The Microbiome and Genetics: The FUT2 Variant and its Role in GI disorders and Chronic Inflammation.

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Workshop Objectives:

- Define gastrointestinal hyperpermeability and its role in chronic inflammation
- Understand the role FUT2 variant and its relationship to multiple conditions
- Treatment considerations to influence gut bacteria
Gastrointestinal complaints are among the leading reasons that patients seek health care.

“Over 95 million Americans experience some kind of digestive problem...total health care costs exceed $40 billion annually.”
Common approaches may alleviate symptoms...

such as occasional indigestion, occasional heartburn, abdominal cramping, urgent bowel movements, or occasional constipation.

They may only temporarily mask the underlying issues and have potential adverse effects.
IBS, IBD, Crohn’s, Ulcerative Colitis

• As many as 20 percent of the adult population, or one in five Americans, have symptoms of IBS, making it one of the most common disorders diagnosed by doctors.

• Irritable bowel syndrome may be a lifelong condition.

• For some people, symptoms are disabling and reduce the ability to work, travel, and attend social events.

No Known Consensus....

- Crohn’s disease and Ulcerative colitis are both major categories of inflammatory bowel diseases (IBD). IBD affects an estimated 1.6 million Americans.

- **What Causes Inflammatory Bowel Disease?**
  - IBD is a disease with an unknown cause. Some agent or a combination of agents -- bacteria, viruses, antigens -- triggers the body's immune system to produce an inflammatory reaction in the intestinal tract.

M’Koma, A. 2013 Aug; 6: 33-47. PMID: 24833941
Inflammation: Friend or Foe?
Inflammation is critical for survival, but excessive inflammation is linked with disease.

**Ancestral populations**
- Pathogens
  - Predators
  - Rivals
- Inflammatory bias
  - Avoidance
  - Alarm
  - Wound healing
  - Fighting infection
- Benefit of robust inflammatory response outweighed potential cost

**Modern life**
- Pathogens
  - Obesogenic environment
  - Chronic stress
  - Environmental toxins
  - Infectious mortality
  - Inflammation
  - Chronic conditions
  - Autoimmunity

**Evolutionary time**

Inflammation & Pain: Key Regulator of Gene Expression

• Nuclear factor-kappa B (NF-κB)
  o Protein complex that controls DNA transcription/genetic expression
  o When activated, controls/regulates the expression of ~500 genes, including:
    – Pro-inflammatory enzymes: PLA$_2$, COX-1, COX-2, LOX
    – Pro-inflammatory cytokines: IL-1β, IL-6, IL-12, TNFα
    – Chemokines: CXCL8 (aka IL-8), MCP-1

Uncontrolled Chronic Inflammation Is Linked to Many Chronic Diseases

- Diabetes
- Depression
- Vascular disease
- Inflammatory bowel disease
- Arthritis
- Autoimmune diseases
- Alzheimer’s disease
- Asthma
- Obesity
- Pancreatitis

Patients with inflammatory bowel disease have increased risk of autoimmune and inflammatory diseases.

Chronic, noncommunicable, and inflammation-associated diseases remain the largest cause of morbidity and mortality globally and within the United States.
The Gastrointestinal Tract

- A 15 foot tube running through the body from mouth to anus where food from the stomach passes into the intestine for further digestion.
- Intestinal wall contains hundreds of different species of healthy and unhealthy bacteria numbering in the billions!
  - **Healthy**: *L. acidophilus* and *Bifidobacteria*
  - **Unhealthy**: Pathogenic bacteria and fungus
- Normalization of gut function results in improved clinical outcomes across many diverse diseases.
Normal Intestinal Permeability

Glucose

Transcellular Pathway
Normal Intestinal Permeability

Hyperpermeability

Toxins

Poor digestion

Dysbiosis

NSAIDs

Antibiotics

Alcohol

Infections

Poor diet

Dysbacteriosis

Antibiotics

Immune system dysregulation

Inflammation

Food allergies & Intolerances

Immune system dysregulation
Major Role of the Gastrointestinal Tract is To act as a barrier to finely regulate the trafficking of macromolecules between the external (food/microbes) and internal environment (systemic, cells, tissues, etc).

