Con il patrocinio di

UNICUSANO

UPDATES ON

INTESTINO PERMEABILE:
LA BARRIERA ALTERATA

Roma, 8 e 9 Novembre 2019

c/o Aula Magna Università Unicusano

Lectine E Antinutrienti Oligosaccaridi Del Latte Umano Nella Sindrome Dell'intestino Permeabile

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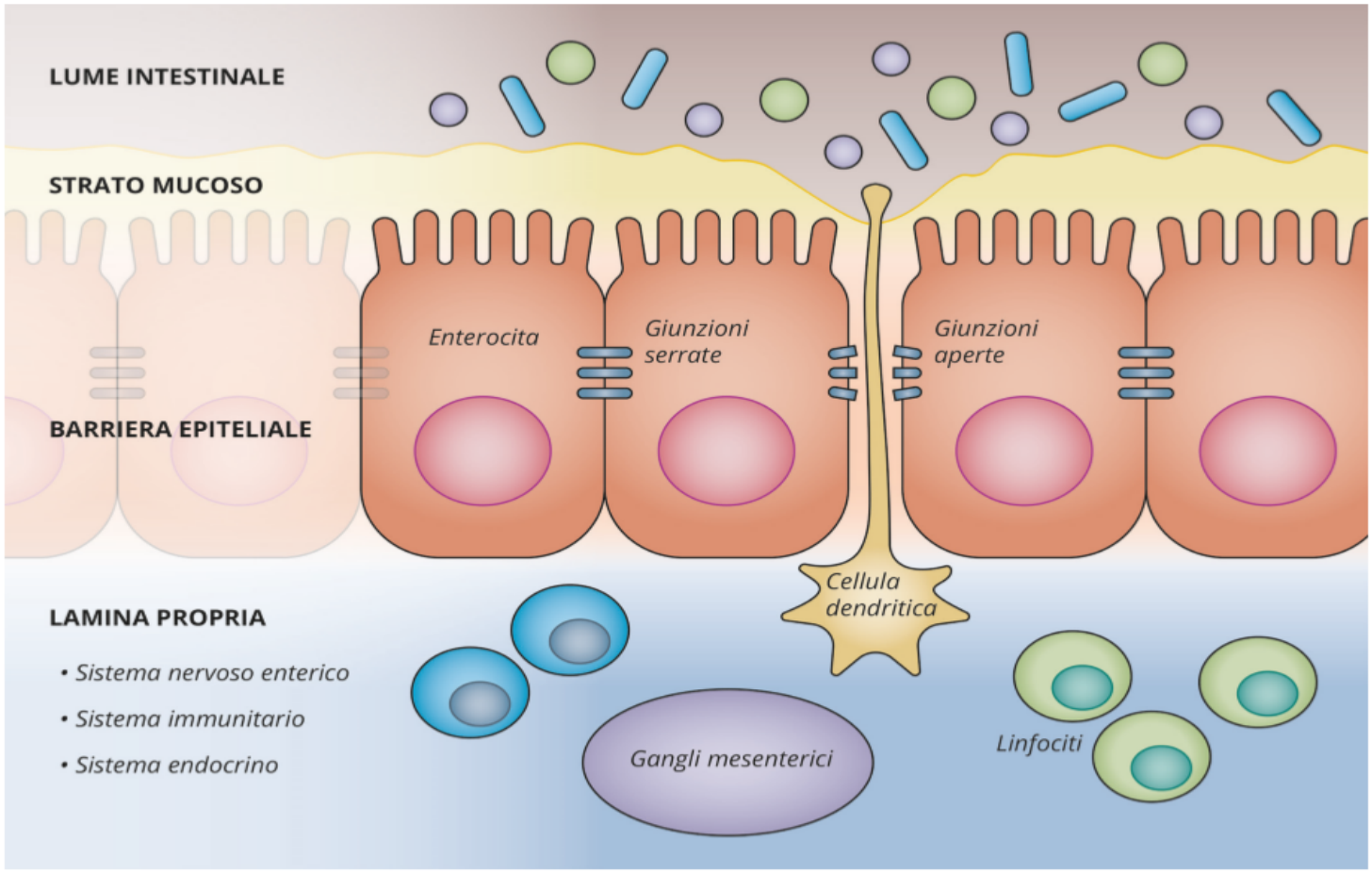
SAPIENZA
UNIVERSITÀ DI ROMA

