro and in Vivo by Inducing Enterocyte Membrane Expression and Localization of TLR-4 and CD14

Shuhong Guo, Rana Al-Sadi, Hamid M. Said, and Thomas Y. Ma The American Journal of Pathology, Vol. 182, No. 2, February 2013

Elevated endotoxin levels in non-alcoholic fatty liver disease

Alison L Harte et al.
Journal of Inflammation 20107:15
Received: 3 September 2009 Accepted: 30 March 2010Published: 30 March 2010

METABOLIC ENDOTOXEMIA AND ELEVATED LPS IN DISEASE

J Exp Med. 1977 May 1;145(5):1250-63.

Induction of autoimmunity in good and poor responder mice with thyroglobulin and lipopolysaccharide.

Esquivel PS, Rose NR, Kong YC.

Cell Immunol. 2001 Oct 10;213(1):52-61.

Immunomodulation of murine cytomegalovirus-induced myocarditis in mice treated with lipopolysaccharide and tumor necrosis factor.

Lenzo JC1, Fairweather D, Shellam GR, Lawson CM.

J Immunol. 2005 Jul 15;175(2):959-66.

Lipopolysaccharide injection induces relapses of experimental autoimmune encephalomyelitis in nontransgenic mice via bystander activation of autoreactive CD4+ cells.

Nogai A1, Siffrin V, Bonhagen K, Pfueller CF, Hohnstein T, Volkmer-Engert R, Brück W, Stadelmann C, Kamradt T.

Diabetes Care. 2012 Feb;35(2):375-82. doi: 10.2337/dc11-1593. Epub 2011 Dec 30.

High Fat intake Leads to Acute Postprandial Exposure to Circulating Endotoxin in type 2 Diabetic Subjects.

Harte AL1, Varma MC, Tripathi G, McGee KC, Al-Daghri NM, Al-Attas OS, Sabico S, O'Hare JP, Ceriello A, Saravanan P, Kumar S, McTernan PG.

"It is known that low-grade chronic systemic inflammation contributes to this risk, which appears altered by several factors such as increasing age, sex, ethnicity, genetics, and dietary influences. However, systemic inflammation appears to persist in type 2 diabetic subjects, despite medication, while the mechanisms and mediators of this continual inflammation appear less clear."

"…clinical studies have also implicated gut-derived endotoxin as a **"primary insult"** to activate the inflammatory state, contributing to metabolic disease, with current cross-sectional data showing elevated systemic endotoxin levels in conditions of obesity, type 2 diabetes, coronary artery disease, and fatty liver disease (8,10,11,14–17). Within these studies, circulating endotoxin is observed to be positively associated with waist circumference, waist-to-hip ratio, insulin levels, inflammatory cytokines and lipids, including total cholesterol, triglycerides (TGs), and LDL cholesterol, and negatively associated with HDL cholesterol (8,10,11,14–17)."

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Randomized Control Trials

Postprandial endotoxemia may influence the development of type 2 diabetes mellitus: From the CORDIOPREV study

Antonio Camargo [a, b, 1], Rosa Jimenez-Lucena [a, b, 1], Juan F. Alcala-Diaz [a, b], Oriol A. Rangel-Zuñiga [a, b], Sonia Garcia-Carpintero [a, b], Javier Lopez-Moreno [a, b], Ruth Blanco-Rojo [a, b], Javier Delgado-Lista [a, b], Pablo Perez-Martinez [a, b], Ben van Ommen [c], Maria M. Malagon [b, d], Jose M. Ordovas [e, f, g], Francisco Perez-Jimenez [a, b], Jose Lopez-Miranda [a, b, *]

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SUMMARY

Background & aims: Insulin resistance (IR) and impaired beta-cell function are key determinants of type 2 diabetes mellitus (T2DM). Intestinal absorption of bacterial components activates the toll-like receptors inducing inflammation, and this in turn IR. We evaluated the role of endotoxemia in promoting inflammation-induced insulin resistance (IR) in the development of T2DM, and its usefulness as predictive biomarker.

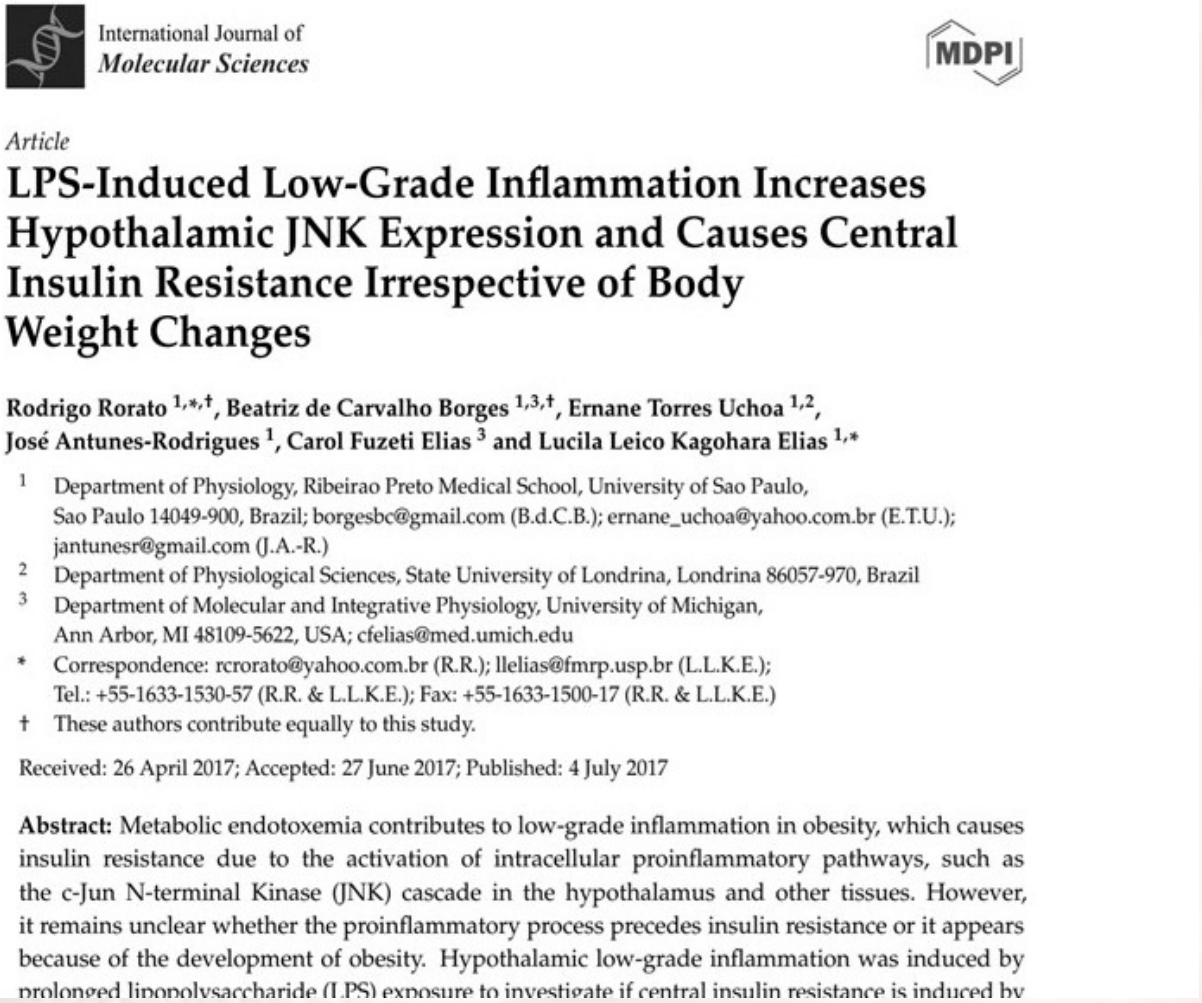
Methods: We included in this study 462 patients from the CORDIOPREV study without T2DM at baseline. Of these, 107 patients developed T2DM according to the American Diabetes Association (ADA) diagnosis criteria after a median follow-up of 60 months (Incident-DIAB group), whereas 355 patients did not developed it during this period of time (Non-DIAB group).

Results: We observed a postprandial increase in lipopolysaccharides (LPS) levels in the Incident-DIAB at baseline ($P < 0.001$), whereas LPS levels were not modified in the Non-DIAB. Disease-free survival curves based on the LPS postprandial fold change improved T2DM Risk Assessment as compared with the previously described FINDRISC score (hazard ratio of 2.076, 95% CI 1.149–3.750 *vs.* 1.384, 95% CI 0.740–2.589). Moreover, disease-free survival curves combining the LPS postprandial fold change and FINDRISC score together showed a hazard ratio of 3.835 (95% CI 1.323–11.114), linked to high values of both parameters.

Conclusion: Our results suggest that a high postprandial endotoxemia precedes the development of T2DM. Our results also showed the potential use of LPS plasma levels as a biomarker predictor of T2DM development.

Clinical trials.gov.identifier: NCT00924937.

"Conclusion: Our results suggest that a high postprandial endotoxemia precedes the development of T2DM. Our results also showed the potential use of LPS plasma levels as a biomarker predictor of T2DM development."



International Journal of *Molecular Sciences*

MDPI

Article

LPS-Induced Low-Grade Inflammation Increases Hypothalamic JNK Expression and Causes Central Insulin Resistance Irrespective of Body Weight Changes

Rodrigo Rorato [1,*,†], Beatriz de Carvalho Borges [1,3,†], Ernane Torres Uchoa [1,2], José Antunes-Rodrigues [1], Carol Fuzeti Elias [3] and Lucila Leico Kagohara Elias [1,*]

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† These authors contribute equally to this study.

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Abstract: Metabolic endotoxemia contributes to low-grade inflammation in obesity, which causes insulin resistance due to the activation of intracellular proinflammatory pathways, such as the c-Jun N-terminal Kinase (JNK) cascade in the hypothalamus and other tissues. However, it remains unclear whether the proinflammatory process precedes insulin resistance or it appears because of the development of obesity. Hypothalamic low-grade inflammation was induced by prolonged lipopolysaccharide (LPS) exposure to investigate if central insulin resistance is induced by

The present data suggest that an increased JNK activity in the hypothalamus *underlies the development of insulin resistance during prolonged exposure to endotoxins.* Our study reveals that weight gain is not mandatory for the development of hypothalamic insulin resistance and the blockade of proinflammatory pathways could be useful for restoring the insulin signaling during prolonged low-grade inflammation as seen in obesity.

Alison L. Harte et al. Dia Care 2017;35:375-382

American Diabetes Association®

frontiers in Immunology

PERSPECTIVE
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doi: 10.3389/fimmu.2017.01064

Microbiome-Derived Lipopolysaccharide Enriched in the Perinuclear Region of Alzheimer's Disease Brain

*Yuhai Zhao[1,2], Lin Cong[1,3], Vivian Jaber[1] and Walter J. Lukiw[1,4,5]**

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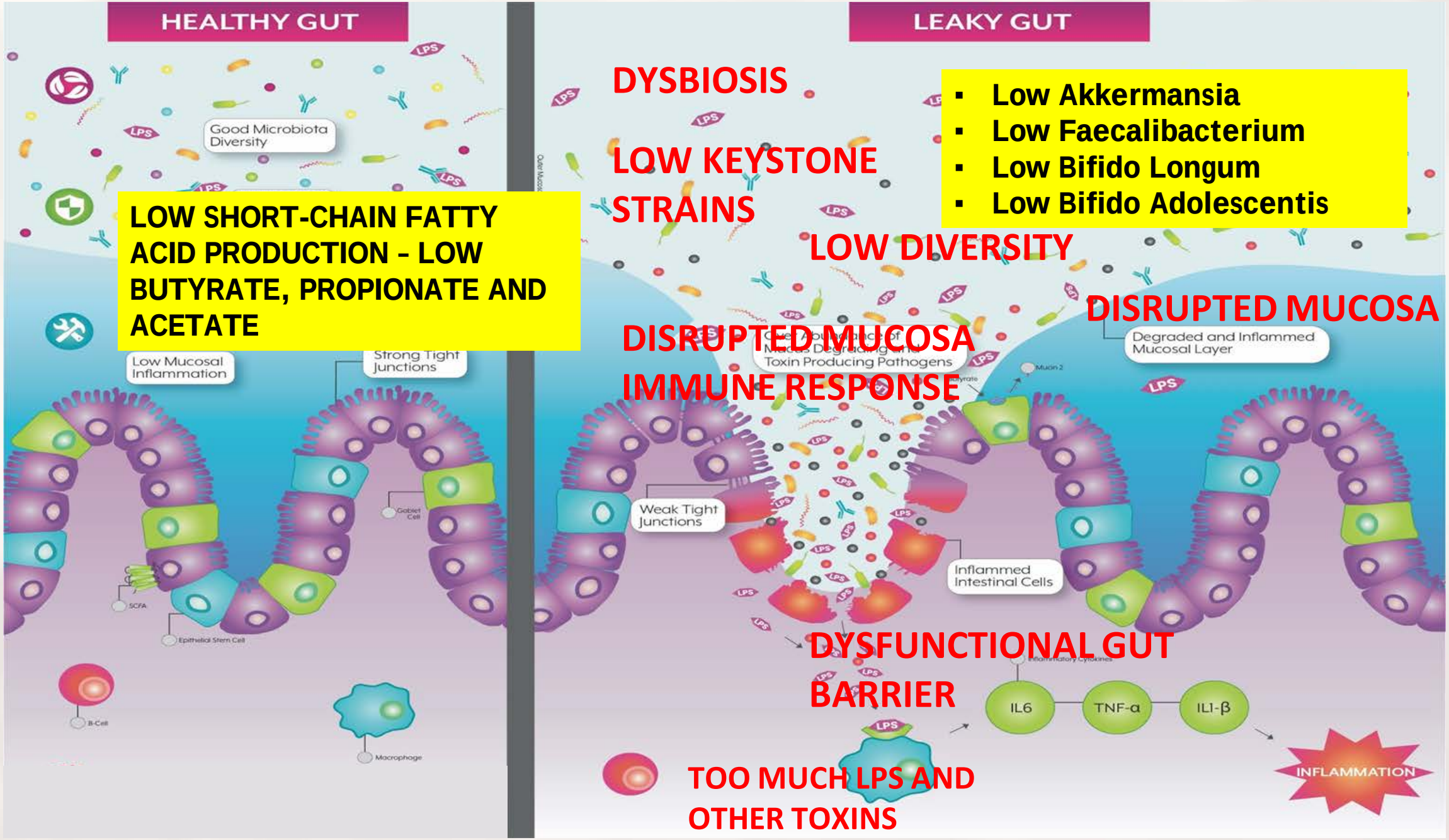
Abundant clinical, epidemiological, imaging, genetic, molecular, and pathophysiological data together indicate that there occur an unusual inflammatory reaction and a disruption of the innate-immune signaling system in Alzheimer's disease (AD) brain. Despite many years of intense study, the origin and molecular mechanics of these AD-relevant pathogenic signals are still not well understood. Here, we provide evidence that an intensely pro-inflammatory bacterial lipopolysaccharide (LPS), part of a complex mixture of pro-inflammatory neurotoxins arising from abundant Gram-negative bacilli of the human gastrointestinal (GI) tract, are abundant in AD-affected brain neocortex and hippocampus. For the first time, we provide evidence that LPS immunohistochemical signals appear to aggregate in clumps in the parenchyma in control brains, and in AD, about 75% of anti-LPS signals were clustered around