When this complex **barrier is broken**, foreign macromolecules can enter, interact with the immune system, and result in an inflammatory response which **can lead to a multitude of local intestinal and systemic extraintestinal diseases.**
What is “Leaky Gut”? 

- **Leaky gut syndrome** is a condition that affects your digestive system. 
- Your intestines have tight junctions, or small gaps, that allow nutrients and water to pass into your bloodstream.
What is “Leaky Gut”?

In **leaky gut syndrome**, these tight junctions loosen, potentially allowing harmful substances like bacteria, toxins, and undigested food particles to enter the bloodstream.
“Disruption of the intestinal TJ barrier, followed by permeation of luminal noxious molecules, induces a perturbation of the mucosal immune system and inflammation, and can act as a trigger for the development of intestinal and systemic diseases.”

Suzuki T Cell Mol Life Sci 2012; DOI 10.1007/s00018-012-1070-x
Leaky gut is associated with numerous acute and chronic diseases:

- Chronic inflammatory response syndrome (CIRS)
- Inflammatory bowel disease
- Type-1 diabetes
- Autoimmune disease
- Allergies
- Asthma
- Arthritis
- Liver disease
- Obesity
- Metabolic syndrome

Qinghui Mu, Jay Kirby, Christopher M. Reilly, Xin M. LuoFront Immunol. 2017; 8: 598. Published online 2017 May 23. doi
Gluten sensitivity may be an underlying factor as well.

“A leaky gut has been recently proposed to be a universal initiating trigger for autoimmune diseases”

Fasano A. Surprises from celiac disease. Sci Am. 2009 Aug;301(2):54-61
- 107,000 hospitalizations
- 16,500 NSAID-related annual deaths
- 15th most common cause of death in the United States
- 80% of patients have no reliable warning signs
- Intestinal injury can begin within 72 hours of use


Consumer Health Alert:

FDA Highlights the Dangers of Acetaminophen and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
Microbes exist on all body surfaces: skin, oral cavity, vagina, gut.

The human microbiome is diverse (The gut contains thousands of species alone).

Dysbiosis or microbial imbalance may play a role in immunological, metabolic and neurological diseases.

The Human Microbiome Project has led to the finding that health conditions are in part defined and influenced by specific microbiota.

http://www.nytimes.com/interactive/2012/06/19/science/0619-microbiome.html?_r=0
http://www.nytimes.com/2013/05/19/magazine/say-hello-to-the-100-trillion-bacteria-that-make-up-your-microbiome.html?pagewanted=all
Establishment of the Gut Microbiota

At birth, the GI tract and immune system are immature.

Colonization with microbes builds after birth.

Once the microbiota are established around age 2-3, the community is relatively stable over time within an individual.

Initial Colonization of the Gut

• Factors affecting initial colonization of the gut in infants:
  • Gestation length
  • Mode of delivery
  • Feeding practices
  • Antibiotic exposures
  • Birth order

• Negative influences on the establishment of a healthy gut microbiota and factors that decrease microbial diversity in infants and young children can have lifelong detrimental health impacts.

Mode of Delivery - Long Term Sequelae

• Children born by C-section are at increased risk of developing:
  • Conditions of the “Atopic Triad”
    • Atopic dermatitis
    • Allergic rhinitis
    • Asthma
    • Type 1 diabetes

Feeding Practices - Long Term Sequelae

• Formula fed infants are at higher risk of:
  • Atopic dermatitis
  • Pediatric inflammatory bowel disease (Ulcerative colitis, Crohn’s disease).
  • Type 2 diabetes later in life
  • Obesity later in life

Research-Proven Benefits of Probiotics

- Improved GI function
  - Better nutrient absorption
  - Reduced constipation, gas & bloating
- Reduce harmful bacteria
- Improved immune function: less sickness
- Reduced allergies
- Reduced urogenital infections
- Improved lactose digestion
The intestinal microflora is a positive health asset that crucially influences the normal structural and functional development of the mucosal immune system. Collectively, the flora has a metabolic activity equal to a virtual organ with an organ.