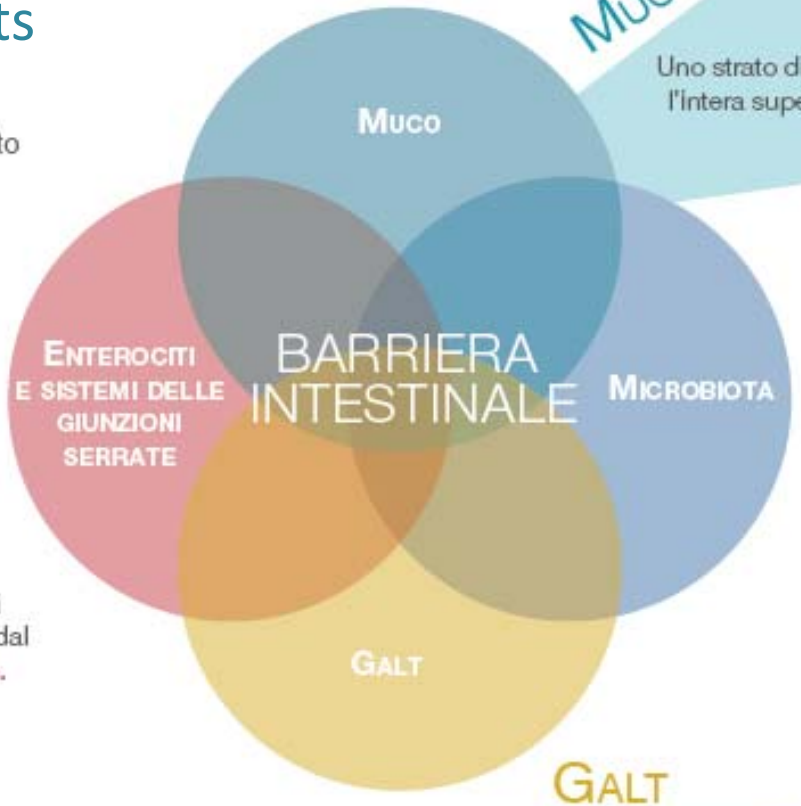
Intestinal permeability – a new target for disease prevention and therapy

STRUTTURA E LIVELLI FUNZIONALI DELL'ECOSISTEMA INTESTINALE E RUOLO DELLA BARRIERA SELETTIVA



GUT BARRIER : the protagonists

Quattro elementi funzionali contribuiscono al funzionamento della barriera intestinale



MUCO

Uno strato di spessore variabile ricopre e protegge l'intera superficie della mucosa intestinale.

ENTEROCITI E GIUNZIONI SERRATE

Lo strato monocellulare degli enterociti crea una barriera la cui permeabilità selettiva è regolata dal **sistema delle giunzioni serrate.**

MICROBIOTA

I batteri del microbiota intestinale modulano la funzione della **barriera,** attraverso la produzione di acidi grassi a catena corta (SCFA) ed esercitano una importante influenza sul **GALT.**

GALT

O SISTEMA IMMUNITARIO (SI) ASSOCIATO ALLA MUCOSA

Oltre il 70 % delle cellule del SI è dislocato nell'intestino.
A livello dell'epitelio troviamo le **cellule di Paneth** (produttrici di peptidi antimicrobici) e le **cellule M** sovrastanti le placche di Peyer. Nella lamina propria si localizzano moltissime cellule immunitarie, proprie sia del **SI innato** (macrofagi, cellule dendritiche,...) sia del **SI adattativo** (linfociti T, cellule produttrici di IgA).

