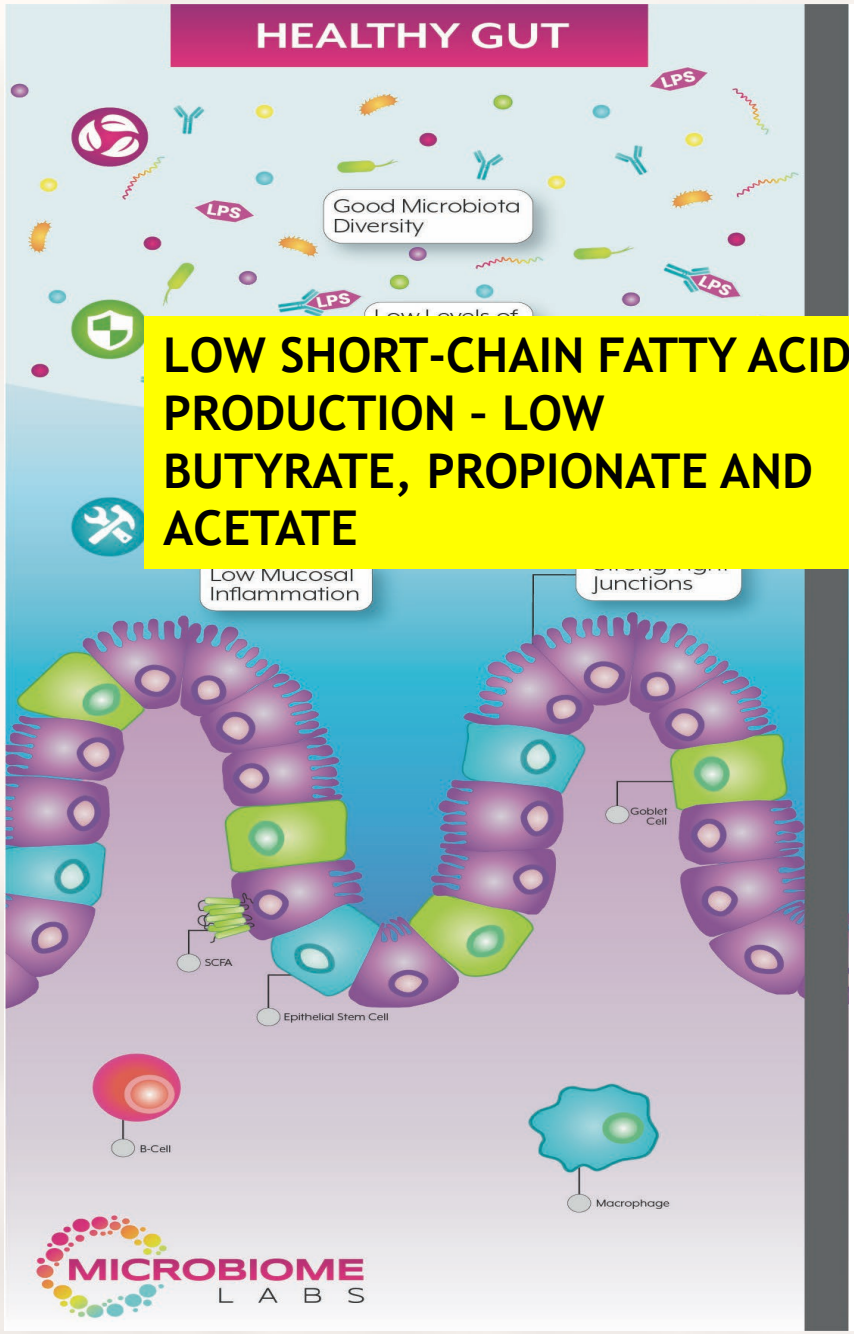
THE MOST COMMON DYSFUNCTIONS OF THE STANDARD AMERICAN GUT IN CHRONIC ILLNESS

KIRAN KRISHNAN, CSO
MICROBIOME LABS



HIGH DIVERSITY AND PROTECTIVE STRAINS

HIGH PRODUCTION OF SCFA

WELL FORMED TIGHT-JUNCTIONS

DISRUPTION OF GUT MICROBIOTA

Review

Beneficial modulation of the gut microbiota

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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

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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**."

GUT MICROBES
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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

IMPORTANCE OF KEYSTONE SPECIES

frontiers in Microbiology

MINI REVIEW
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KEYSTONE STRAINS – A. MUCINIPHILA

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

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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

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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."

DYSFUNCTION OF MUCOSAL BARRIER

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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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 eluate 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

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MUCOSAL DYSFUNCTION

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)

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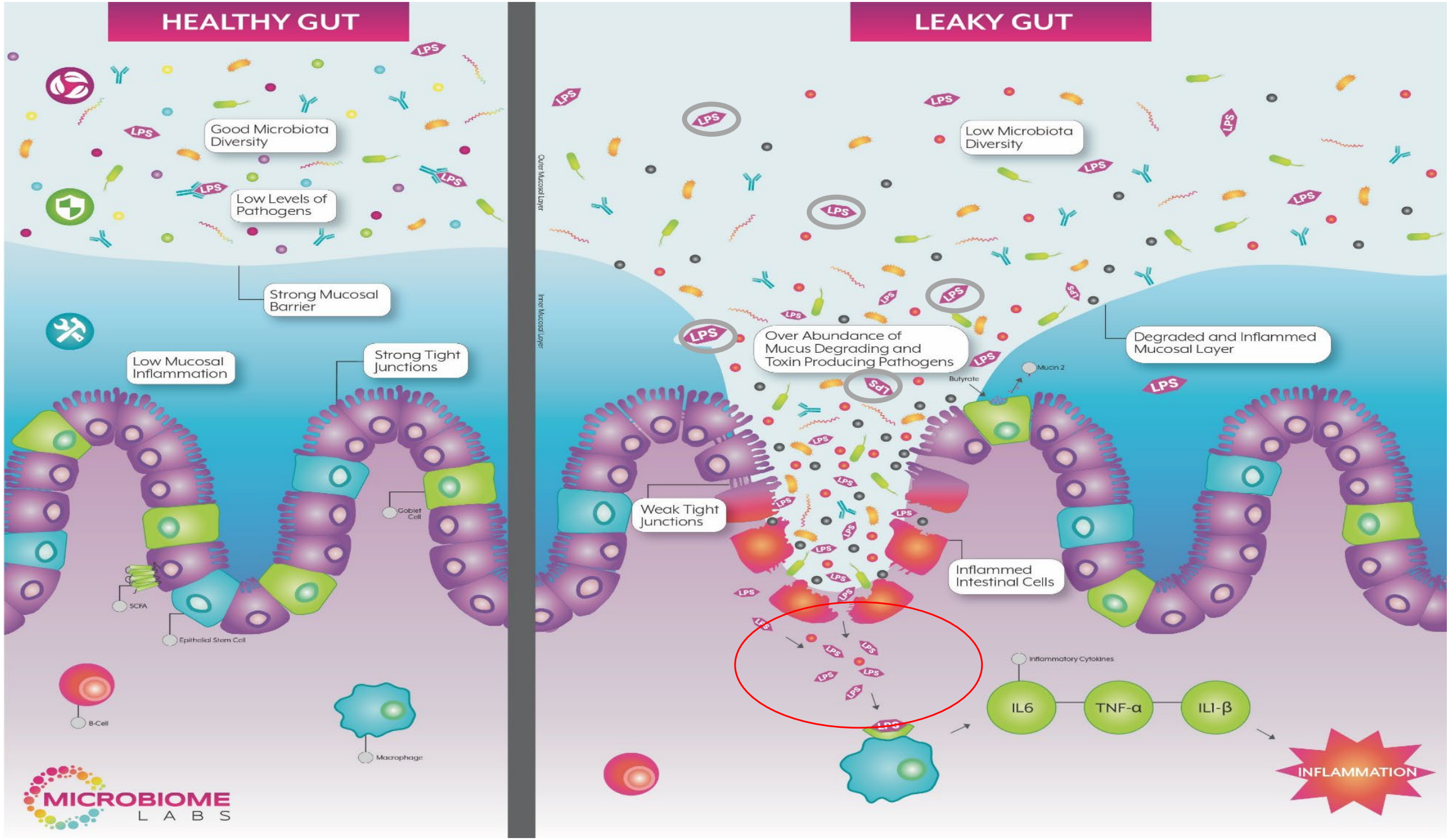
"Early HIV infection is consistently associated with a rapid, dramatic, and largely irreversible depletion of mucosal CD4+ memory T-cells, particularly those expressing the HIV coreceptor CCR5."