Pharmabiotic is a generic term to encompass any form of therapeutic exploitation of the commensal flora, including the use of live probiotic bacteria, probiotic-derived biologically active metabolites, prebiotics, synbiotics or genetically modified commensal bacteria.

Manipulation of the flora is becoming a realistic therapeutic and prophylactic strategy for many infectious, inflammatory and even neoplastic diseases within the gut.

O’Hara A et al. EMBO reports 2006 7(7) 688-692
Quality assurance criteria for probiotic bacteria\textsuperscript{1–4}

Elina Tuomola, Ross Crittenden, Martin Plyne, Erika Isolauri, and Seppo Salminen

ABSTRACT Acid and bile tolerance is another important adhesion property. The quality control of probiotics should be tested on a selection of probiotics, including plasmid stability; carbohydrate and protein utilization patterns; acid and bile tolerance and survival and growth; bile metabolism; intestinal epithelial adhesion properties; production of antimicrobial substances; antibiotic resistance patterns; ability to inhibit known gut pathogens, spoilage organisms, or both; and immunogenicity.

KEY WORDS Probiotics, stability, viability

INTRODUCTION

Probiotics are viable bacteria that beneficially influence the health of the host (1, 2). Probiotic bacteria selected for commercial use in foods and in therapeutics must retain the characteristics for which they were originally selected (1–3). These include characteristics for growth and survival during manufacture and, after consumption, during transit through the stomach and small intestine. Importantly, probiotics must retain the characteristics that are responsible for their health effects. Growth (4). All of these in vitro systems provide valuable information on the ability of probiotics to adhere and colonize the intestine.

Adhesion to colonic or intestinal biopsy samples, if possible, should be considered as a final in vitro adhesion test that would be most like the in vivo situation. Not only would this be a better approximation of the in vivo situation, it would allow for the study of adhesion to different parts of the intestine. This is especially important regarding immune stimulation by oral administration of probiotics.

Adhesion is also considered important for stimulation of the immune system. Adhesion to M cells or Peyer’s patches may facilitate antigen transport to the gut-associated lymphoid tissue and thus may be important for immune stimulation by probiotics. The importance of adhesion in the immune system is further supported by the finding that the absence of adhesion to M cells results in failure of the bacteria to stimulate immune responses (1, 2).
Determining a probiotic

“defined viable microorganisms, sufficient amounts of which reach the intestine in an active state and thus exert positive health effects.”


- Found in humans
- “defined”
- “viable”
- “sufficient amounts of which reach the intestine in an active state”
- “exert positive health effects.”
"Here we demonstrate that Lactobacillus salivarius UCC118, a recently sequenced and genetically tractable probiotic strain of human origin, produces a bacteriocin in vivo that can significantly protect mice against infection with the invasive foodborne pathogen Listeria monocytogenes."

Corr, et al. 2007 PNAS 104;18:7617-7621
Although many strains are commercially available, very few have supporting clinical data.
Mechanism of protection of transepithelial barrier function by *Lactobacillus salivarius*: strain dependence and attenuation by bacteriocin production

Eiji Miyauchi, 1,2,3 John O’Callaghan, 1,2 Ludovica F. Buttó, 1,2 Gráinne H. Soichi Tamabe, 3 Fergus Shanahan, 1,4 Kenneth Nally, 1 and Paul W. O’Toole 1

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2Department of Science, Hiroshima University, Japan
3Department of Medicine, University College Cork, Cork, Ireland.

Submitted 4 January 2012, accepted in final form 4 September 2012.