Intestinal permeability – a new target for disease prevention and therapy

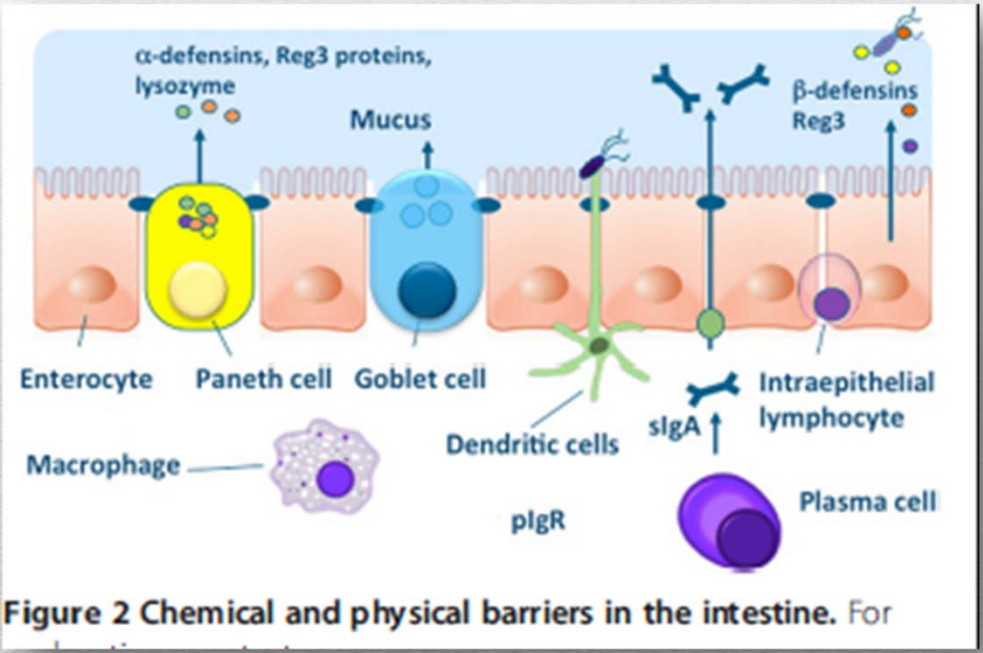
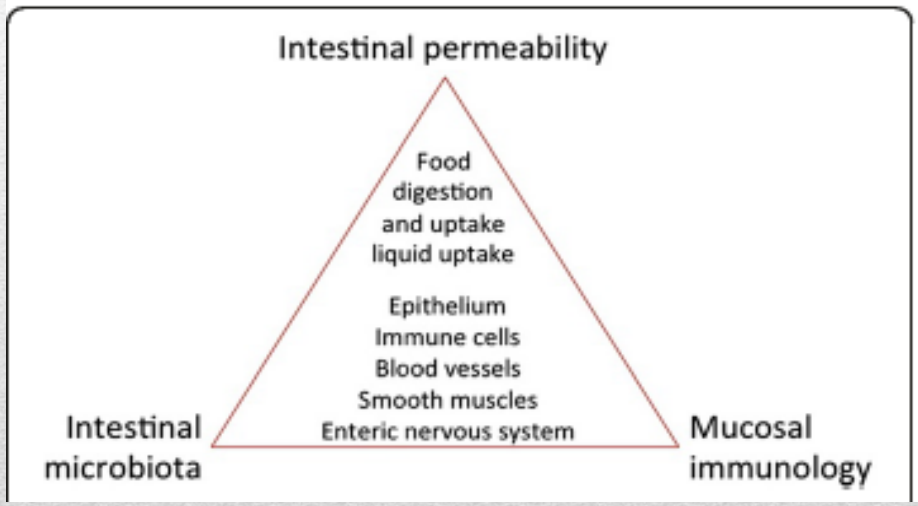


Figure 2 Chemical and physical barriers in the intestine. For



Bischoff *et al. BMC Gastroenterology* 2014, **14**:189
http://www.biomedcentral.com/1471-230X/14/189

BMC Gastroenterology

Intestinal permeability – a new target for disease prevention and therapy

Table 1 Definitions

Intestinal barrier	*is a functional entity separating the gut lumen from the inner host, and consisting of mechanical elements (mucus, epithelial layer), humoral elements (defensins, IgA), immununological elements (lymphocytes, innate immune cells), muscular and neurological elements*
Intestinal permeability	*is defined as a functional feature of the intestinal barrier at given sites, measurable by analyzing flux rates across the intestinal wall as a whole or across wall components of defined molecules that are largely inert during the process and that can be adequately measured in these settings*
Normal intestinal permeability	*is defined as a stable permeability found in healthy individuals with no signs of intoxication, inflammation or impaired intestinal functions*
Impaired intestinal permeability	*is defined as a disturbed permeability being non-transiently changed compared to the normal permeability leading to a loss of intestinal homeostasis, functional impairments and disease*