CONDITION	MECHANISM
Leptin Resistance	LPS enters and causes inflammation in the enteric nervous system leading to a disruption in the gut-brain axis of communication.
Chronic Constipation	LPS enters the enteric nervous system and causes disruption in signals for gastric emptying and bowel motility.
Mood and Appetite Disorders	LPS disrupts ghrelin function which has a direct impact on appetite and mood,
Depression	LPS can migrate to the blood-brain barrier and cause inflammation along with inhibition of dopamine receptors.
Cognitive Decline	Inflammation in the blood brain barrier leads to cognitive decline.
Loss of Memory and Recall	LPS can get into the amygdala and hippocampus which disrupts memory function.
Depression	LPS can increase the turnover of serotonin in the synapse and CNS reducing the concentration in those regions.
Anorexia Nervosa	The reduction of serotonin in the synapse and CNS is proposed as a possible mechanism for anorexia.
Anxiety	LPS disrupts key communication between the hypothalamic-adrenal-pituitary axis thereby increasing the expression of corticosteroid releasing hormone.
Chronic Pain	Elevated LPS in sensory neurons in the dorsal root stimulate nociceptors.
Parkinson's	Intra-cranially LPS causes microglial activation and neuronal loss.
Hypogonadism (low testosterone)	Increased circulating LPS and the subsequent chronic immune activation has feedback inhibition of testosterone production. GELDING theory.
Autoimmunity	Chronic activation of the innate immune system in various tissues leads to the by-stander effect where self-tissues inadvertently become targeted by the immune system.

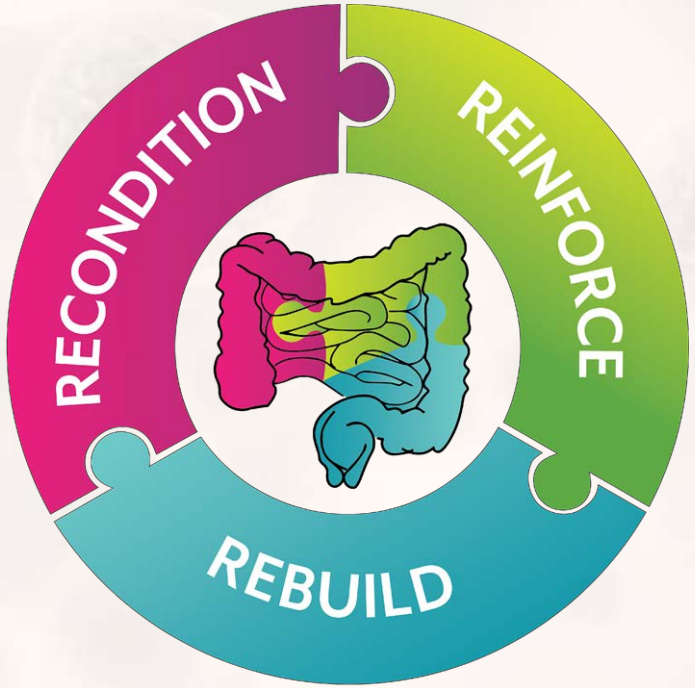

HEALTHY GUT
LEAKY GUT
Good Microbiota Diversity
LOW SHORT-CHAIN FATTY ACID PRODUCTION – LOW BUTYRATE, PROPIONATE AND ACETATE
Low Mucosal Inflammation
Strong Tight Junctions
Goblet Cell
SCFA
Epithelial Stem Cell
B-Cell
Macrophage
DYSBIOSIS
LOW KEYSTONE STRAINS
Low Akkermansia
Low Faecalibacterium
Low Bifido Longum
Low Bifido Adolescentis
LOW DIVERSITY
DISRUPTED MUCOSA
IMMUNE RESPONSE
Toxin Producing Pathogens
DISRUPTED MUCOSA
Degraded and Inflammed Mucosal Layer
Mucin 2
Weak Tight Junctions
Inflammed Intestinal Cells
DYSFUNCTIONAL GUT BARRIER
IL6
TNF-α
IL1-β
INFLAMMATION
TOO MUCH LPS AND OTHER TOXINS
LPS

TOTAL GUT RESTORATION

SPORE BASED
PROBIOTIC

RECONDITION
the gut

FIX THE MICROBIOME:
- **INCREASE KEYSTONE STRAINS**
- **INCREASE DIVERSITY**



PRECISION
PREBIOTIC

REINFORCE
beneficial changes

AFFIRM THE NEW MICROBIOME:
- **ESTABLISH HIGHER MORE STABLE POPULATIONS**
- **INCREASE KEY POST-BIOTICS (SCFA)**

IMMUNOGLOBULINS, POLYPHENOLS
AND AMINO ACIDS

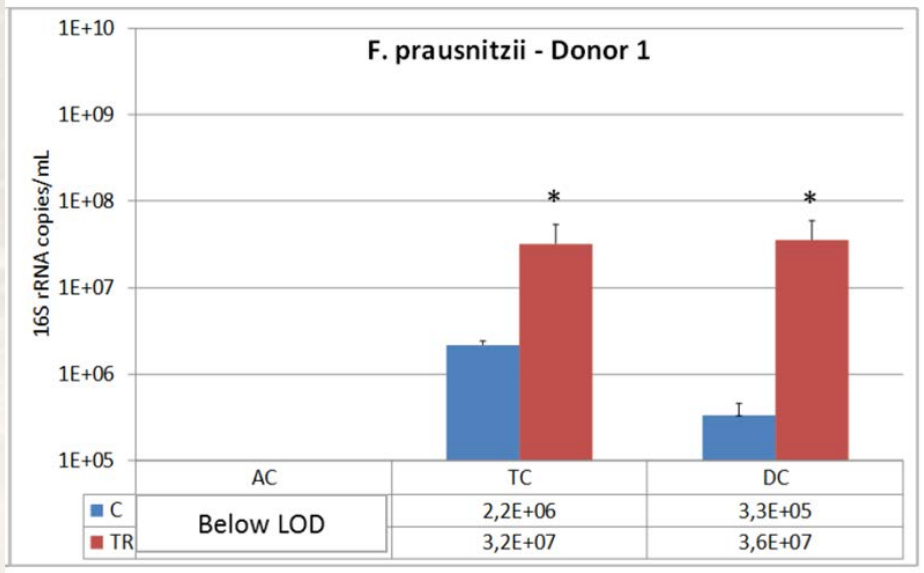
REBUILD
intestinal mucosa

ALLOW FOR REBUILDING OF THE MUCOSA:
- **REDUCE MUCOSAL AND INTESTINAL INFLAMMATION**
- **MODULATE MUCOSAL IMMUNE RESPONSE**
- **PROVIDE MUCOSAL BUILDING BLOCKS**
- **REDUCE PATHOGEN EFFECT**