The protective effects of *Lactobacillus salivarius* strain UCC118 on H2O2-induced barrier impairment in human epithelial Caco-2 cells. These strains showed markedly different effects on H2O2-induced reduction in transepithelial resistance (TER). The effective strains such as UCC118 and UCCG80808 attenuated H2O2-induced disassembly and relocalization of tight junction proteins, but the ineffective strain AH43324 did not. Strains UCC118 and UCCG80808 induced phosphorylation of extracellular signal-regulated kinase (ERK) in Caco-2 cells, and the ERK inhibitor U0126 attenuated the barrier-protecting effect of these strains. In contrast, the AH43324 strain induced phosphorylation of Akt and p38, which was associated with an absence of a protective effect. Global transcriptome analysis of UCC118 and AH43324 revealed that some genes in a bacteriocin gene cluster were upregulated in AH43324 under TER assay conditions. A bacteriocin-negative UCC118 mutant displayed significantly greater protective effect on H2O2-induced reduction in TER compared with wild-type UCC118. The wild-type strain augmented H2O2-induced phosphorylation of Akt and p38, whereas a bacteriocin-negative UCC118 mutant did not. These observations indicate that *L. salivarius* strains are widely divergent in their capacity for barrier protection, and this is underpinned by differences in the activation of intracellular signaling pathways. Furthermore, bacteriocin production appears to have an attenuating influence on lactobacilli-mediated barrier protection.

**Tight junction proteins**
- Occludin
- JAM-1
- Claudin-1
- ZO-1

**Control**
**H2O2**
**UCC118**
L. salvarius UCC118

In an *in vitro*, validated model of human intestinal epithelial cells, researchers assessed the effects of *L. salivarius* exposure on localization of tight junction proteins by confocal microscopy.¹

- Hydrogen peroxide (H2O2) exposure disrupted and redistributed the tight junction proteins occludin, JAM-1, and claudin-1.¹

- Pretreatment with *L. salvarius* UCC118 helped maintain tight junction protein integrity (Figure 1).*¹

- In separate preclinical research, *L. salivarius* UCC118 has been shown to produce a bacteriocin, a beneficial protein that may influence intestinal microbial composition.*²,⁵,⁶,⁷

* These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.
Bacteriocins are peptides produced by bacteria that kill or inhibit other bacterial strains.
Probiotics
Influence More than Just Gut Health*

Leaky Gut-Leaky Brain
Anxiety, Depression

Reference:

* These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure, or prevent any disease.
Prebiotic Fiber Supports Healthy Probiotic Bacteria

Prebiotics are food for beneficial microbes that live on or in us. They are metabolized by the “good” gut microbes, positively impacting the gut environment with an overall health benefit.*

Source: International Scientific Association for Probiotics and Prebiotics

* These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure, or prevent any disease.
### Prebiotic Foods

- Asparagus
- Banana
- Dandelion greens
- Eggplant
- Endive
- Garlic
- Honey
- Jerusalem artichokes (sunchokes)
- Jicama
- Leeks
- Legumes
- Onions
- Peas
- Radicchio
- Whole grains
Gut Health and Your Genes – FUT2 Genetic Variants

Genetic variant: An alteration in the most common DNA nucleotide sequence. The term variant can be used to describe an alteration that may be benign, pathogenic, or of unknown significance. The term variant is increasingly being used in place of the term mutation.
Gene Coding

• The gene coding for your blood type lies on chromosome 9q34. However, a separate gene (called FUT2) actually interacts with your blood type gene, and determines your ability to secrete your blood type antigens into body fluids and tissues, such as saliva, mucus (in the digestive tract and the respiratory cavities), tears, and sweat.

• Whether you secrete your blood type plays a significant role in the type of bacteria that dwell in our gut microbiome
Secretor or Non-Secretor

• The determination of secretor status is important because secretor status is associated with a wide variety of diseases (like urinary tract infections, diabetes, digestive disorders, etc.)

• Frequency of ABH secretor status in the world population is about 80% secretors and 20% non-secretors with some geographic and racial differences.

FUT2 influence of Gut Bacteria

• When FUT2 SNPs are present, we are unable to feed healthy bacteria due to the gut lacking its pre-biotic.
• This changes the balance between the good and bad bacteria, allowing the bad bacteria to dominate over the gut.
• Diseases derive from this such as SIBO, IBS, Chronic Constipation and diarrhea, mood issues, sleep issues, and focus issues.