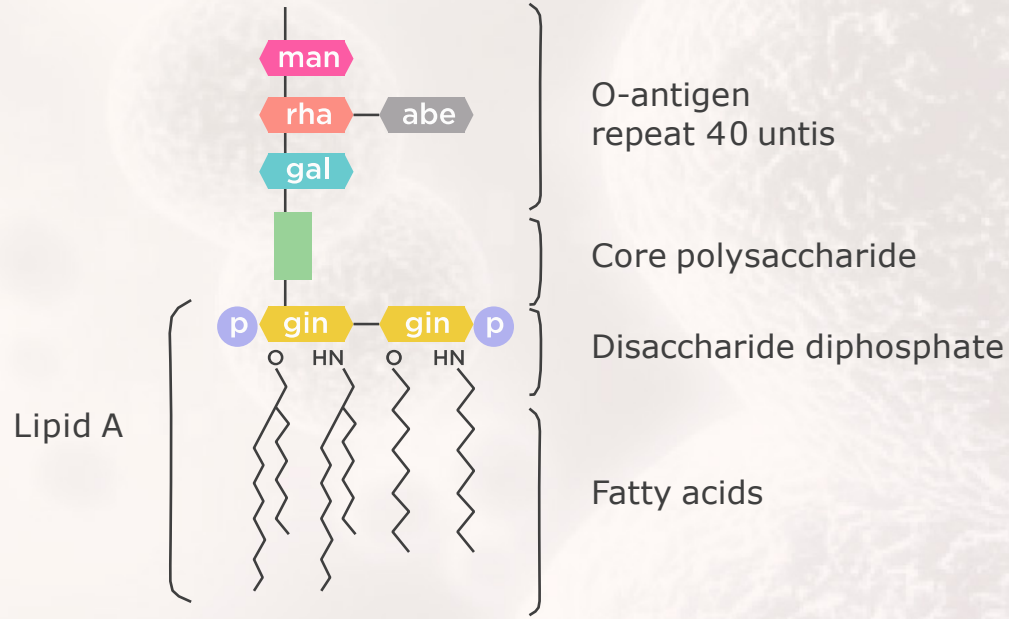
"In conclusion, further studies are needed to solve the complex riddle of how the interaction between primate lentiviruses and the host mucosal immune system leads to the **severe mucosal immune dysfunction associated with progression to AIDS**."


HEALTHY GUT
LPS
Good Microbiota Diversity
Low Levels of Pathogens
Strong Mucosal Barrier
Low Mucosal Inflammation
Strong Tight Junctions
Goblet Cell
SCFA
Epithelial Stem Cell
B-Cell
Macrophage
MICROBIOME LABS
LEAKY GUT
Outer Mucosal Layer
Inner Mucosal Layer
Low Microbiota Diversity
Over Abundance of Mucus Degrading and Toxin Producing Pathogens
Degraded and Inflammed Mucosal Layer
Mucin 2
Butyrate
Weak Tight Junctions
Inflammed Intestinal Cells
Inflammatory Cytokines
IL6
TNF-α
IL1-β
INFLAMMATION

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

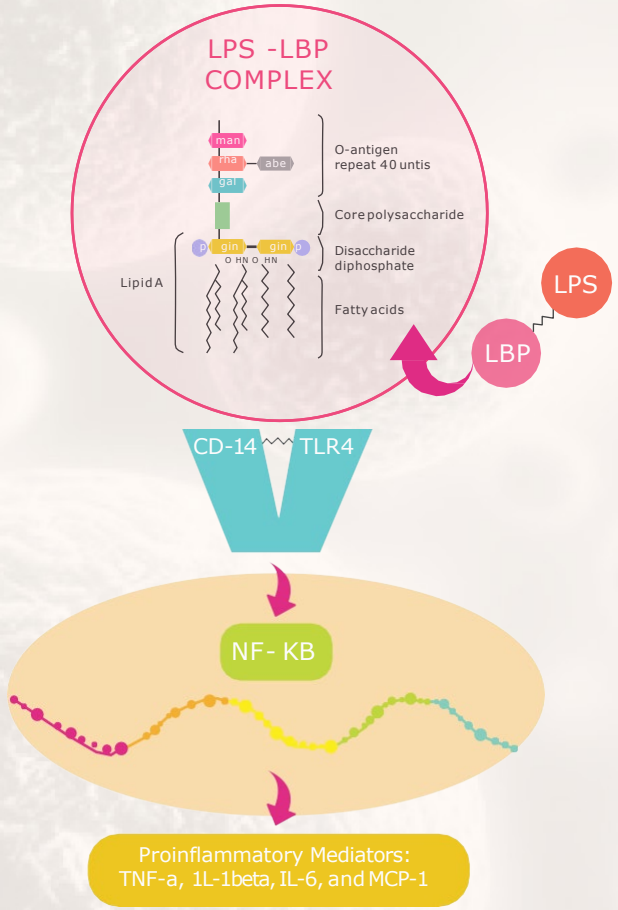


Structure of Lipopolysachharide

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



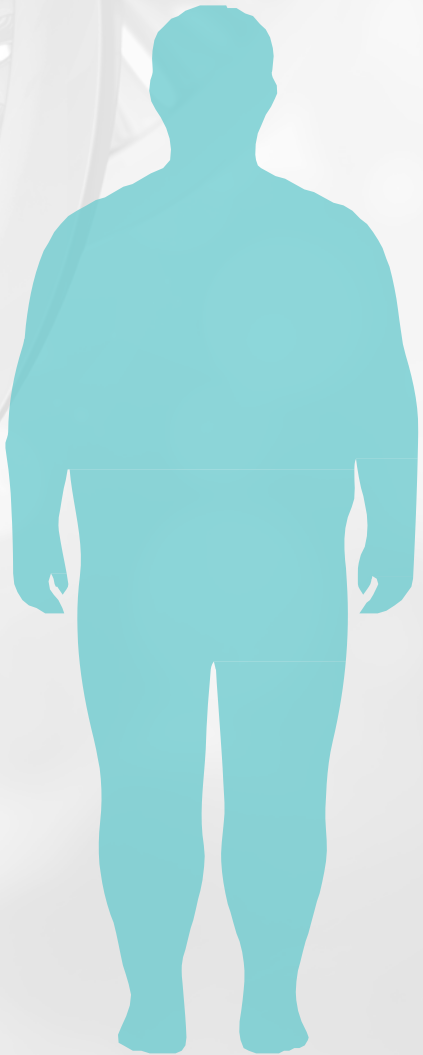
- TLR4 is an important signaling protein in innate immunity and is found on the surfaces of innate immune defense cells like Macrophages and dendritic cells.
- Circulating LPS gets bound by a phospholipid transfer protein called LBP, which carriers LPS to the CD14-TLR complex for examination.
- Once 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



Obesity Studies

Metabolic Endotoxemia Initiates Obesity and Insulin Resistance

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https://doi.org/10.2337/db06-1491

American Diabetes Association. diabetes

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."