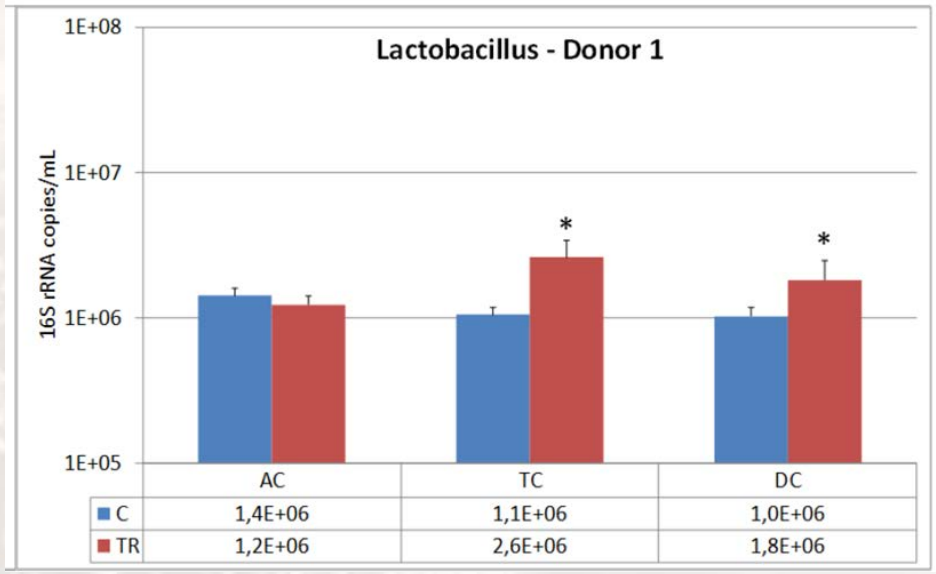
RECONDITION the gut

REINFORCE beneficial changes

PROBIOTIC ONLY

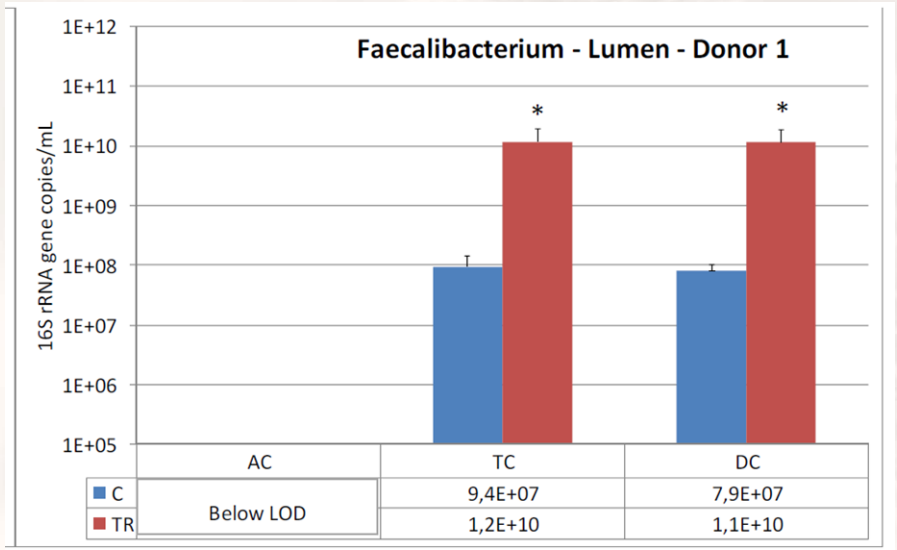


	AC	TC	DC
C	Below LOD	2,2E+06	3,3E+05
TR		3,2E+07	3,6E+07

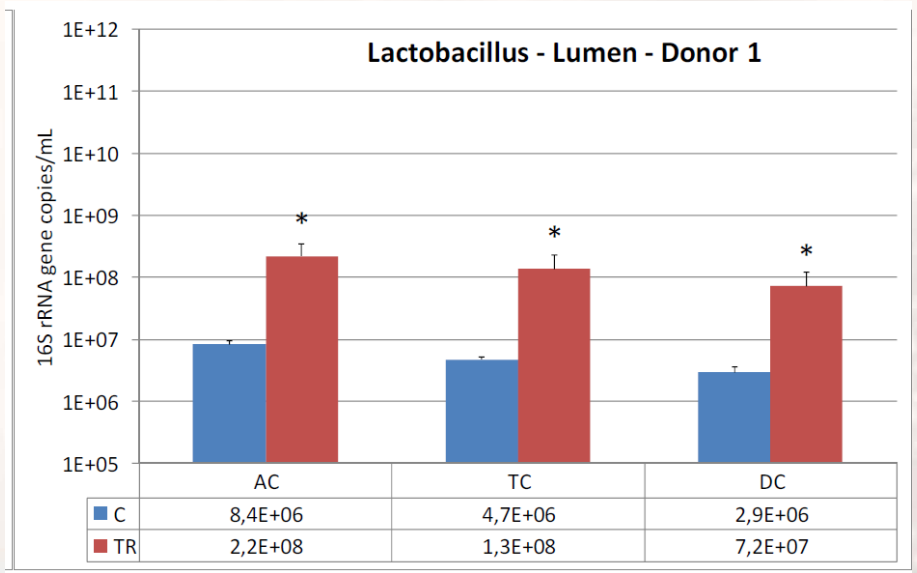


	AC	TC	DC
C	1,4E+06	1,1E+06	1,0E+06
TR	1,2E+06	2,6E+06	1,8E+06

SYNBIOTIC



	AC	TC	DC
C	Below LOD	9,4E+07	7,9E+07
TR		1,2E+10	1,1E+10

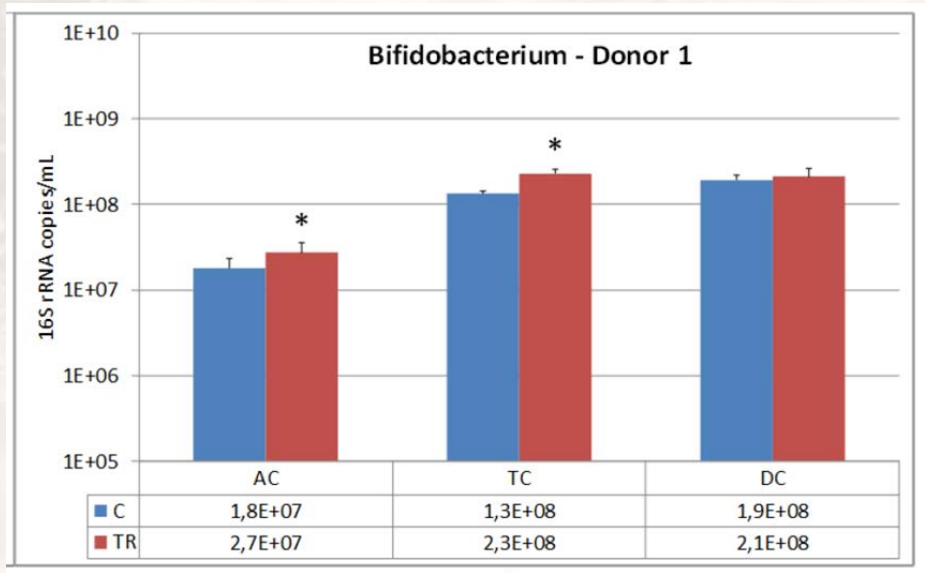


	AC	TC	DC
C	8,4E+06	4,7E+06	2,9E+06
TR	2,2E+08	1,3E+08	7,2E+07

RECONDITION the gut

REINFORCE beneficial changes

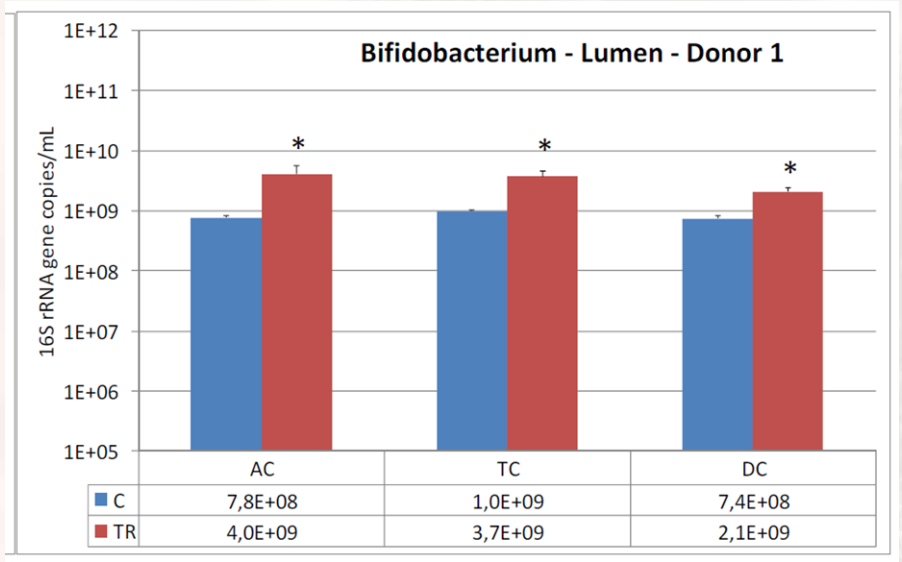
PROBIOTIC ONLY



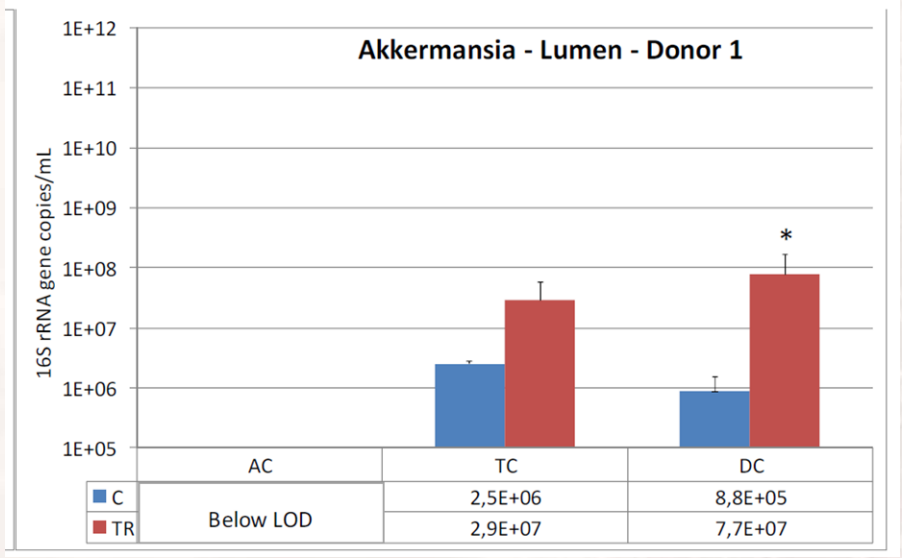
	AC	TC	DC
C	1,8E+07	1,3E+08	1,9E+08
TR	2,7E+07	2,3E+08	2,1E+08

AKKERMANSIA – BELOW DETECION LEVEL

SYNBIOTIC



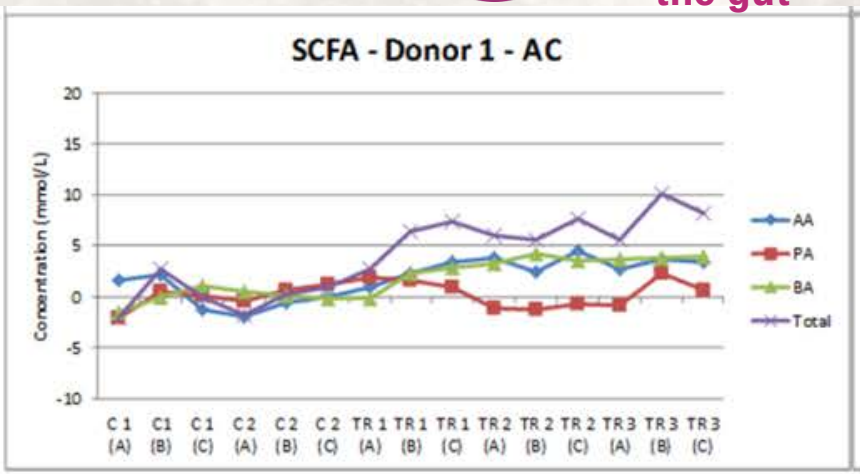
	AC	TC	DC
C	7,8E+08	1,0E+09	7,4E+08
TR	4,0E+09	3,7E+09	2,1E+09

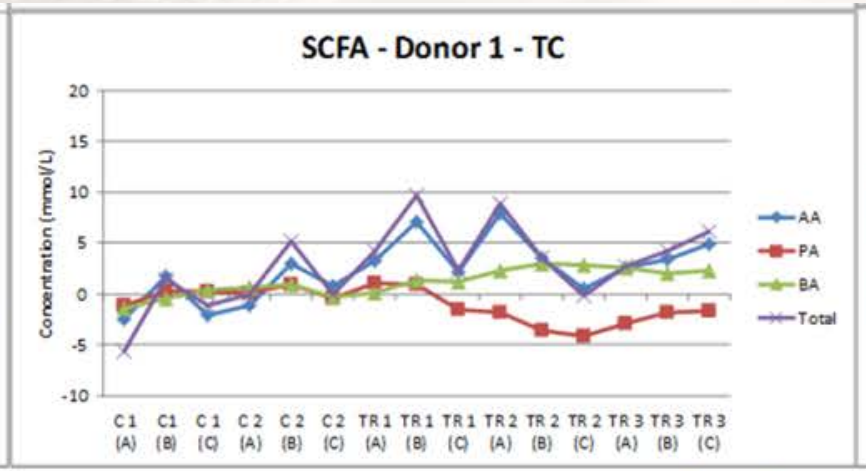


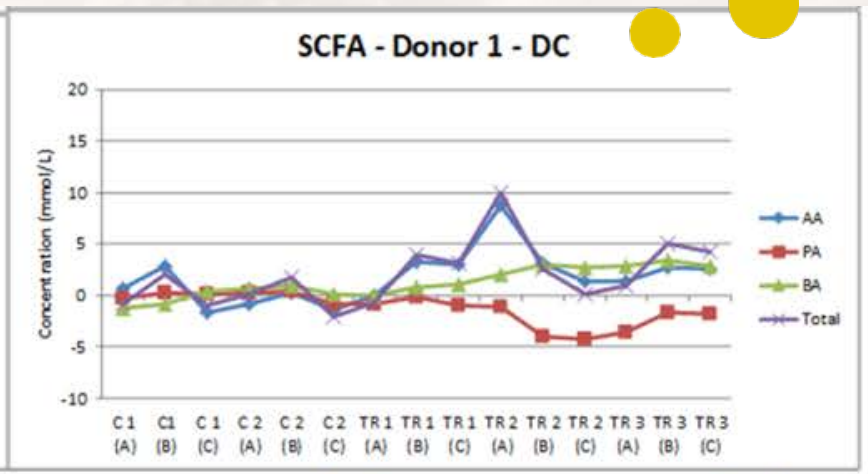
	AC	TC	DC
C	Below LOD	2,5E+06	8,8E+05
TR		2,9E+07	7,7E+07

RECONDITION
the gut

PROBIOTIC ONLY



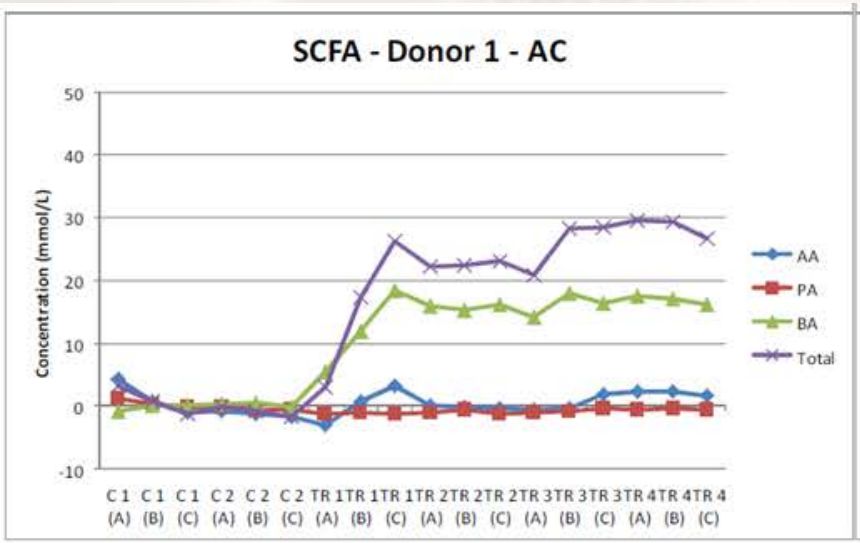


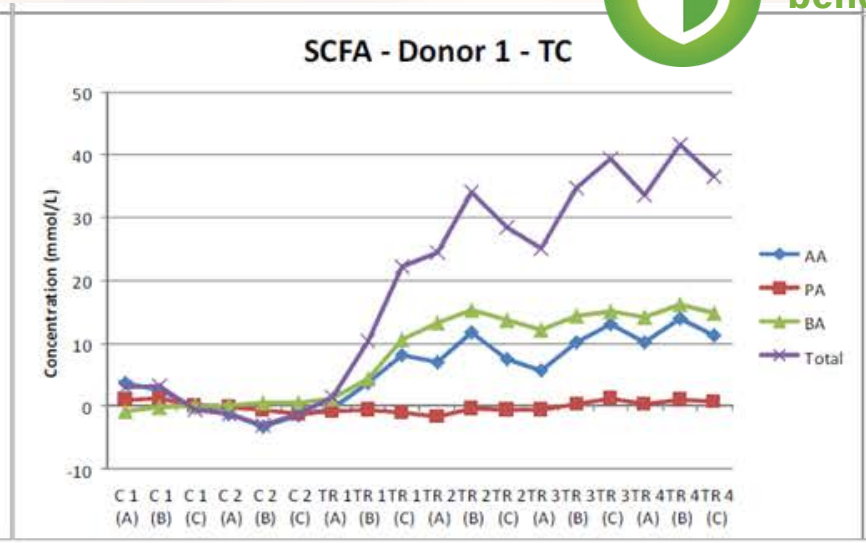


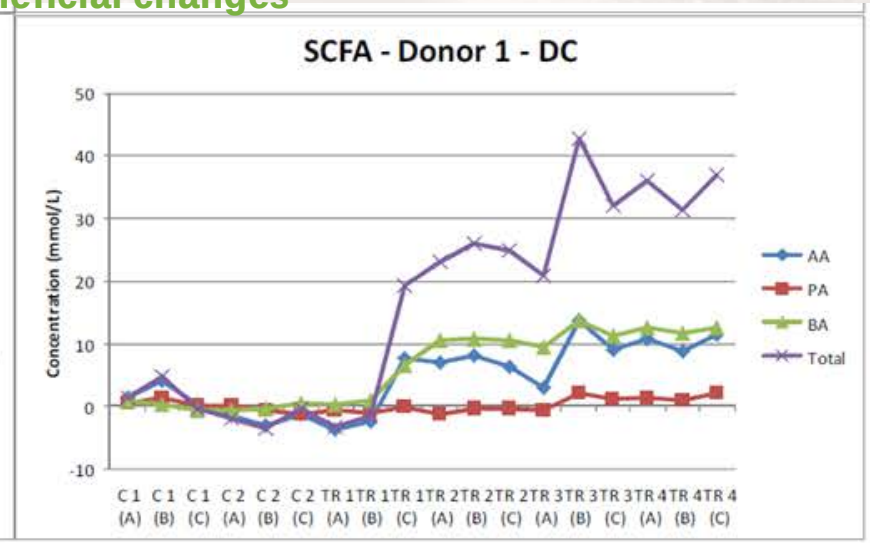
Spore treatment **significantly increased butyrate concentrations** during the f**inal weeks of treatment**. An increase of 3.9 mM (**70.2%**) in the AC, 2.8 mM (**24.1%**) in the TC and 3.6 mM (**28.4%**) in the DC was observed