ISME J. 2014 Nov;8(11):2193-206. PMID: 24781901
The Secretor Status and infection risk

• Several studies show that secretor status affects susceptibility to infection.

• Because our ABO blood group antigens are a carbohydrate food source for many bacteria, the presence or absences of these antigens effect the population of the gut bacteria and provide protection against certain pathogenic bacteria.

• Non-secretors are at an increased risk for development of celiac disease (up to 48% of patients with celiac disease have been reported to be Non-secretors).

Nash, G ND, 2019 “FUT2 Secretor Status: Effects on Gut Health”
Less dental caries among secretors than among non-secretors

As a general rule, a higher intensity of oral disease is found among Non-secretors. This includes dysplasia (precancerous changes to the tissue) and an increase in cavities.

**FUT2** might be a target of natural selection due to evolving pathogens

Being homozygous for the inactive “non-secretor” rs601338(A) allele confers resistance to certain infections (e.g. *Norovirus, Rotavirus*) and susceptibility to others (e.g. *Haemophilus influenza, Streptococcus pneumonia*).

Microbiome. 2015 Apr 10;3:13. PMID: 25922665

FUT2 Enzyme and IBD

- Crohn’s Disease (CD)
  - Non-Secretors, who are homozygous for the loss-of-function alleles of FUT2 gene, have increased susceptibility to Crohn’s Disease.
  - However, the molecular mechanism of the association between non-secretor status and CD remains unknown.
- Ulcerative Colitis (UC)
  - Dysbiosis of intestinal microbiota has been shown in ulcerative colitis.

ISME J. 2014 Nov;8(11):2193-206. PMID: 24781901
What are Human Milk Oligosaccharides (HMOs)?

• **2'-Fucosyllactose***
  
  • A human milk oligosaccharide (HMO), similar to that found in breast milk*
  
  • Targeted prebiotic to promote healthy intestinal mucosal health and nourish beneficial microorganisms
  
  • Encourages the production of short-chain fatty acids (SCFA)

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*The 2'FL in UGIR is not derived from human breast milk
What are Human Milk Oligosaccharides (HMOs)?

- HMOs are a group of carbohydrate compounds unique to human milk. To date over 150 unique carbohydrate structures have been identified. 2’Fucosyllactose* is the most abundant HMO.

- HMOs have prebiotic effects, selectively serving as a source of energy and nutrients for desired bacteria to colonize the intestine.

- HMOs have been shown to be anti-adhesive, mimicking the attachment sites for certain pathogens and blocking their adhesion, colonization, and invasion.

- HMOs might also have intestinal epithelial cell surface glycome-modifying effects, changing the glycosylation machinery of intestinal epithelial cells, altering the expression profiles of pathogen attachment sites, and reducing infectious diseases.

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*The 2'FL in UGIR is not derived from human breast milk
2’-FL also supports GI health by blocking certain potentially harmful bacterial strains from adhering to their host cell receptors; 2’-FL mimics host cell surface receptors and acts as a decoy. 27 2’-FL has been shown to act as an anti-adhesive antimicrobial to Campylobacter jejuni, Vibrio cholera, Escherichia coli, and Norovirus.

A Medical Food (UGIR) Reduces Gastrointestinal Symptoms and Beneficially Alters Gut Microbiota in Adults with IBS and IBD
Functional Medicine Considerations for IBD

- Genetics, Environmental triggers, and an Inflammatory response
- Leaky Gut contributors, diet, gluten, stress, medication
- Calm gut inflammation (probiotics)
- Prebiotics through diet and supplementation
- Nutritional Kinase modulation (NF-kB)
- Consider genetic variants: FUT2
“... but if you remove the environmental pressure, the epigenetic marks will eventually fade, and the DNA code will — over time — begin to revert to its original programming.”
GENETIC TESTING

MTHFR SUPPORT

MTHFR Support Variant Report v2.5
Based on: AncestryDNA.zip
http://www.mthfrsupport.com

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