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Randomized Control Trials

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

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[g] *CNIC, Madrid, Spain*

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."***

frontiers in Immunology

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

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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

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Research Paper

Increased gut permeability in cancer cachexia: mechanisms and clinical relevance

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Keywords: *cancer cachexia; gut barrier function; gut dysbiosis; lipopolysaccharide-binding protein; Enterobacteriaceae*

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ABSTRACT

Intestinal disorders often occur in cancer patients, in association with body weight loss, and this alteration is commonly attributed to the chemotherapy. Here, using a mouse model of cancer cachexia induced by ectopic transplantation of C26 cancer cells, we discovered a profound alteration in the gut functions (gut permeability, epithelial turnover, gut immunity, microbial dysbiosis) independently of any chemotherapy. These alterations occurred independently of anorexia and were driven by interleukin 6. Gut dysfunction was found to be resistant to treatments with an anti-inflammatory bacterium (*Faecalibacterium prausnitzii*) or with gut peptides involved in intestinal cell renewal (teduglutide, a glucagon-like peptide 2 analogue). The translational value of our findings was evaluated in 152 colorectal and lung cancer patients with or without cachexia. The serum level of the lipopolysaccharide-binding protein, often presented as a reflection of the bacterial antigen load, was not only increased in cachectic mice and cancer patients, but also strongly correlated with the serum IL-6 level and predictive of death and cachexia occurrence in these patients. Altogether, our data highlight profound alterations of the intestinal homeostasis in cancer cachexia occurring independently of any chemotherapy and food intake reduction, with potential relevance in humans. In addition, we point out the lipopolysaccharide-binding protein as a new biomarker of cancer cachexia related to gut dysbiosis.

"The translational value of our findings was evaluated in ***152 colorectal and lung cancer*** *patients with or without cachexia. The serum level of* ***the lipopolysaccharide binding protein****, often presented as a reflection of the bacterial antigen load, was* ***not only increased in cachectic mice and cancer patients, but also strongly correlated with the serum IL-6 level and predictive of death and cachexia occurrence in these patients****.*

Altogether, our data highlight profound alterations of the intestinal homeostasis in cancer cachexia occurring independently of any chemotherapy and food intake reduction, with potential relevance in humans. In addition, we point out the lipopolysaccharide-binding protein as a new biomarker of cancer cachexia related to gut dysbiosis."

Lipopolysaccharide Challenge of Humans as a Model for Chronic Obstructive Lung Disease Exacerbations

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Author affiliations

Sjobring U, Taylor JD (eds): Models of Exacerbations in Asthma and COPD. Contrib Microbiol. Basel, Karger, 2007, vol 14, pp 83-100
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Abstract

Endotoxin, or lipopolysaccharide (LPS), is a constituent of the outer cell membrane of Gram-negative bacteria. LPS is a highly potent proinflammatory substance, that, when inhaled, dose-dependently causes fever, chills, and bronchoconstriction. These symptoms are accompanied by a proinflammatory response in sputum and bronchoalveolar lavage fluid with elevation of neutrophils, macrophages and certain cytokines/chemokines. This response can be partially modified with certain drugs. Similar inflammatory changes are observed both in the stable state of chronic obstructive lung disease (COPD) and during exacerbations of this disease. Cigarette smoke, which contains bioactive LPS, is the most common cause of COPD and may also precipitate exacerbations. In addition, the presence of Gram-negative bacteria in the lower airways is a distinguishing feature both of stable COPD and of exacerbations. Based on this knowledge we argue here that inhaled LPS provocation of healthy volunteers can be used as a model or COPD as well as for exacerbations of this disease.

"...proinflammatory response in sputum and bronchoalveolar lavage fluid with elevation of neutrophils, macrophages and certain cytokines/chemokines."

*"In addition, the presence of **Gram-negative** bacteria in the lower airways is a distinguishing feature both of stable COPD and of exacerbations."*

PLOS ONE

RESEARCH ARTICLE

Lipopolysaccharide-induced endotoxemia in corn oil-preloaded mice causes an extended course of lung injury and repair and pulmonary fibrosis: A translational mouse model of acute respiratory distress syndrome

Chaomin Wu[1,2,3], Colin E. Evans[1,2,4], Zhiyu Dai[1,2], Xiaojia Huang[1,2], Xianming Zhang[1,2], Hua Jin[1,2], Guochang Hu[1,5], Yuanlin Song[6], You-Yang Zhao[1,2]*

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Abstract

Acute respiratory distress syndrome (ARDS) is characterized by acute hypoxemia respiratory failure, bilateral pulmonary infiltrates, and pulmonary edema of non-cardiac origin. Effective treatments for ARDS patients may arise from experimental studies with transla-

Long-Term Intratracheal Lipopolysaccharide Exposure in Mice Results in Chronic Lung Inflammation and Persistent Pathology

Juanita H. J. Vernooy, Mieke A. Dentener, Robert J. van Suylen, Wim A. Buurman, and Emiel F. M. Wouters