SYNBIOTIC

REINFORCE
beneficial changes





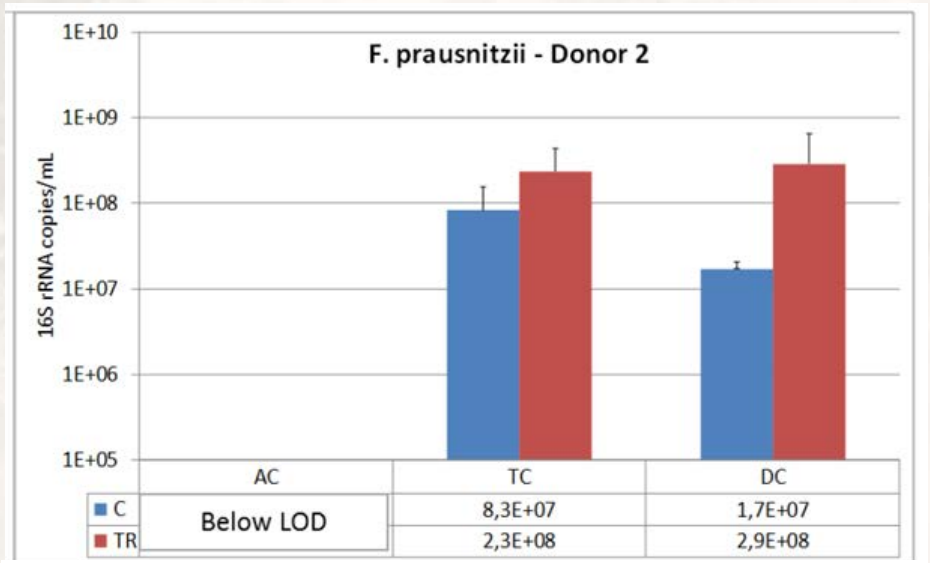


80-140% increase in SCFA production

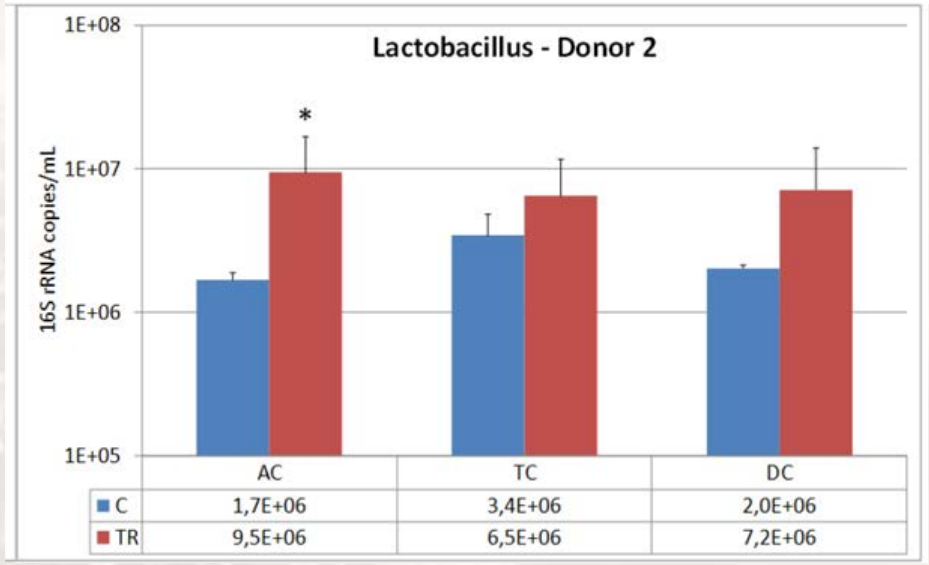
RECONDITION the gut

REINFORCE beneficial changes

PROBIOTIC ONLY

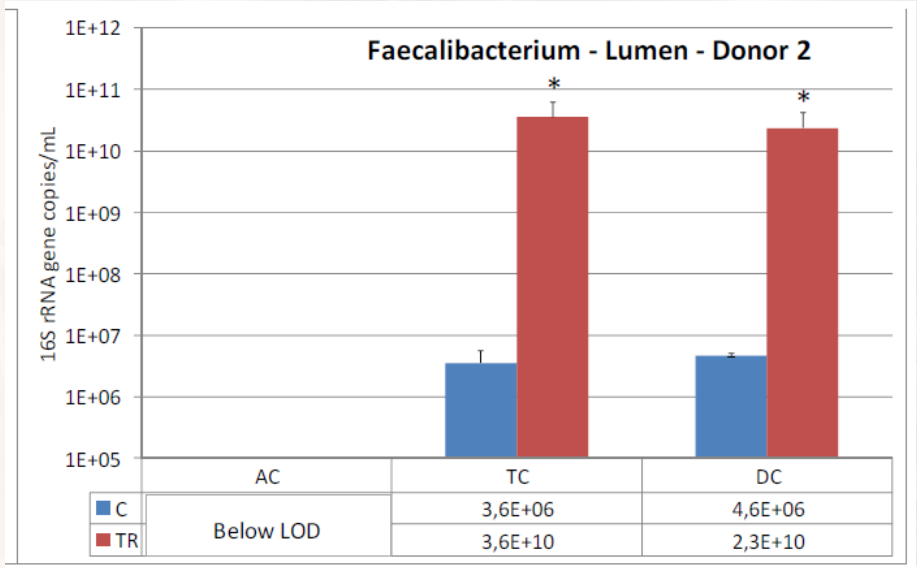


	AC	TC	DC
C	Below LOD	8,3E+07	1,7E+07
TR		2,3E+08	2,9E+08

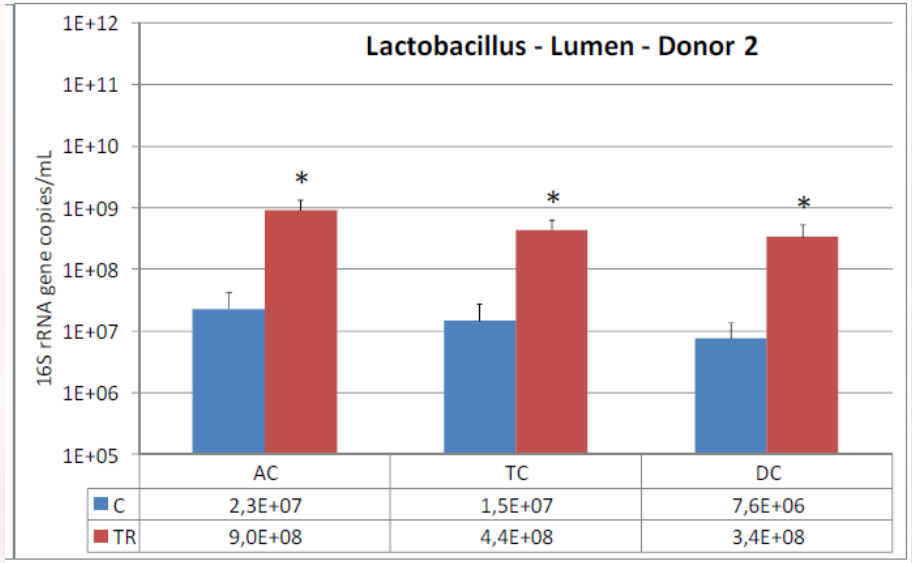


	AC	TC	DC
C	1,7E+06	3,4E+06	2,0E+06
TR	9,5E+06	6,5E+06	7,2E+06

SYNBIOTIC



	AC	TC	DC
C	Below LOD	3,6E+06	4,6E+06
TR		3,6E+10	2,3E+10

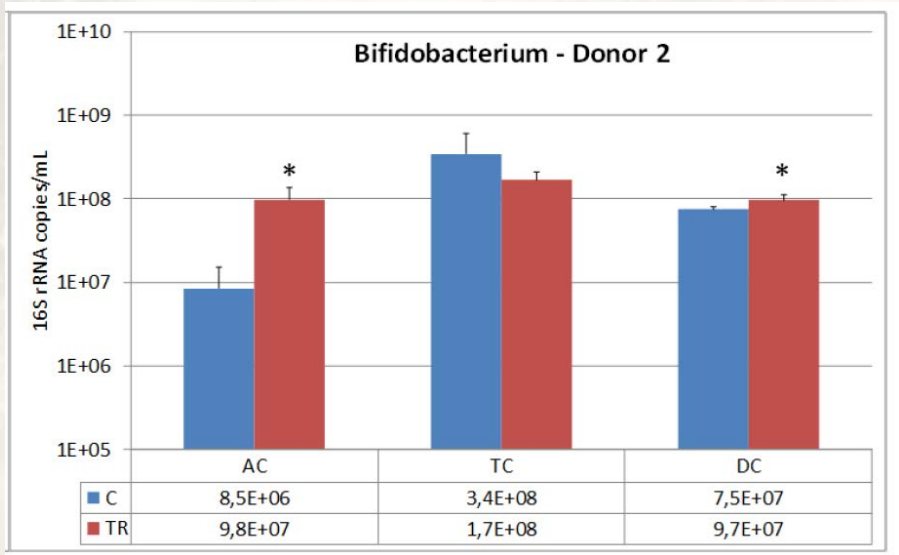


	AC	TC	DC
C	2,3E+07	1,5E+07	7,6E+06
TR	9,0E+08	4,4E+08	3,4E+08

RECONDITION the gut

REINFORCE beneficial changes

PROBIOTIC ONLY



	AC	TC	DC
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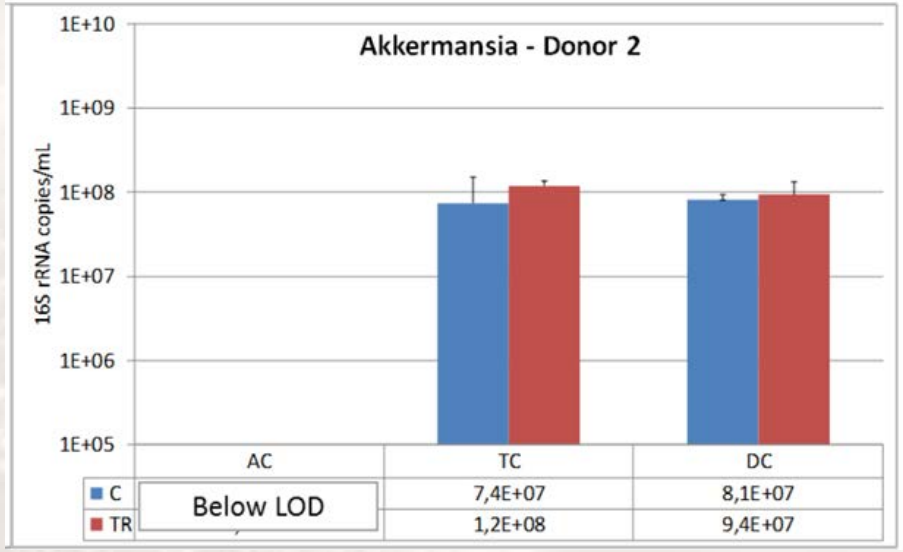
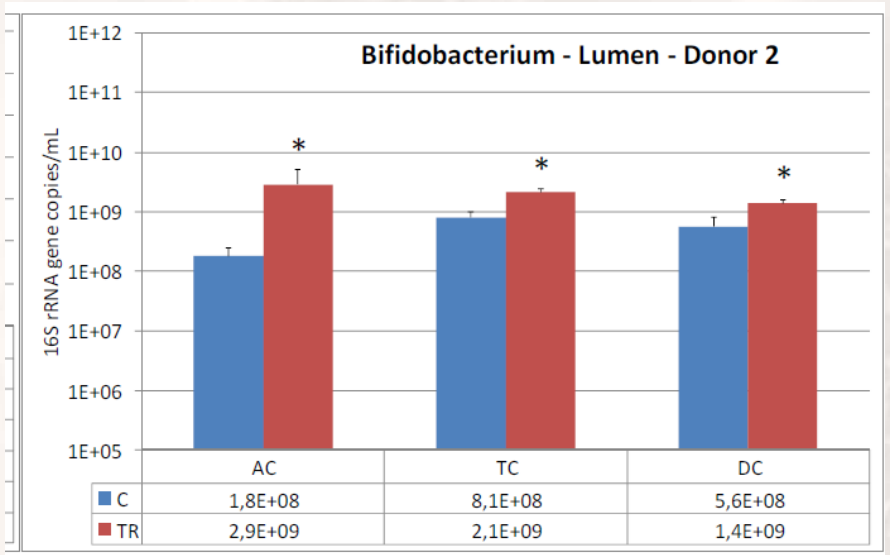
TR	9,8E+07	1,7E+08	9,7E+07