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Table 7 Possible causes of impairment of the intestinal barrier

Nutritional factors	Tight junction downregulation
	Histone deacetylase (HDAC) inhibitors
	ENS modulators
Infections & toxins	Viral intestinal infections
	Environmental toxins
	Toxic food
"Hygiene hypothesis"	Sterile environment
	Lack of farming
"Lifestyle hypothesis"	Impaired function and diversity of the intestinal microbiota
Endogenous factors	Hypoperfusion of the intestine
	Chronic inflammation/autoimmunity

Table 8 Factors proposed to support the gut barrier

Dietetic approach	Avoidance of high amounts of sugar and fat
	Avoidance of energy-dense Western-style diet
	FODMAP diet
	Prebiotics/fibers
	Glutamine
	Other immune-modulating formula
Probiotic approach	Selected probiotics
	Probiotic cocktails (multispecies concept)
	Synbiotics (combination of probiotics and prebiotics)
Drugs/others	Short-chain fatty acids (SCFA)
	Metformin
	Quercetin and other flavonoids

Bischoff *et al. BMC Gastroenterology* 2014, **14**:189
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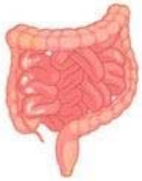
RISK FACTORS for LEAKY GUT SYNDROME

POOR DIET

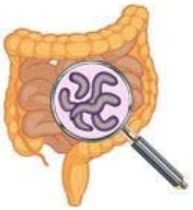
CHRONIC STRESS

EXCESS TOXINS



CANDIDA OVERGROWTH IN THE INTESTINES

MEDICATIONS



DYSBIOSIS

ALCOHOL CONSUMPTION

ZINC DEFICIENCY

Western-style diet

Rich in fat (in particular saturated fatty acids)
Rich in sugars (in particular fructose)
Poor in fibers

↓

Energy-dense food uptake
Inadequate energy balance

↓

Change in microbiota composition in the intestine
(e.g. Induction of firmicutes)

↓

Enhancement of energy harvest
High energy load

↓

Obesity
Joint disease
Depression

↓

Translocation of bacteria and bacterial products in the intestine

↓

Enhanced endotoxin in the portal vein

↓

Low-grade liver Inflammation

↓

NAFLD / NASH
Insulin resistance
Metabolic disease

Related diseases

- Rheumatoid arthritis
- Type 1 diabetes mellitus
- Celiac disease
- IgA nephropathy
- thyroiditis
- Lupus
- Allergies
- Asthma
- Hypercholesterolemia
- Atherosclerosis
- Congestive heart failure
- Hypertension
- Hypoglycemia
- hyperinsulinemia
- Chronic fatigue
- Fibromyalgia
- IBS
- Recurrent GI and Candida Infections
- GI malabsorption
- Growth deficit
- autism
- ADD / ADHD
- Schizophrenia
- Osteoporosis
- Cancer
- Hyper- and hypocortisolemia
- Adrenal insufficiency
- Obesity
- Hormonal alterations including low levels of testosterone and DHEA, PCOS

Anti-nutrients

Anti-nutrients

The term "anti-nutrients" suggests what they are.

Whereas nutrients are substances that nourish plants and animals to grow and live, **anti-nutrients earn their title because they can block the absorption of nutrients**.
Anti-nutrients are naturally found in animals and many plant-based foods. In plants, they are compounds designed to protect from bacterial infections and being eaten by insects.

It is not known how much nutrient loss occurs in our diets because of anti-nutrients, and the effects vary among individuals based on their metabolism and how the food is cooked and prepared.

Many anti-nutrients like phytates, lectins, and glucosinolates can be removed or deactivated by soaking, sprouting, or boiling the food before eating.