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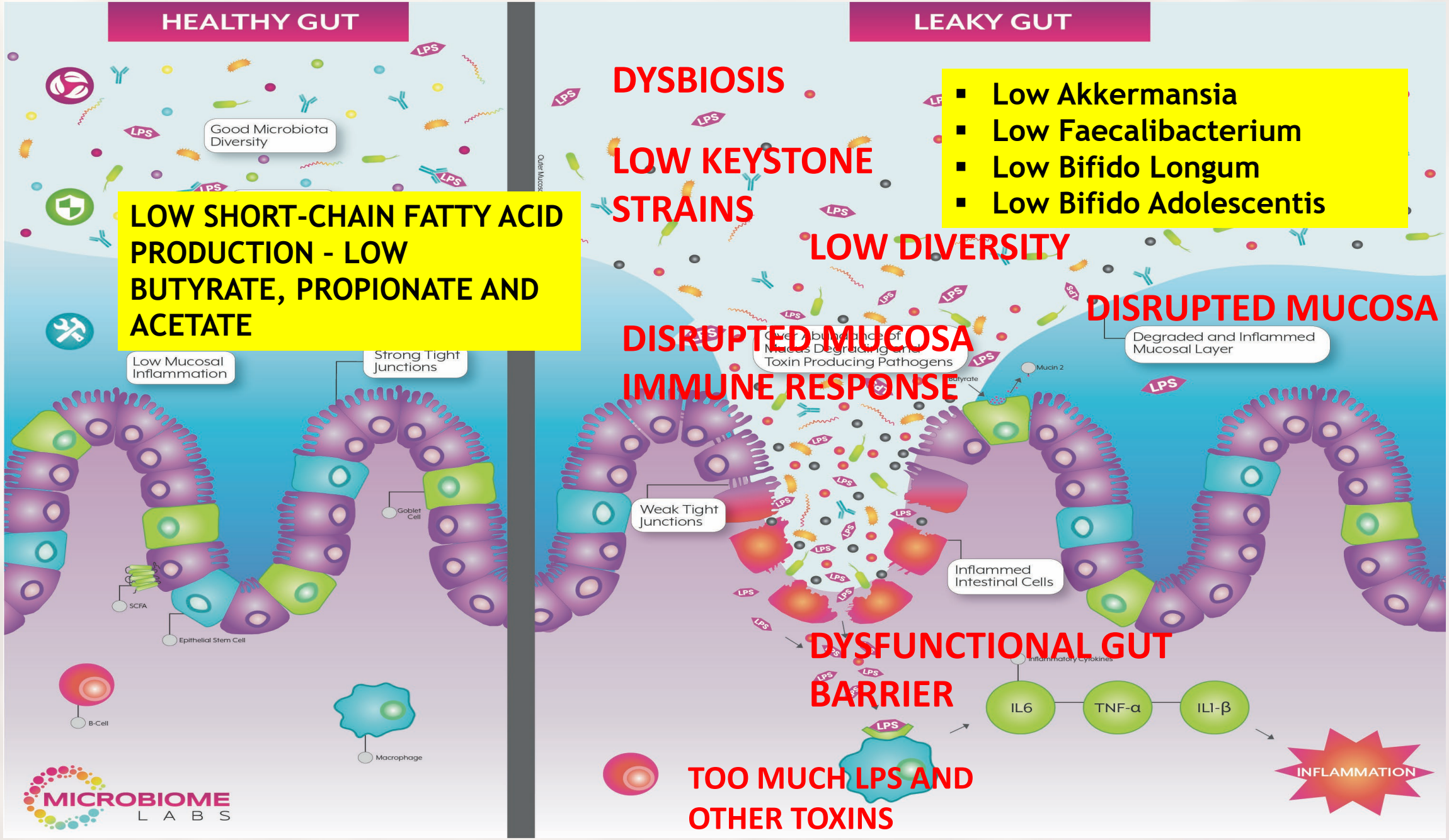
Lipopolysaccharide (LPS), a major proinflammatory glycolipid component of the gram-negative bacterial cell wall, is one of the agents ubiquitously present as contaminant on airborne particles, including air pollution, organic dusts, and cigarette smoke. Chronic exposure to significant levels of LPS is reported to be associated with the development and/or progression of many types of lung diseases, including asthma, chronic bronchitis, and progressive irreversible airflow obstruction, that are all characterized by chronic inflammatory processes in the lung. In the present study, pathologic effects of long-term LPS exposure to the lung were investigated in detail. To this end, a murine model in which mice were exposed to repeated intratracheal instillation of *Escherichia coli* LPS was developed. We show that long-term LPS instillation in mice results in persistent chronic pulmonary inflammation, characterized by peribronchial and perivascular lymphocytic aggregates ($CD4^+$, $CD8^+$, and $CD19^+$), parenchymal accumulation of macrophages and $CD8^+$ T cells, and altered cytokine expression. Furthermore, airway and alveolar alterations such as mucus cell metaplasia, airway wall thickening, and irreversible alveolar enlargement accompanied the chronic inflammatory response. Interestingly, the observed inflammatory and pathologic changes mimic changes observed in human subjects with chronic inflammatory lung diseases, especially chronic obstructive pulmonary disease (COPD), suggesting that this murine model could be applicable to dissect the role of inflammation in the pathogenesis of these disease conditions.

The respiratory system is continuously exposed to the extory response, which manifests itself at both the pulmonary and the systemic level. In addition, this response is accompanied by clinical symptoms, including fever and airflow decline (6, 7). Extensive studies investigating acute inflammation using laboratory animals have demonstrated that LPS activates alveolar macrophages via LPS-binding protein (LBP)/CD14/Toll-like receptor (TLR)-4–dependent pathway to produce specific cytokines, resulting in a rapid but transient neutrophil infiltration into the lung (interstitium, alveoli, and airway) (8).

In contrast to short-term LPS exposure, chronic exposure to significant levels of LPS is reported to be associated with the development and/or progression of many types of lung diseases, including asthma, chronic bronchitis, and progressive irreversible airflow obstruction, all characterized by chronic inflammatory processes in the lung. Michel and colleagues reported that the concentration of LPS in the domestic setting is associated with the clinical severity of asthma (9). Moreover, individuals with asthma (10) and those with chronic bronchitis (11) develop airflow obstruction at lower concentrations of inhaled LPS compared with healthy subjects, and thus respond more sensitively to LPS. Chronic occupational exposure to LPS contained in organic dusts, such as grain dust and swine dust, is known to

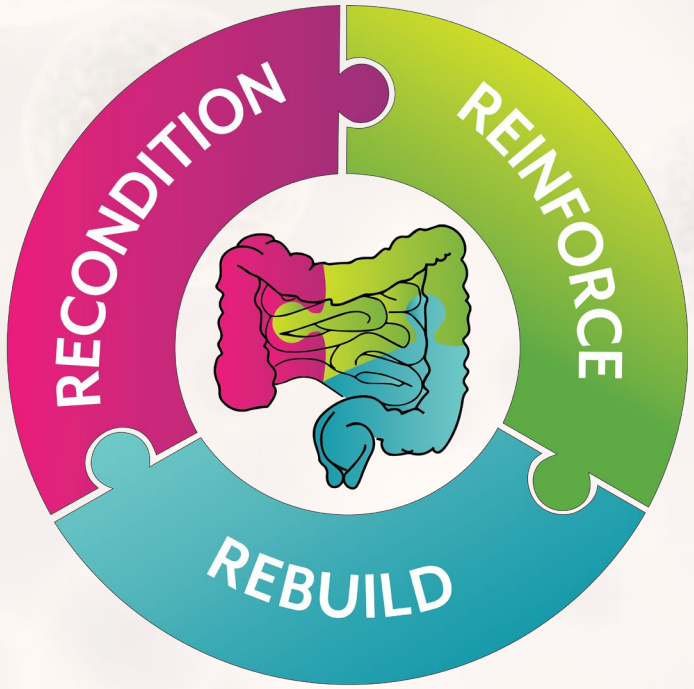
CONDITION	MECHANISM
Leptin Resistance	LPS enters and causes inflammation in the enteric nervous system leading to a disruption in the gut-brain axis of communication.
Chronic Constipation	LPS enters the enteric nervous system and causes disruption in signals for gastric emptying and bowel motility.
Mood 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
MICROBIOME LABS
DYSBIOSIS
LOW KEYSTONE STRAINS
Low Akkermansia
Low Faecalibacterium
Low Bifido Longum
Low Bifido Adolescentis
LOW DIVERSITY
DISRUPTED MUCOSA
IMMUNE RESPONSE
DISRUPTED MUCOSA
Degraded and Inflammed Mucosal Layer
Mucin 2
Butyrate
Weak Tight Junctions
Inflammed Intestinal Cells
DYSFUNCTIONAL GUT BARRIER
Inflammatory Cytokines
IL6
TNF-α
IL1-β
INFLAMMATION
TOO MUCH LPS AND OTHER TOXINS
LPS

TOTAL GUT RESTORATION

RECONDITION the gut

FIX THE MICROBIOME:
- INCREASE KEYSTONE STRAINS
- INCREASE DIVERSITY



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

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A synbiotic concept containing spore-forming *Bacillus* strains and a prebiotic fiber blend consistently enhanced metabolic activity by modulation of the gut microbiome *in vitro*

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ARTICLE INFO

Keywords:
Faecalibacterium prausnitzii
Endotoxemia
Fructooligosaccharides
Galactooligosaccharides
Xylooligosaccharides
Obesity