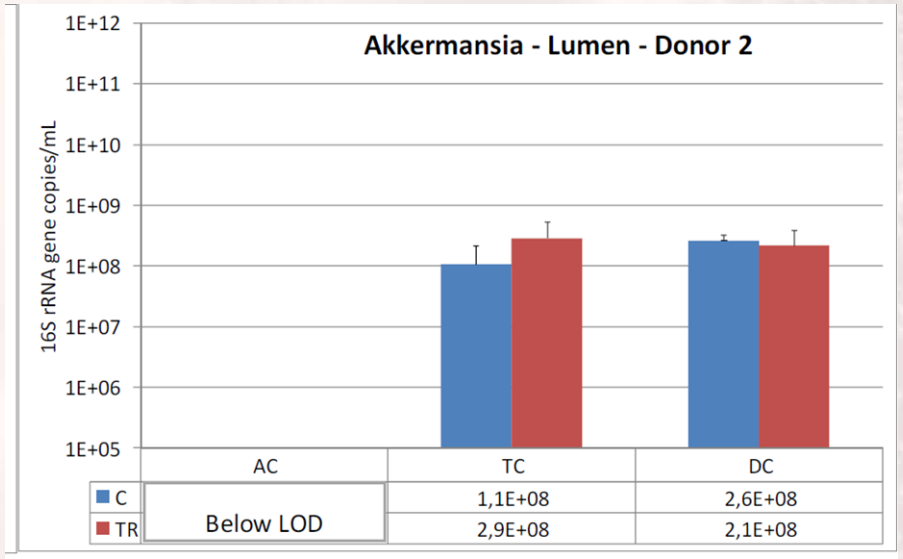


	AC	TC	DC
C	Below LOD	7,4E+07	8,1E+07
TR		1,2E+08	9,4E+07

SYNBIOTIC



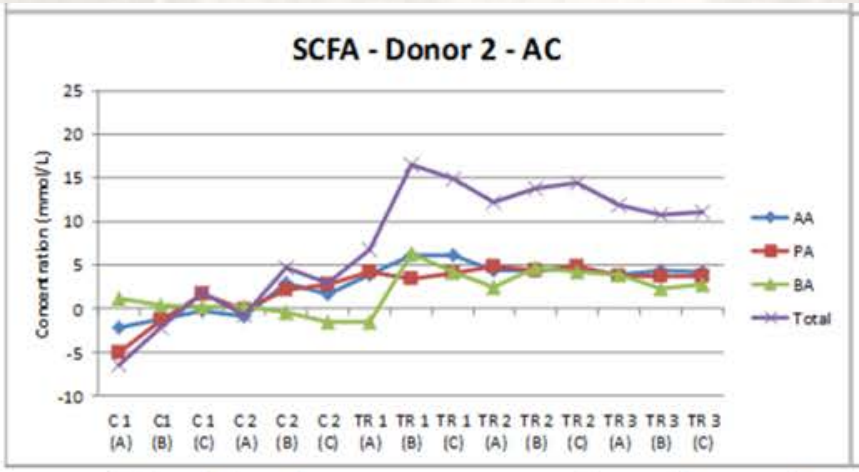
	AC	TC	DC
C	1,8E+08	8,1E+08	5,6E+08
TR	2,9E+09	2,1E+09	1,4E+09

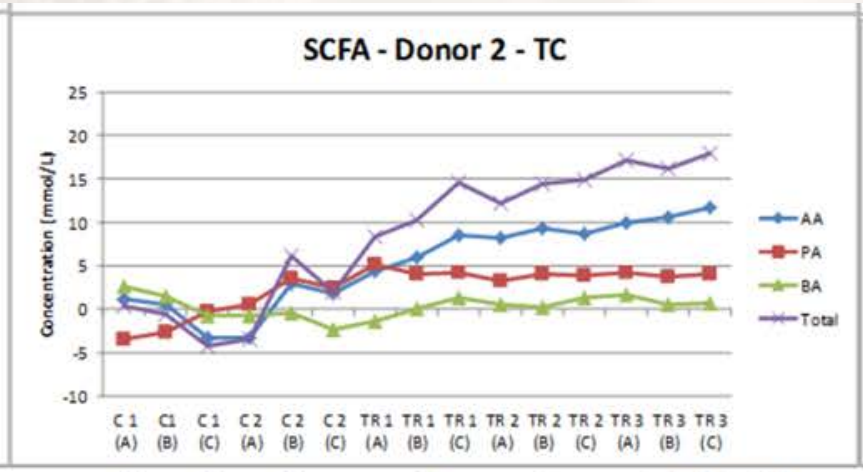


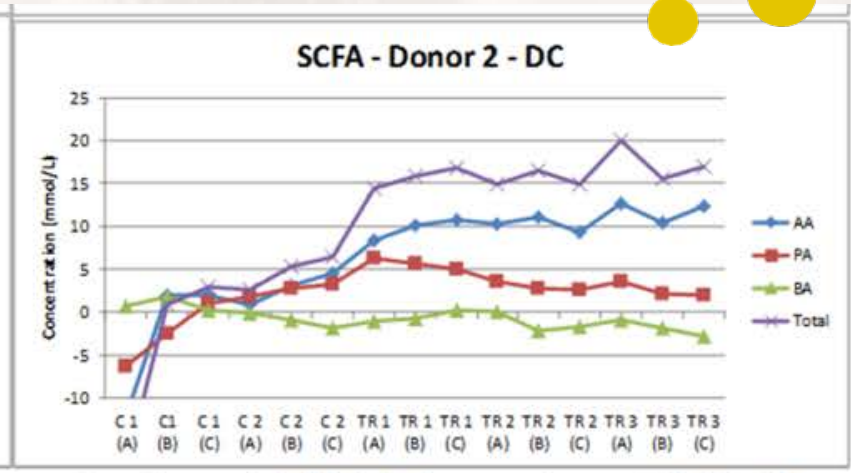
	AC	TC	DC
C	Below LOD	1,1E+08	2,6E+08
TR		2,9E+08	2,1E+08

RECONDITION
the gut

PROBIOTIC ONLY

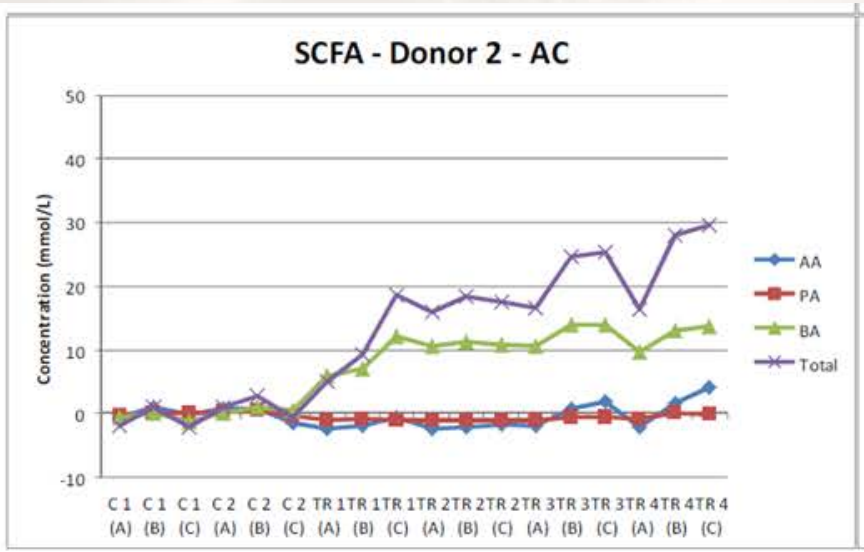


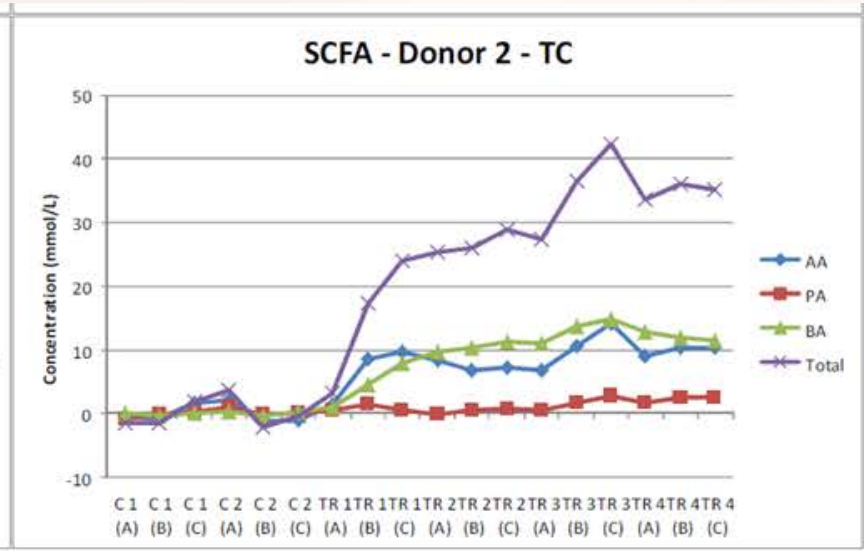


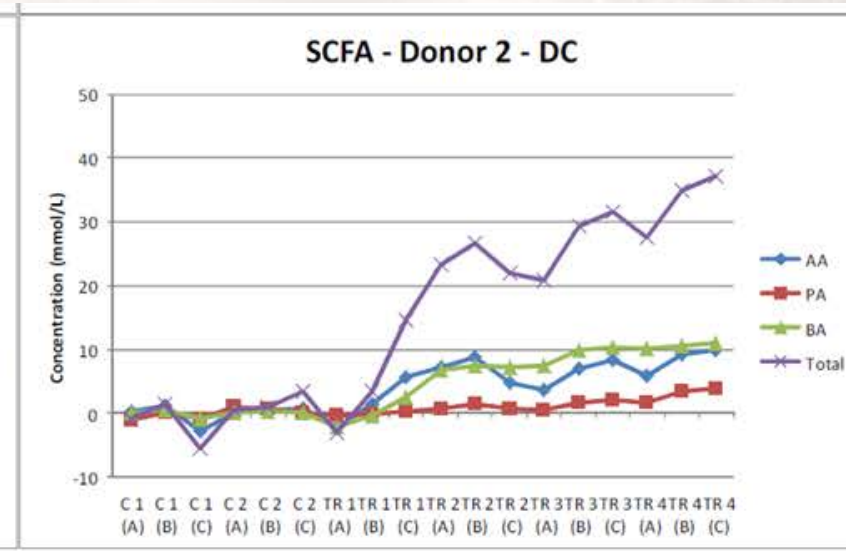


REINFORCE
beneficial changes

SYNBIOTIC







DIVERSITY INCREASE IN THE MICROBIOME

RECONDITION the gut

PROBIOTIC ONLY

DONOR 1	AC		TC		DC	
	C	TR	C	TR	C	TR
Reciprocal Simpson Diversity Index	2,61	5,28	8,09	11,18	8,12	9,06

DONOR 2	AC		TC		DC	
	C	TR	C	TR	C	TR
Reciprocal Simpson Diversity Index	2,99	4,72	6,65	12,40	9,39	9,49

REINFORCE beneficial changes

SYNBIOTIC

		Donor 1		Donor 2		Donor 3	
		CTRL	TR	CTRL	TR	CTRL	TR
Lumen	AC	5,6	4,5	5,6	5,2	6,6	2,6
	TC	12,4	14,1	11,0	18,7	13,9	15,8
	DC	11,4	13,4	11,9	15,3	13,6	18,9
Mucus	AC	4,8	3,6	8,5	5,1	7,3	5,0
	TC	4,3	7,3	7,5	14,4	9,1	20,9
	DC	7,4	10,9	7,3	13,5	11,8	16,1

BOVINE IgG IN GUT RESTORATION

REBUILD
intestinal mucosa

OPEN

Oral serum-derived bovine immunoglobulin improves duodenal immune reconstitution and absorption function in patients with HIV enteropathy

David M. Asmuth[a,b], Zhong-Min Ma[c,d], Anthony Albanese[b], Netanya G. Sandler[e], Sridevi Devaraj[f], Thomas H. Knight[a], Neil M. Flynn[a], Tammy Yotter[a], Juan-Carlos Garcia[a], Emily Tsuchida[g], Tsung-Teh Wu[h], Daniel C. Douek[e] and Christopher J. Miller[b,c]

Objectives: To examine the impact of serum-derived bovine immunoglobulin, an oral medical food known to neutralize bacterial antigen and reduce intestinal inflammation, on restoration of mucosal immunity and gastrointestinal function in individuals with HIV enteropathy.

Design: Open-label trial with intensive 8-week phase of bovine serum immunoglobulin (SBI) 2.5 g twice daily with a 4-week washout period and an optional 9-month extension study.