1. https://www.hsph.harvard.edu/nutritionsource/anti-nutrients/
2.Schlemmer U, Frølich W, Prieto RM, Grases F. Phytate in foods and significance for humans: food sources, intake, processing, bioavailability, protective role and analysis. Mol Nutr Food Res. 2009 Sep;53 Suppl 2:S330-75.
3.Stevenson L, Phillips F, O'Sullivan K, Walton J. Wheat bran: its composition and benefits to health, a European perspective. Int J Food Sci Nutr. 2012 Dec; 63(8): 1001–1013.

Anti-nutrients

- **Glucosinolates** in cruciferous vegetables (broccoli, Brussels sprouts, cabbage)—can prevent the absorption of iodine, which may then interfere with thyroid function and cause goiter.

- **Lectins** in legumes (beans, peanuts, soybeans), whole grains (gluten) —can interfere with the absorption of calcium, iron, phosphorus, and zinc.

- **Oxalates** in green leafy vegetables, tea—can bind to calcium and prevent it from being absorbed.

- **Phytates** (phytic acid) in whole grains, seeds, legumes, some nuts—can decrease the absorption of iron, zinc, magnesium, and calcium.

- **Saponins** in legumes, whole grains—can interfere with normal nutrient absorption.

- **Tannins** in tea, coffee, legumes—can decrease iron absorption.

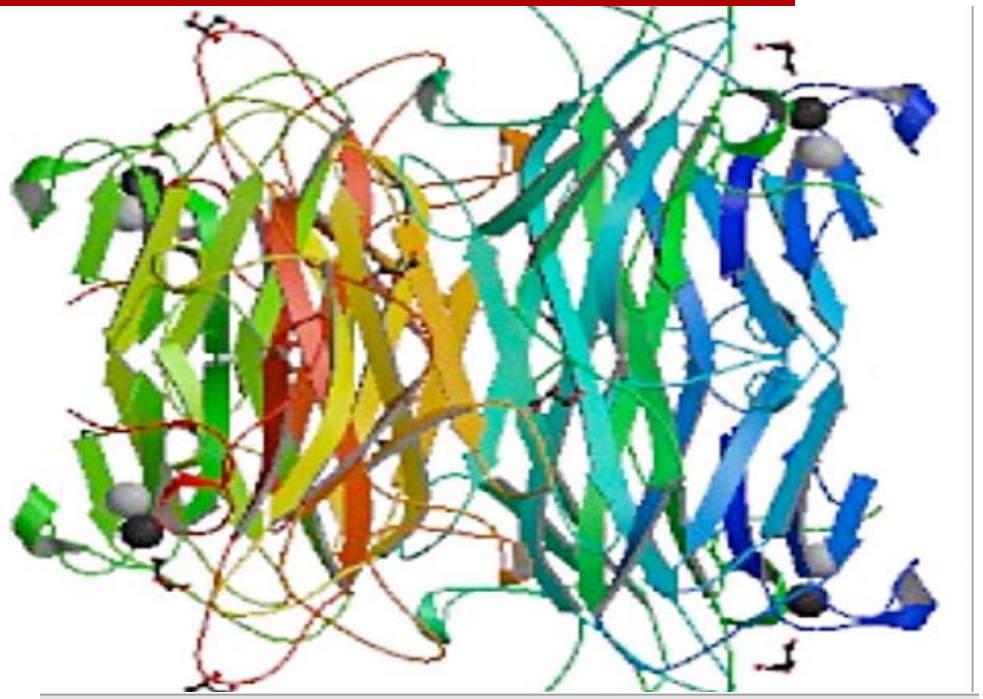
Anti-nutrients

Keep in mind that anti-nutrients may also exert health benefits.

Phytates, for example, have been found to **lower cholesterol, slow digestion**, and **prevent sharp rises in blood sugar.**

Many anti-nutrients have antioxidant and anticancer actions, so avoiding them entirely is not recommended.

A few studies have found a small but **significant increase risk of disease with higher intakes of glucosinolates**, whic are obtained mainly through **cruciferous vegetables**.



Structure of concanavaline A *Canavalia ensiformis*.

In two studies following three large prospective cohorts of 42,170 male and 168,404 female health professionals for several years, a higher intake of glucosinolates was associated with a **slightly higher risk of heart disease and type 2 diabetes in men and women**. Individuals with the highest intakes of glucosinolates had a 19% increased risk of type 2 diabetes compared with those with the lowest intakes, even after adjusting for other factors that can affect diabetes, such as BMI, physical activity, and smoking.