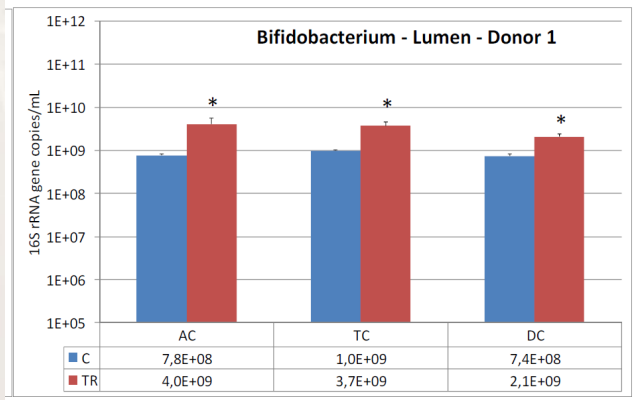
ABSTRACT

A standardized *in vitro* simulation of the human gastrointestinal tract (M-SHIME®) was used to assess the effect of repeated daily administration of a synbiotic formulation, containing five spore-forming *Bacillus* strains and a prebiotic fiber blend, on the microbial activity and composition of three simulated human subjects. Firstly, while confirming recent findings, deeper phylogenetic insight was obtained in the resident M-SHIME® microbiota, demonstrating that the model maintains a diverse and representative, colon region-specific luminal and mucosal microbial community. Supplementation of the synbiotic concept increased microbial diversity in the distal colon areas, whereas specific enhancement of *Bacillaceae* levels was observed in the ascending colon suggesting a successful engraftment of the *Bacillus* spores, which probably resulted in a stimulatory effect on, among others,

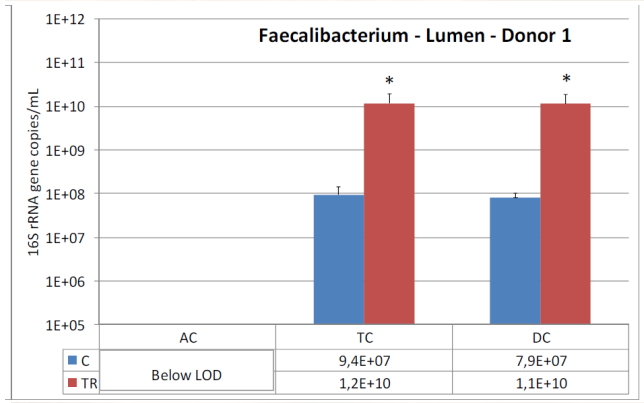
RECONDITION the gut

REINFORCE beneficial changes

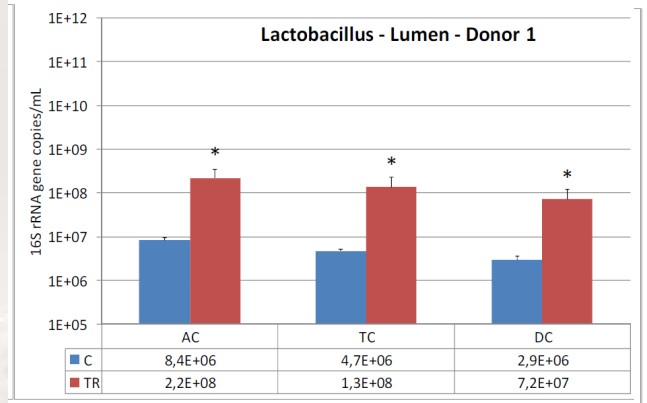
TYPICAL SUBJECT DATA



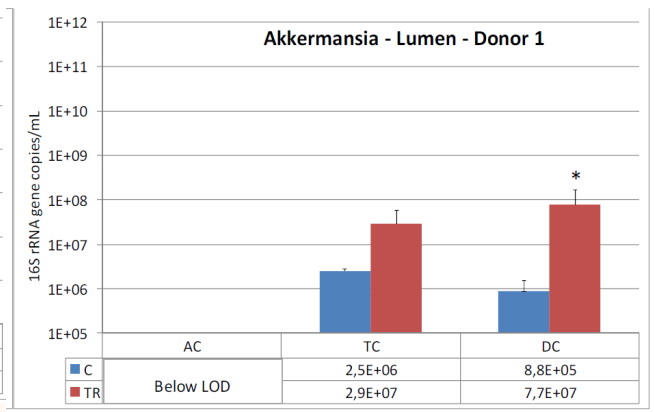
	AC	TC	DC
C	7,8E+08	1,0E+09	7,4E+08
TR	4,0E+09	3,7E+09	2,1E+09



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

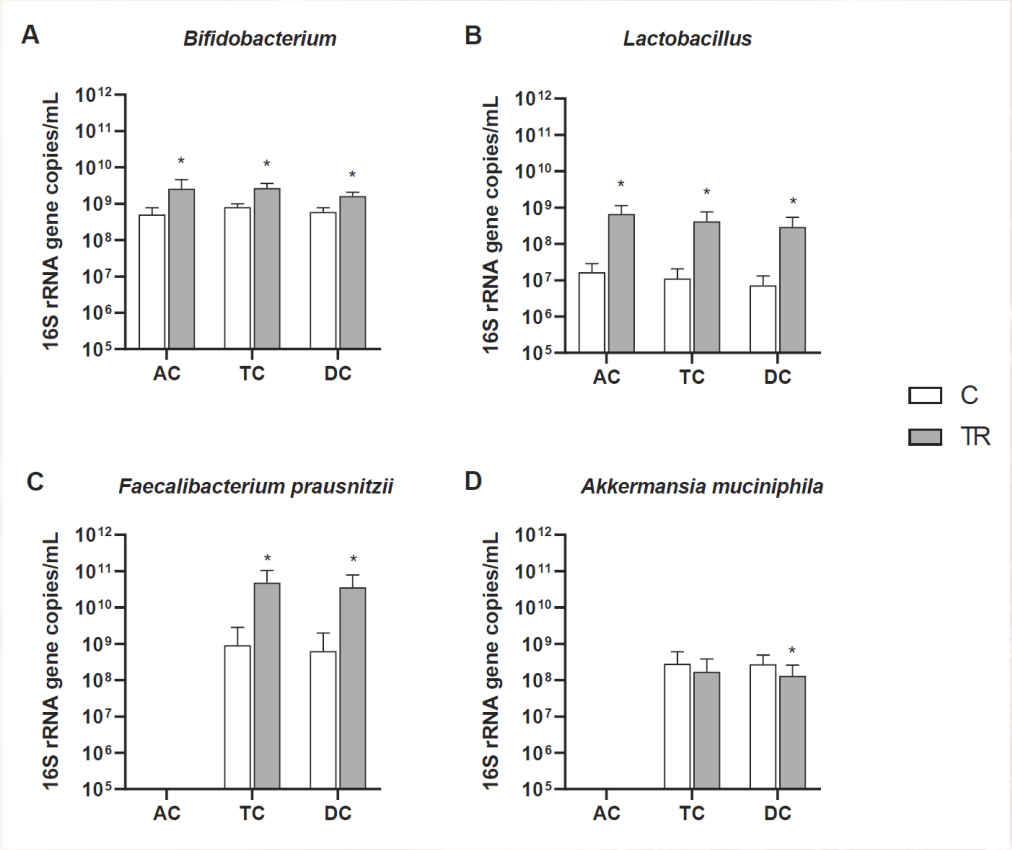


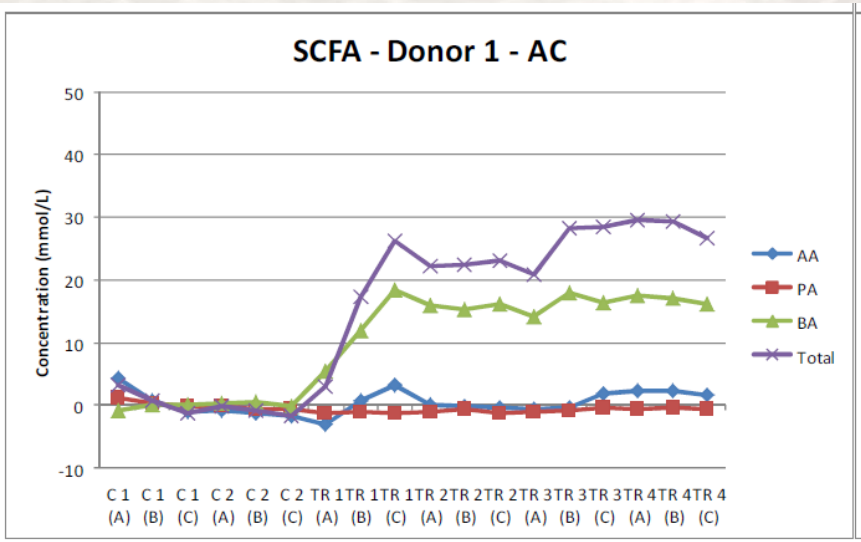
	AC	TC	DC
C	8,4E+06	4,7E+06	2,9E+06
TR	2,2E+08	1,3E+08	7,2E+07