Methods: HIV enteropathy was defined as chronic gastrointestinal symptoms including frequent loose or watery stools despite no identifiable, reversible cause. Upper endoscopy for tissue immunofluorescent antibody assay and disaccharide gut permeability/absorption studies were performed before and after 8 weeks of SBI to test mucosal immunity and gastrointestinal function. Blood was collected for markers of microbial translocation, inflammation, and collagen kinetics. A validated gastrointestinal questionnaire assessed changes in symptoms.

Results: All eight participants experienced profound improvement in symptoms with reduced bowel movements/day ($P = 0.008$) and improvements in stool consistency ($P = 0.008$). Gut permeability was normal before and after the intervention, but D-xylose absorption increased in seven of eight participants. Mucosal $CD4^+$ lymphocyte densities increased by a median of 139.5 cells/mm^2 from 213 to 322 cells/mm^2 ($P = 0.016$). Intestinal-fatty acid binding protein (I-FABP), a marker of enterocyte damage, initially rose in seven of eight participants after 8 weeks ($P = 0.039$), and then fell below baseline in four of five who continued receiving SBI ($P = 0.12$). Baseline serum I-FABP levels were negatively correlated with subsequent rise in mucosal $CD4^+$ lymphocyte densities ($r = -0.74$, $P = 0.046$).

Conclusion: SBI significantly increases intestinal mucosal $CD4^+$ lymphocyte counts, improves duodenal function, and showed evidence of promoting intestinal repair in the setting of HIV enteropathy.

AIDS 2013, **27**:2207–2217

Oral serum-derived bovine immunoglobulin improves duodenal immune reconstitution and absorption function in patients with HIV enteropathy. AIDS. 2013;27:2207-2217.

- SBI increases intestinal mucosal CD4+ lymphocytes
- Improves duodenal function
- Promotes intestinal repair in HIV enteropathy

Clinical and Pathologic Remission of Pediatric Ulcerative Colitis with Serum-Derived Bovine Immunoglobulin Added to Standard Treatment Regimen. Case Rep Gastroenterol. 2017; 11(2):335-343.

- SBI heals gastric mucosa in pediatric UC case study
- Decrease in pediatric UC activity index

Serum-derived bovine immunoglobulin/protein isolate binds and neutralizes clostridium difficile toxins A and B. Gastroenterology. 2014; 146(5): S289-S290.

- Binds and neutralizes several toxins from C. difficile strains, including hypervirulent strains

POLYPHENOLS IN THE GUT MICROBIOME

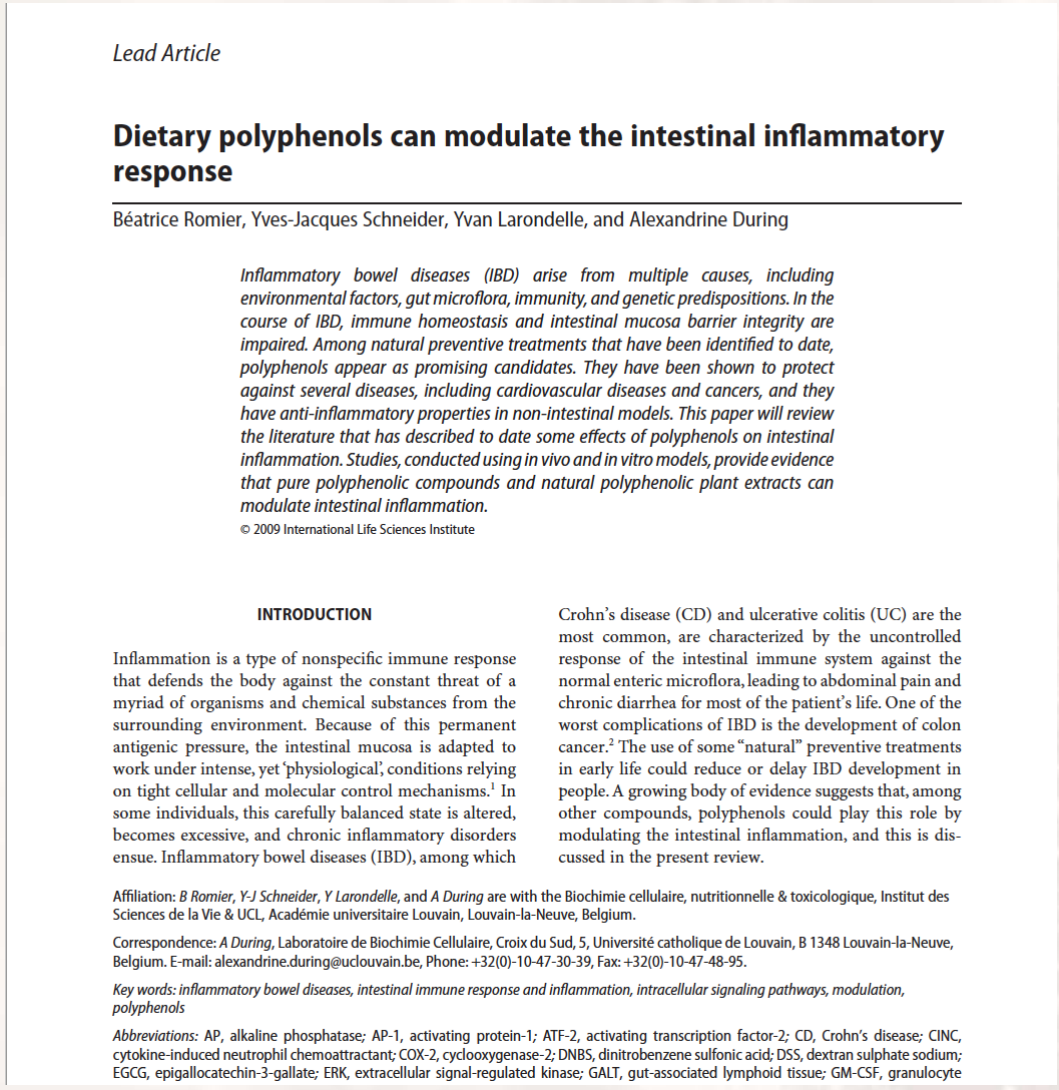
REBUILD intestinal mucosa

Dietary polyphenols can modulate the intestinal inflammatory response. Nutr Rev. 2009; 67(7): 363-378.

- Reduce intestinal inflammation by inhibiting activation of NF-kB cascade
- Block JNK stress-activated pathways
- Protect against experimental colitis
- Reduce risk of IBD

Efficacy of Citrus Polyphenols on Microbiome Composition and Gut Inflammation in Healthy Overweight Individuals. BioActor Report. 2017: 1-22.

- Increased butyrate production by 21%
- Reduced fecal calprotectin levels by 22%



Lead Article

Dietary polyphenols can modulate the intestinal inflammatory response

Béatrice Romier, Yves-Jacques Schneider, Yvan Larondelle, and Alexandrine During

Inflammatory bowel diseases (IBD) arise from multiple causes, including environmental factors, gut microflora, immunity, and genetic predispositions. In the course of IBD, immune homeostasis and intestinal mucosa barrier integrity are impaired. Among natural preventive treatments that have been identified to date, polyphenols appear as promising candidates. They have been shown to protect against several diseases, including cardiovascular diseases and cancers, and they have anti-inflammatory properties in non-intestinal models. This paper will review the literature that has described to date some effects of polyphenols on intestinal inflammation. Studies, conducted using in vivo and in vitro models, provide evidence that pure polyphenolic compounds and natural polyphenolic plant extracts can modulate intestinal inflammation.

INTRODUCTION

Inflammation is a type of nonspecific immune response that defends the body against the constant threat of a myriad of organisms and chemical substances from the surrounding environment. Because of this permanent antigenic pressure, the intestinal mucosa is adapted to work under intense, yet 'physiological', conditions relying on tight cellular and molecular control mechanisms.[1] In some individuals, this carefully balanced state is altered, becomes excessive, and chronic inflammatory disorders ensue. Inflammatory bowel diseases (IBD), among which Crohn's disease (CD) and ulcerative colitis (UC) are the most common, are characterized by the uncontrolled response of the intestinal immune system against the normal enteric microflora, leading to abdominal pain and chronic diarrhea for most of the patient's life. One of the worst complications of IBD is the development of colon cancer.[2] The use of some "natural" preventive treatments in early life could reduce or delay IBD development in people. A growing body of evidence suggests that, among other compounds, polyphenols could play this role by modulating the intestinal inflammation, and this is discussed in the present review.

Affiliation: *B Romier*, *Y-J Schneider*, *Y Larondelle*, and *A During* are with the Biochimie cellulaire, nutritionnelle & toxicologique, Institut des Sciences de la Vie & UCL, Académie universitaire Louvain, Louvain-la-Neuve, Belgium.

Correspondence: *A During*, Laboratoire de Biochimie Cellulaire, Croix du Sud, 5, Université catholique de Louvain, B 1348 Louvain-la-Neuve, Belgium. E-mail: alexandrine.during@uclouvain.be, Phone: +32(0)-10-47-30-39, Fax: +32(0)-10-47-48-95.

Key words: inflammatory bowel diseases, intestinal immune response and inflammation, intracellular signaling pathways, modulation, polyphenols

Abbreviations: AP, alkaline phosphatase; AP-1, activating protein-1; ATF-2, activating transcription factor-2; CD, Crohn's disease; CINC, cytokine-induced neutrophil chemoattractant; COX-2, cyclooxygenase-2; DNBS, dinitrobenzene sulfonic acid; DSS, dextran sulphate sodium; EGCG, epigallocatechin-3-gallate; ERK, extracellular signal-regulated kinase; GALT, gut-associated lymphoid tissue; GM-CSF, granulocyte

MUCIN BUILDING BLOCKS

REBUILD
intestinal mucosa

Nutrition and Disease

Specific Amino Acids Increase Mucin Synthesis and Microbiota in Dextran Sulfate Sodium–Treated Rats

Magali Faure,*[1] Christine Mettraux,* Denis Moennoz,* Jean-Philippe Godin,* Jacques Vuichoud,* Florence Rochat,* Denis Breuillé,* Christiane Obled,† and Irène Corthésy-Theulaz*

**Nestlé Research Center, Nutrition and Health Department, Lausanne, Switzerland and †Unité de Nutrition et Métabolisme Protéique, INRA, Theix, France*

ABSTRACT During the anabolic response associated with inflammation, mucin synthesis and colonic protection may be compromised by the limited availability of specific amino acids. We therefore determined the effect of dietary amino acid supplementation on the microbiota, mucin status, and mucosal damage in dextran sulfate sodium (DSS)-treated rats. From 8 d before to 28 d after colitis induction, male Sprague-Dawley rats (10 mo old, $n = 8$/group) were fed a control diet supplemented or not with 2 different doses of an amino acid cocktail containing L-threonine, L-serine, L-proline, and L-cysteine. All diets were isonitrogenous (adjusted with L-alanine). The higher dose of amino acids increased the number of Muc2-containing goblet cells in the surface epithelium of the ulcerated area, stimulated mucin production in the colon, and restored the mucin amino acid composition and mucosal content to healthy, control values. The colonic mucin synthesis rate was specifically stimulated by 95%, whereas the protein turnover was unchanged. All bacterial populations, markedly altered by the DSS treatment, were promoted. In conclusion, in inflammatory situations, an increase in threonine, serine, proline, and cysteine dietary supply can promote mucin synthesis, reequilibrate the gut microbiota, and thus favor colonic protection and mucosal healing. J. Nutr. 136: 1558–1564, 2006.

KEY WORDS: • *mucin* • *amino acids* • *protein synthesis* • *intestine* • *rats*

L-threonine,
L-serine,
L-proline &
L-cysteine
increased colonic mucin synthesis by 95%

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World J Gastrointest Pathophysiol 2017 August 15; 8(3): 117-126

DOI: 10.4291/wjgp.v8.i3.117

ISSN 2150-5330 (online)

ORIGINAL ARTICLE

Prospective Study

Oral spore-based probiotic supplementation was associated with reduced incidence of post-prandial dietary endotoxin, triglycerides, and disease risk biomarkers

Brian K McFarlin, Andrea L Henning, Erin M Bowman, Melody M Gary, Kimberly M Carbajal

Brian K McFarlin, Andrea L Henning, Erin M Bowman, Melody M Gary, Applied Physiology Laboratory, University of North Texas, Denton, TX 76203, United States

Brian K McFarlin, Andrea L Henning, Kimberly M Carbajal, Department of Biological Sciences, University of North Texas, Denton, TX 76203, United States

Author contributions: McFarlin BK designed the study, collected data, interrupted findings, and prepared manuscript; Henning AL, Bowman EM, Gary MM and Carbajal KM collected data, interrupted findings, and prepared manuscript.

Institutional review board statement: The study was reviewed

Manuscript source: Invited manuscript

Correspondence to: Brian K McFarlin, PhD, FACSM, FTOS, Associate Professor, Applied Physiology Laboratory, University of North Texas, 1921 West Chestnut Street, PEB Room 209, Denton, TX 76203, United States. brian.mcfarlin@unt.edu
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Fax: +1-940-5654904

Received: January 26, 2017
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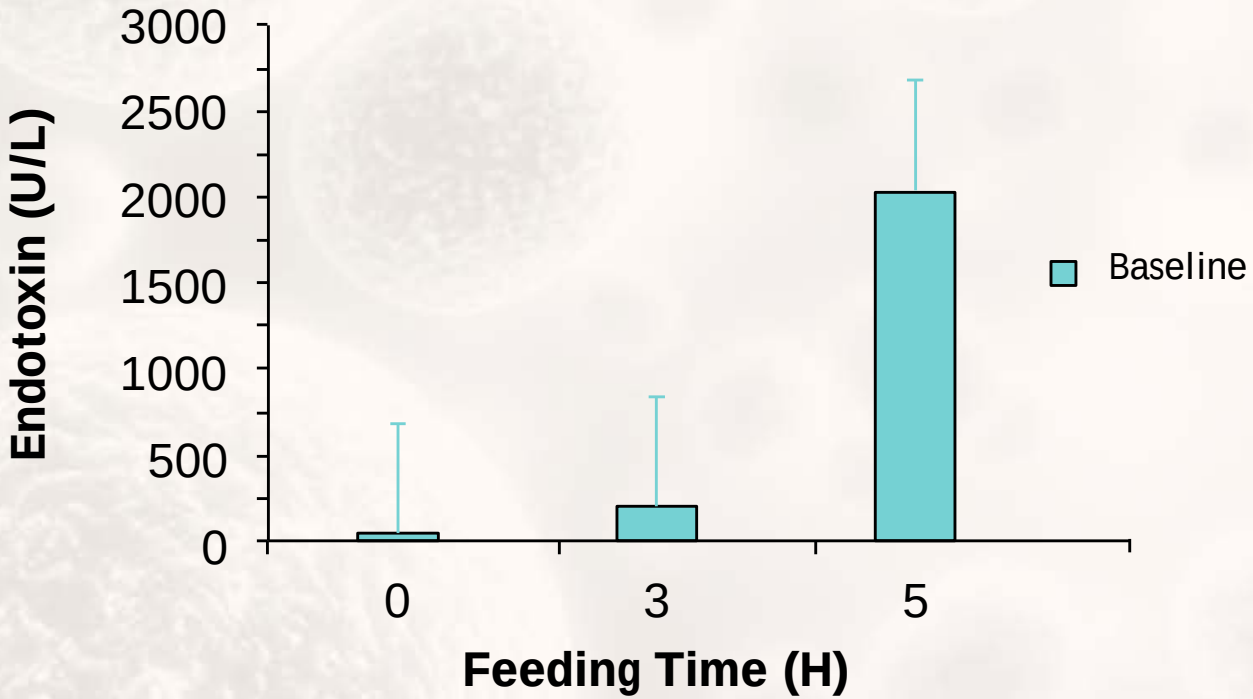
First decision: April 17, 2017

The effect of 30-days of probiotic supplementation on post-prandial responses to a high-fat meal: Pilot Study

Principal Investigator: Brian K. McFarlin, PhD, FACSM, FTOS
University of North Texas



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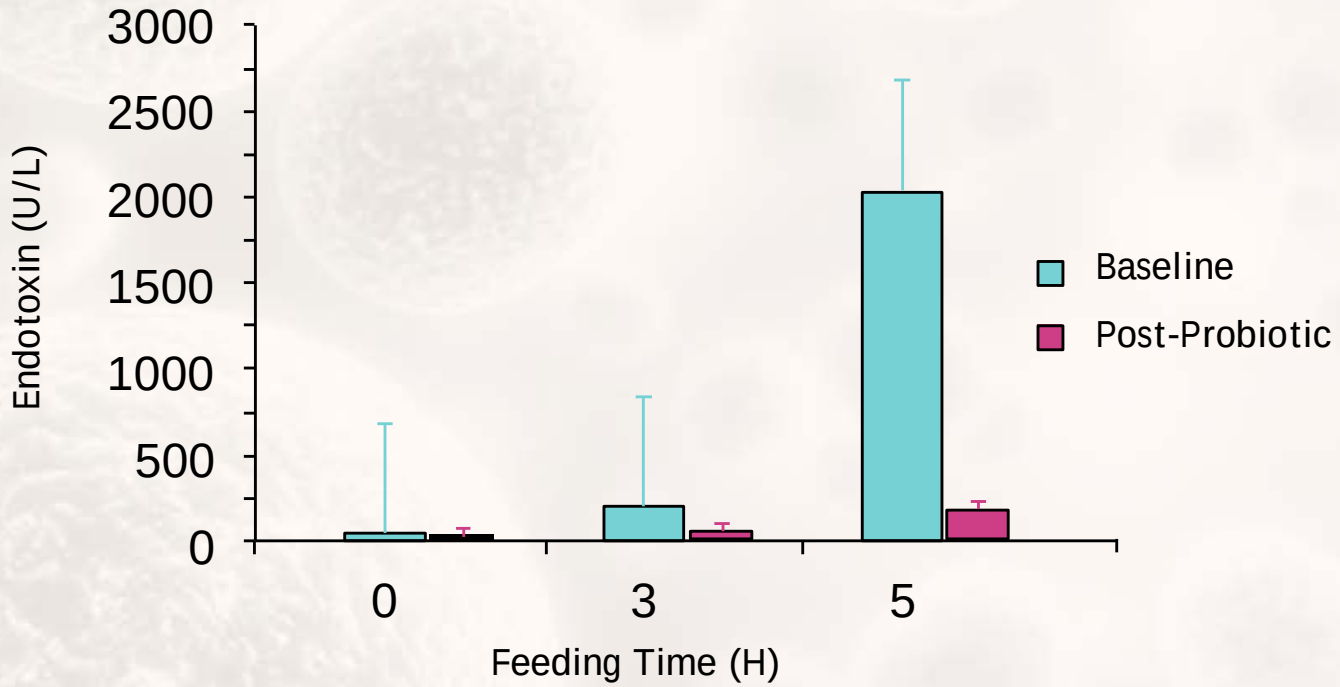

The effect of 30-days of probiotic supplementation on post-prandial responses to a high-fat meal: An Expanded Pilot Study

Principal Investigator: Brian K. McFarlin, PhD, FACSM,
FTOS University of North Texas

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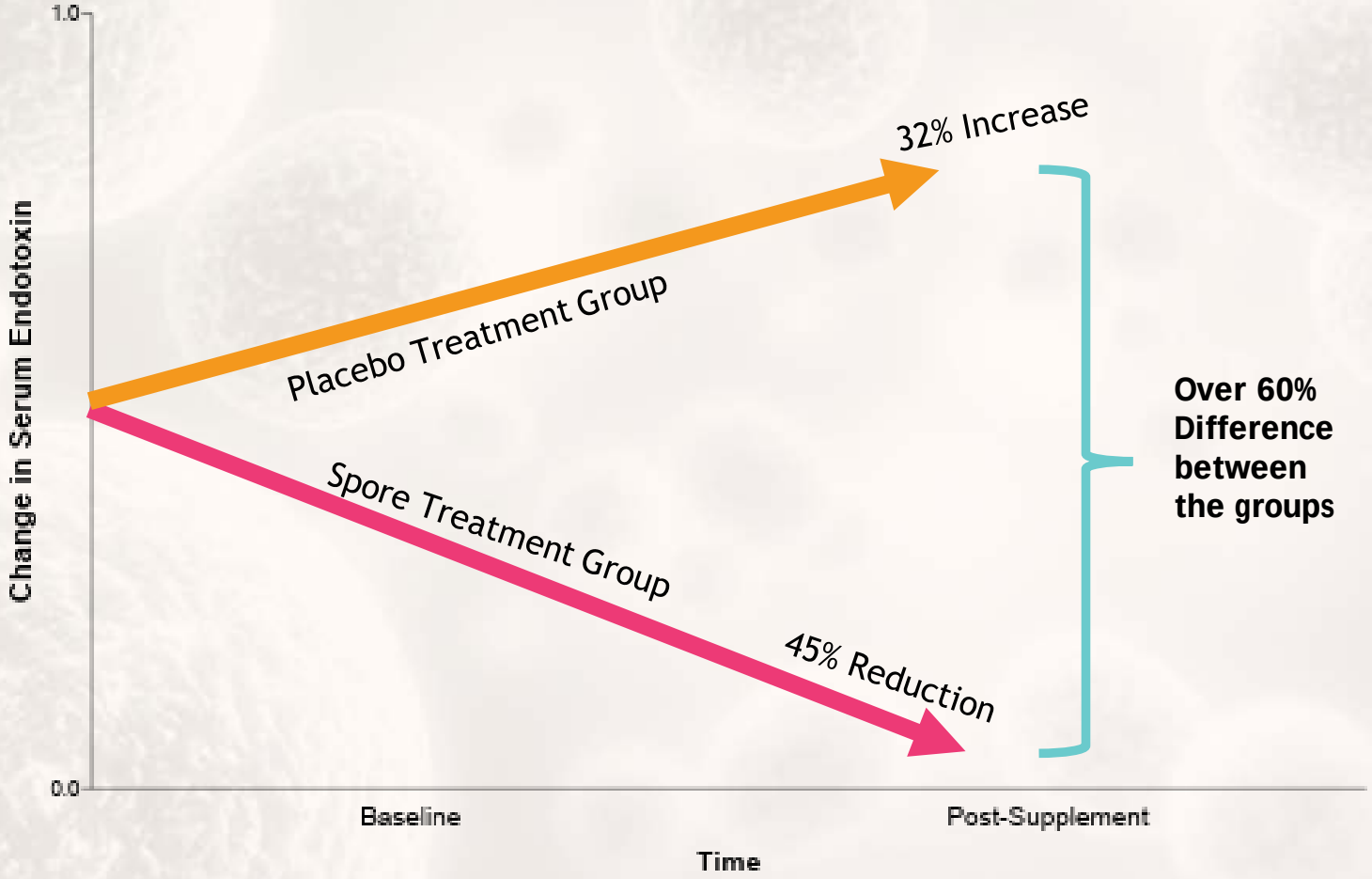

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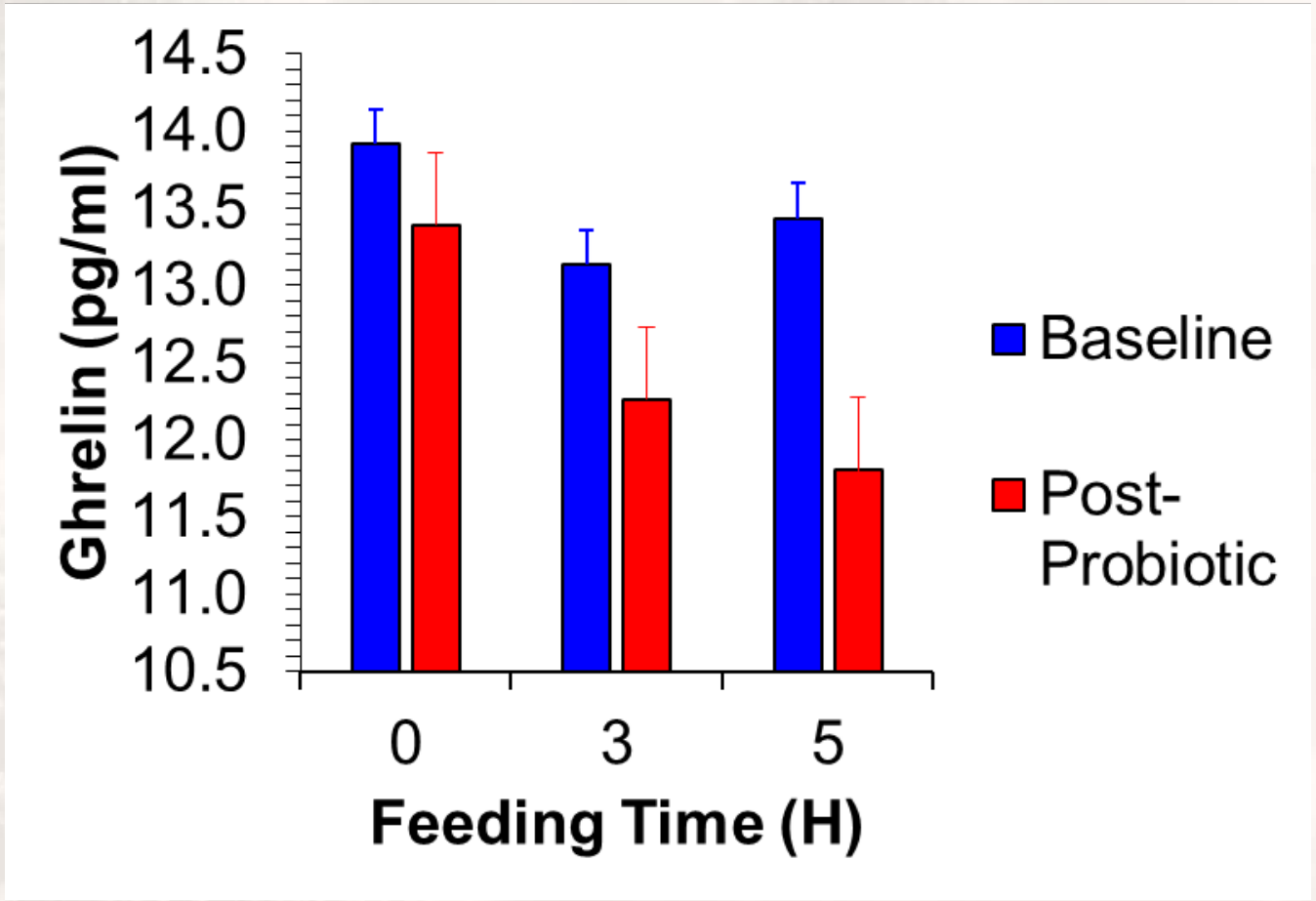