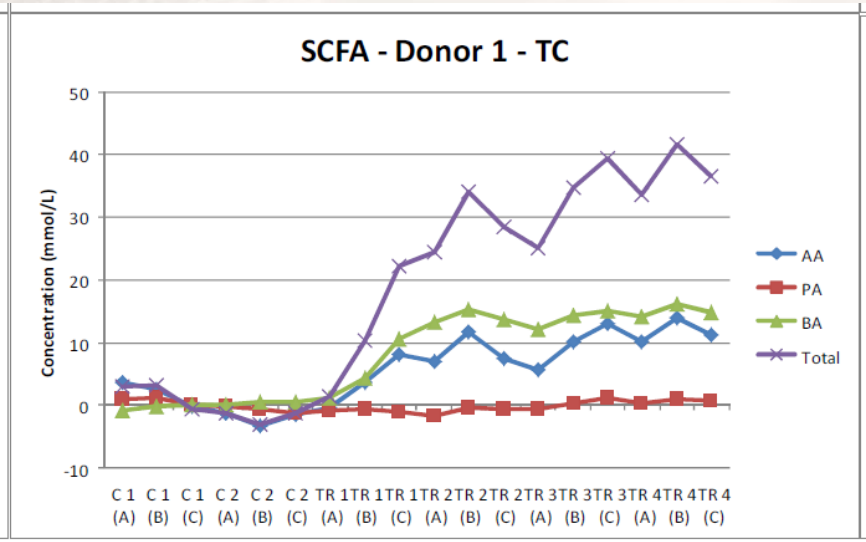


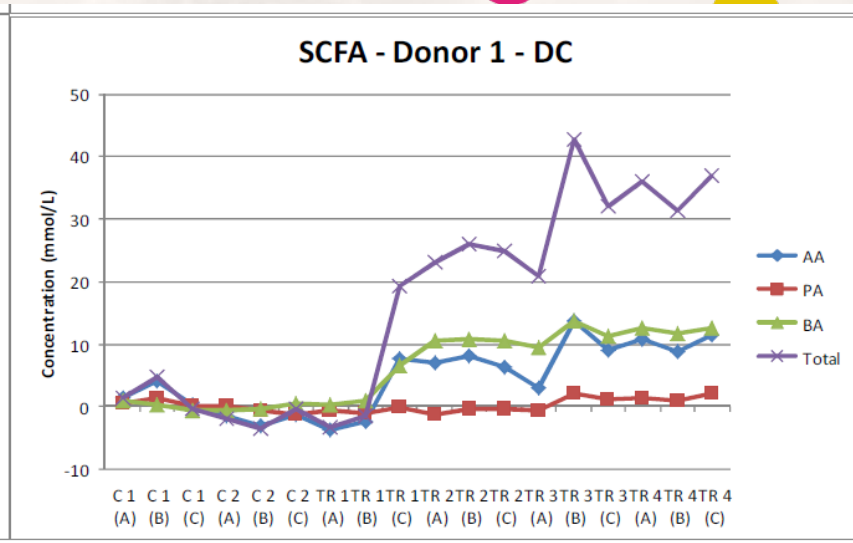
	AC	TC	DC
C	Below LOD	2,5E+06	8,8E+05
TR		2,9E+07	7,7E+07

COHORT DATA





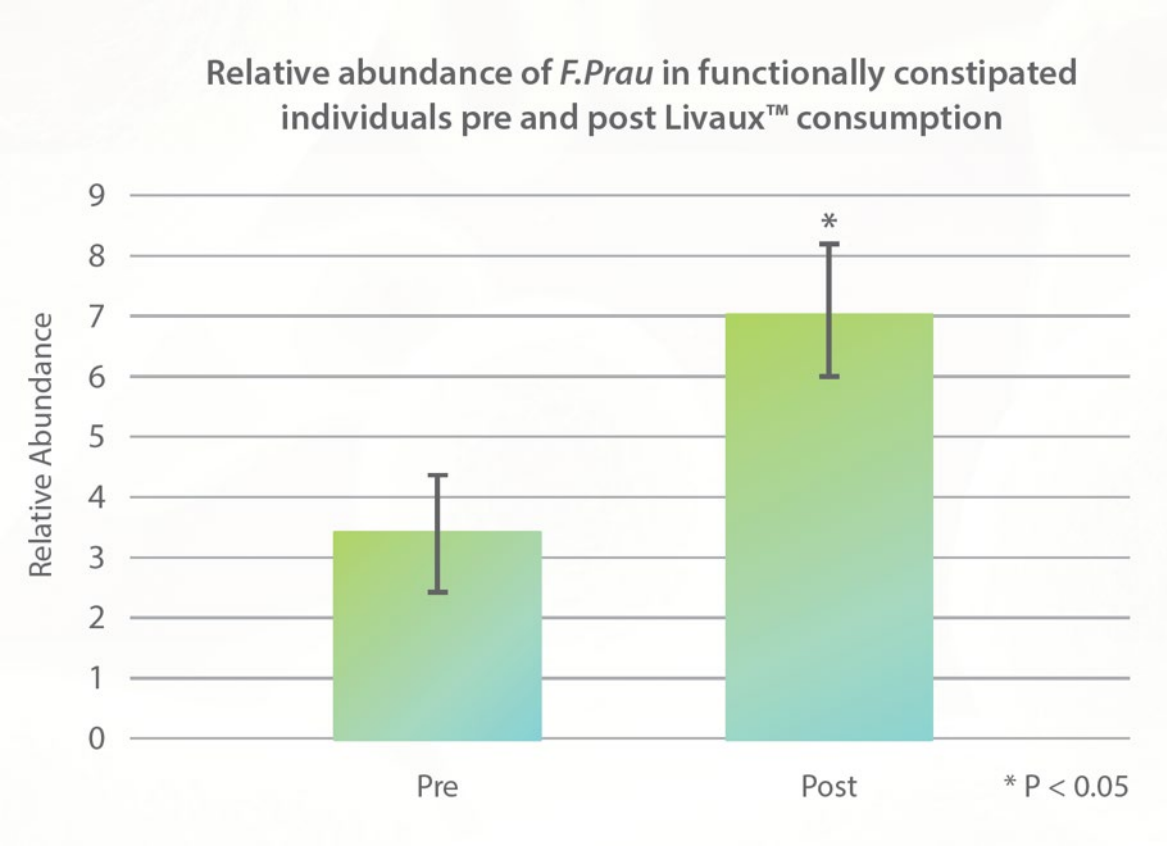




80-140% increase in SCFA production

		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

MICROBIAL CHANGES FROM OLIGOSACCHARIDES



- **FOS** ↑ *F. prau* by 100% in 4 weeks
- **FOS** ↑ *A. mucin* by 8,000% in 5 weeks
- **GOS** ↑ *Bifido* by 67% in 1 week
- **XOS** ↑ *Bifido* by 21% in 4 weeks