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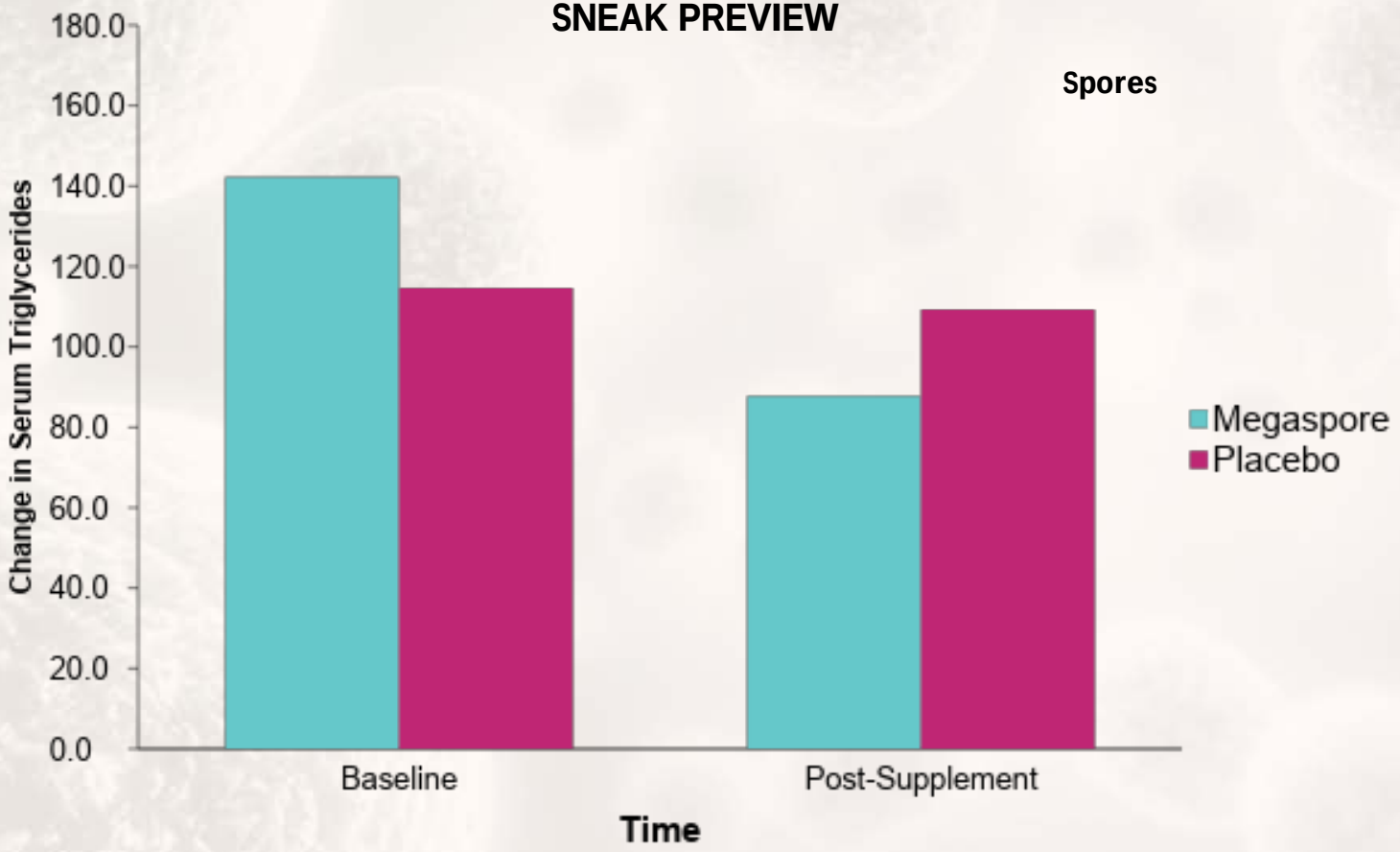
SNEAK PREVIEW



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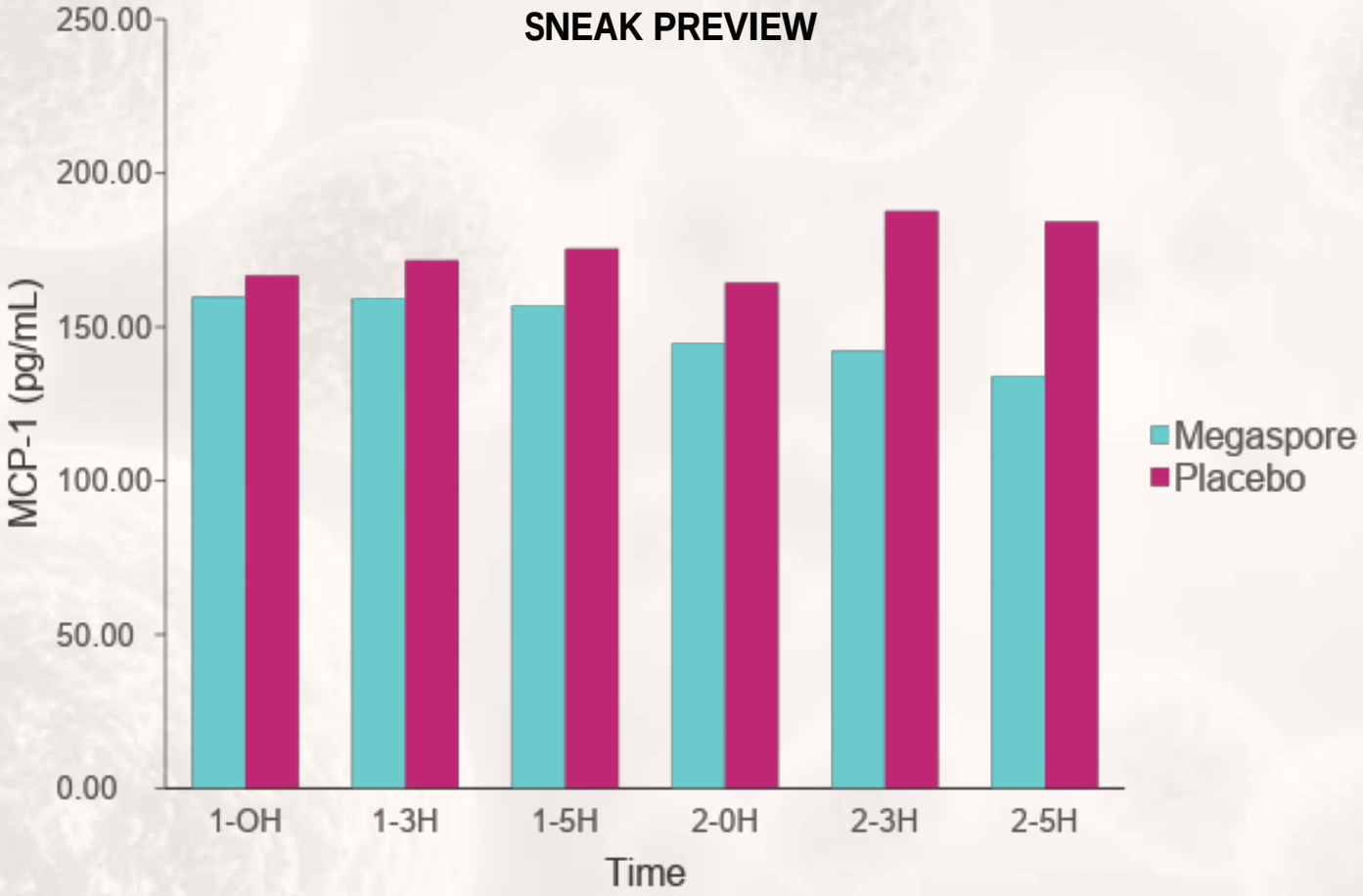

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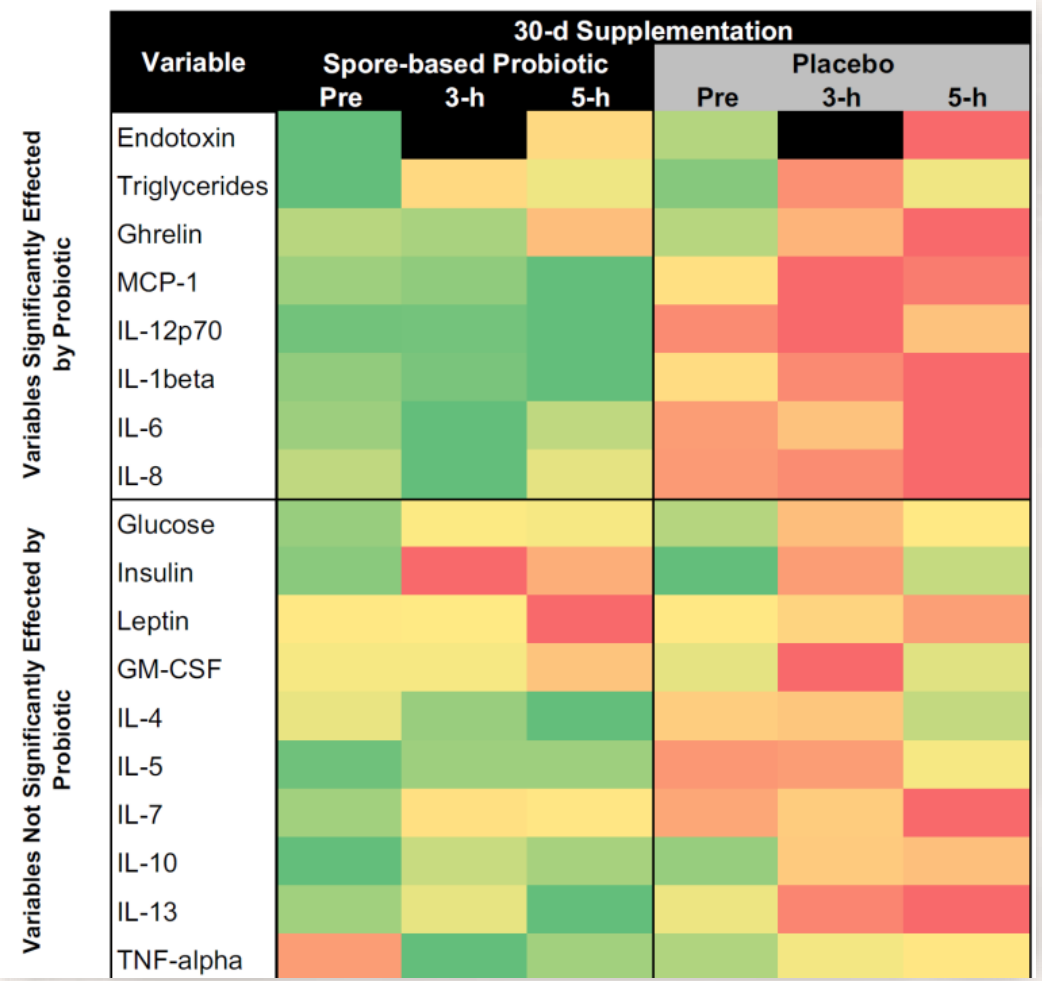
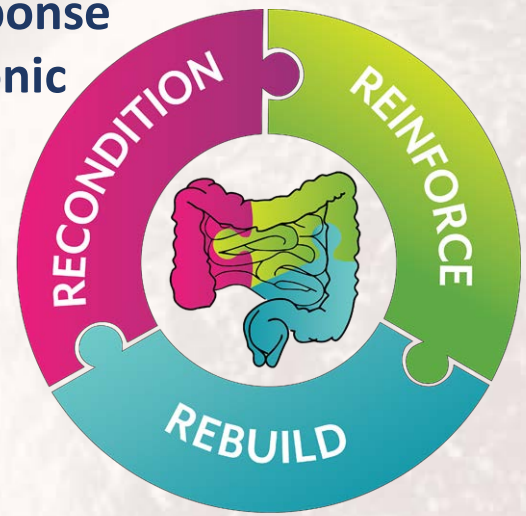


TOTAL GUT RESTORATION

- Understanding the pathophysiology of the gut and microbiome's involvement in disease causation and progression, is paramount to treating the conditions.
- Diseases are quite varied and yet the gut associated dysfunctions are essentially the same.
- This means that there can be some degree of uniformity in baseline treatment of various conditions like autoimmune disease, cardiometabolic syndrome, depression, IBD, reflux, etc.
- Strategically addressing dysfunctions in the microbiota, the mucosal immune response and barrier structures can prove to be highly effective in treating a variety of chronic illnesses.
- The same treatment can be preventative for numerous conditions

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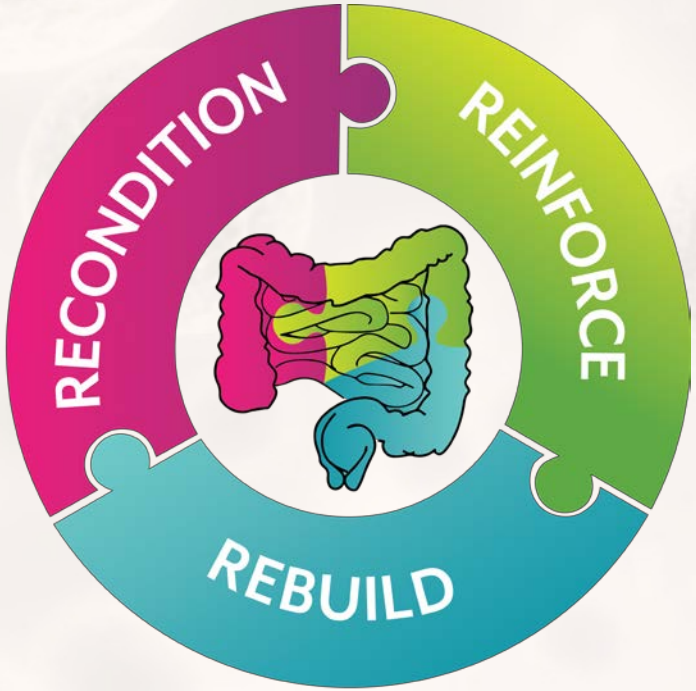
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