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

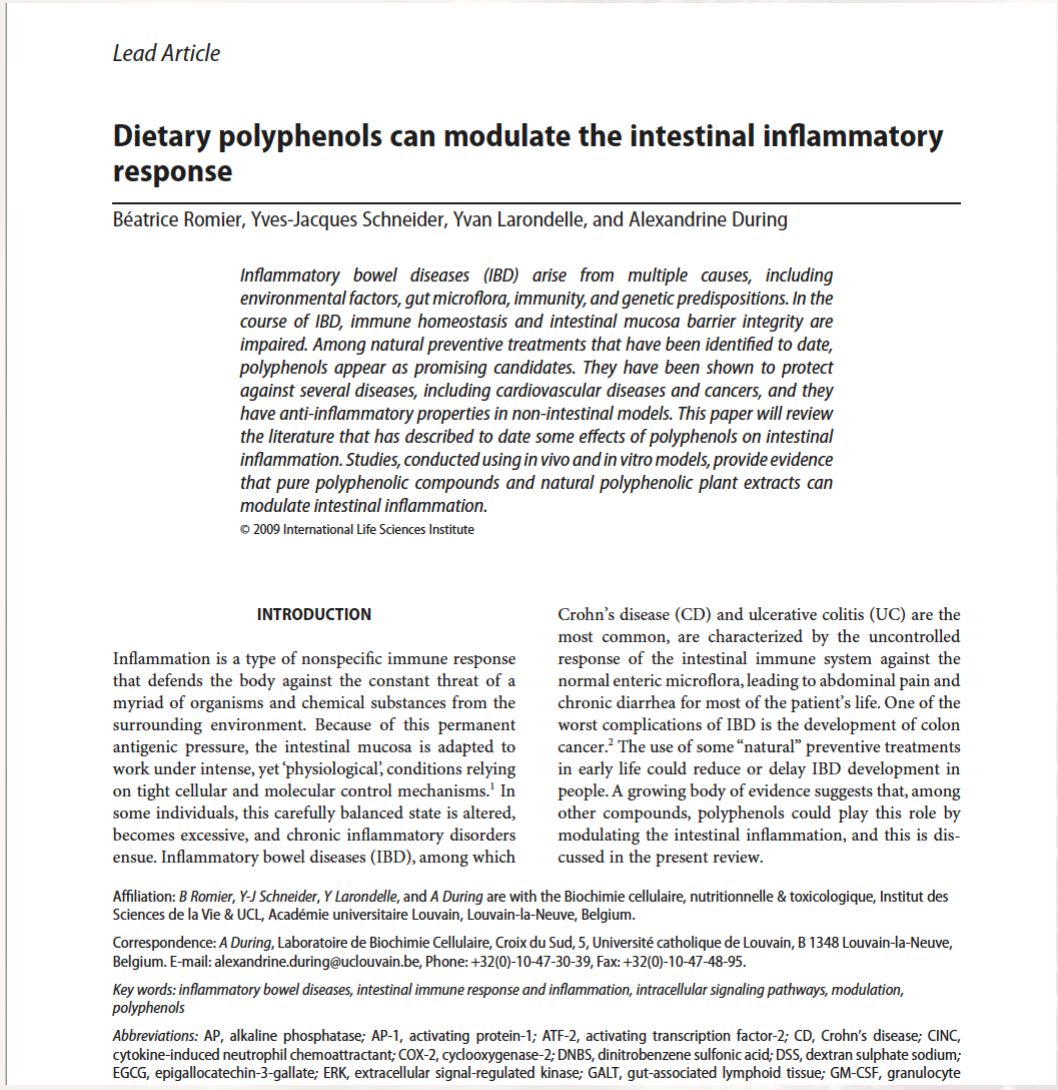
REBUILD
intestinal mucosa

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.

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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*

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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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ORIGINAL ARTICLE

Prospective Study

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

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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

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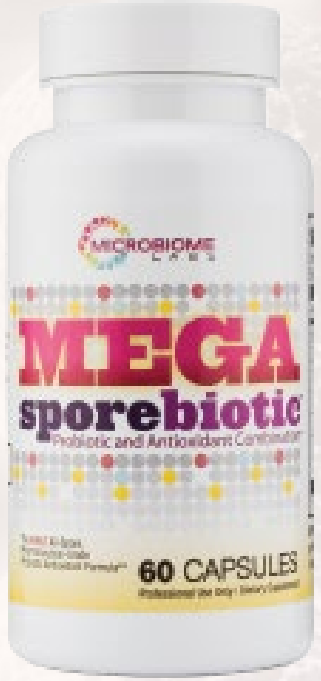
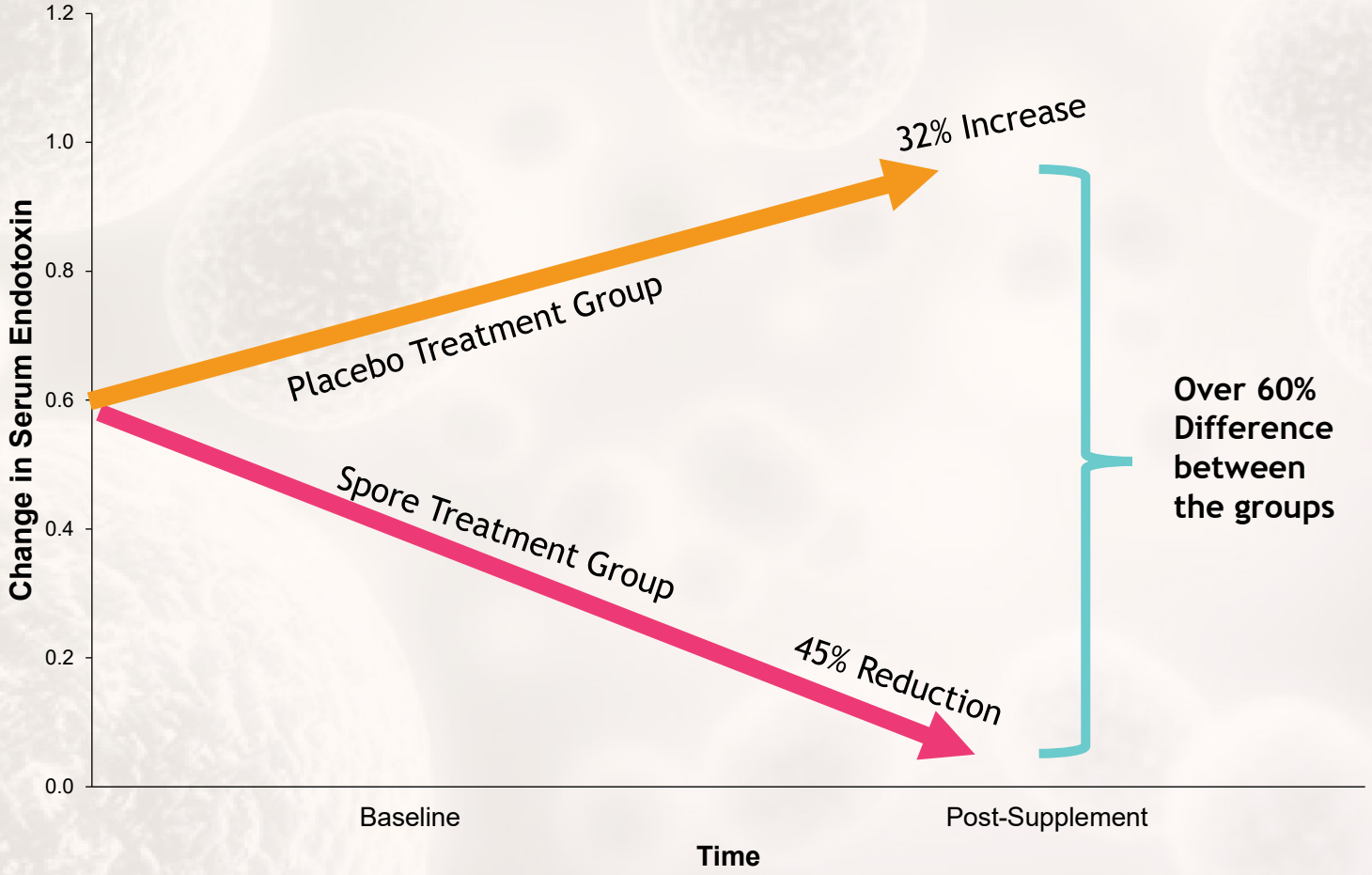


The effect of 30-days of probiotic supplementation on post-prandial responses to a high-fat meal: An Expanded Pilot Study

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



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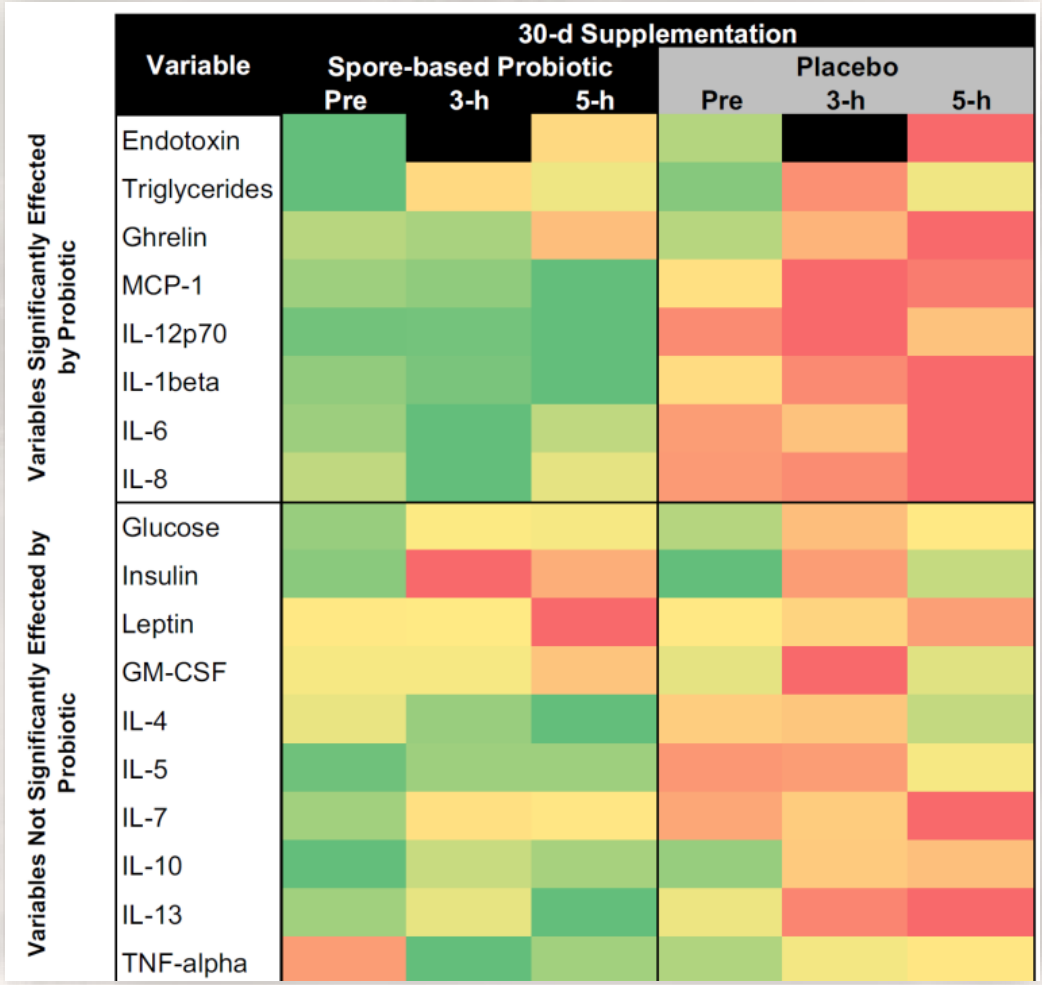
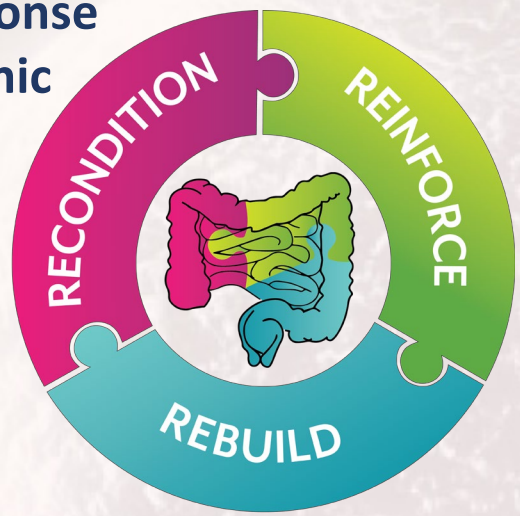


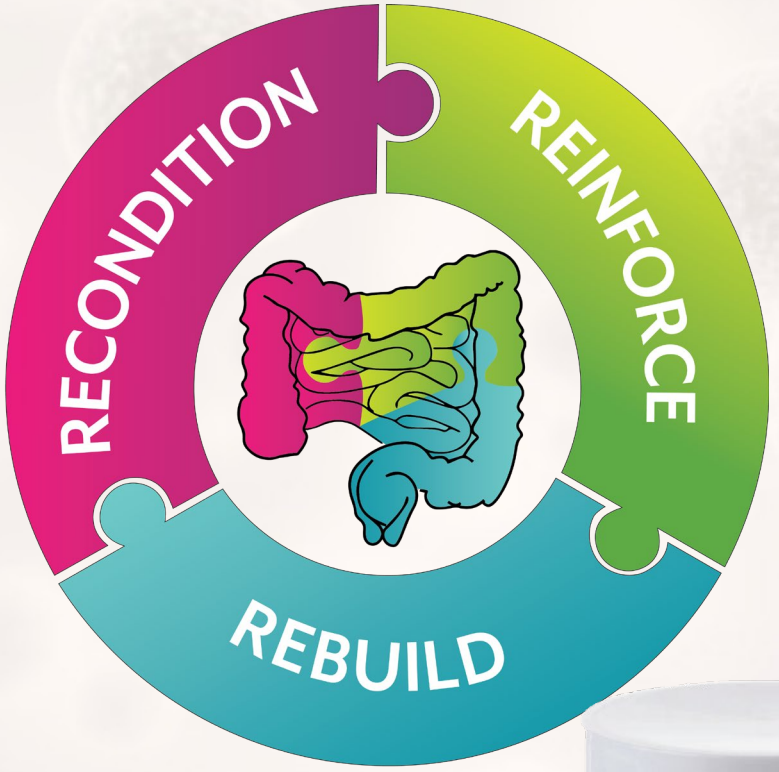
TOTAL GUT RESTORATION

- 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



TOTAL GUT RESTORATION

RECONDITION
the gut



REINFORCE
beneficial changes

REBUILD
intestinal mucosa

Thank you