4.Liu Z, Luo Y, Zhou TT, Zhang WZ. Could plant lectins become promising anti-tumour drugs for causing autophagic cell death? Cell Prolif. 2013 Oct;46(5):509-15.
5.Ma L, Liu G, Sampson L, Willett WC, Hu FB, Sun Q. Dietary glucosinolates and risk of type 2 diabetes in 3 prospective cohort studies. Am J Clin Nutr. 2018 Apr 1;107(4):617-625.
6.Ma L, Liu G, Zong G, Sampson L, Hu FB, Willett WC, Rimm EB, Manson JE, Rexrode KM, Sun Q. Intake of glucosinolates and risk of coronary heart disease in three large prospective cohorts of US men and women. Clin Epidemiol. 2018 Jun 28;10:748-762.


What Are
Lectins?

Lectins are proteins that bind to specific carbohydrates.
The Latin word legere, meaning to choose or select, is the basis for the word lectin

The term lectin in general refers to **"all sugar-specific agglutinins of nonimmune origin, irrespective of source and blood type specificity"**

They are found **in most plants, as well as in humans, microorganisms, animals, and fish**. The most concentrated forms appear to be in edible seeds such as those found in cereal grains and legumes.

Lectin levels in plants and food crops can vary significantly depending on environmental conditions such as drought and salinity.

Lectin compounds may have evolved in plants as a survival mechanism, reducing the chance the they will be consumed in large amounts.

Lectins are the most widely studied molecules in glycobiology: they are **capable of reversibly binding monosaccharides, oligosaccharides, and polysaccharides (glycans), including glycans found on cell walls or membranes.**

These interactions can be as **specific as the binding of antibodies to antigens, or enzymes to target substrates**. They are capable of binding multiple molecules/cells, creating a clump or mass.

Due to their biological activity, **some lectins may be detrimental** (occurring as toxins in raw foods) while others may have **anti-cancer effects or act as mediators for targeted drug delivery**

Potential functions of lectins:

- Carbohydrate transport
- Specific cellular recognition
- Embryonic development
- Cohesion
- Binding of carbohydrates

Seeds	Anticoagulant and antiplatelet properties; coagulant, mitogenic, antibacteria, antifungal, and antitumor activities
Bark	Antifungal and insecticidal activities
Heartwood	Termiticidal activity
Stem	Antiviral and apoptosis-inducing activities
Leaves	Antiviral, antibacterial and antifungal activities
Fruits	Mitogenic and antiviral activities
Roots	Antifungal and termicidal activities
Tubers	Insecticidal and antitumor activities
Bulbs	Proteolytc activities
Rhizomes	Antiproliferative, immuno-stimulatory, antiviral, antifungal, antitumor and apoptosis-inducing activities

Sources of Plant Lectins

Lectins are found in the greatest concentration in raw beans and grains (especially wheat), followed by dairy, seafood, and plants in the nightshade family (e.g. tomato, potato, eggplant, bell pepper). Wheat germ agglutinin (WGA) is considered the most common food lectin consumed.

Lectins exist primarily in the raw forms of foods. Heating and cooking appears to degrade most lectins, although **pre-soaking beans** is most effective at eliminating lectin activity. Dry heat or roasting may not be as effective at deactivating lectins.

- Germogli di soia
- Patate
- Melanzane
- Lenticchie
- Peperoni
- Germe di grano
- Fagioli rossi
- Piselli
- Pomodori
- Arachidi

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HIGH-LECTIN FOODS

Grains & Animal Foods

GRAINS & GRAIN PRODUCTS
Barley / Bulgur
Buckwheat / Millet / Quinoa
Kamut / Rye / Spelt / Wheat
Oats
Rice, Brown & White

GRAIN-FED ANIMAL FOODS
Milk / Kefir / Sour Cream
Frozen Yogurt / Ice Cream
Cheese / Cottage Cheese
Fish / Poultry / Meat

Legumes

LEGUMES
Legumes
Beans
Cacao Beans
Chickpeas
Kidney Beans
Lentils
Mung
Peas
Peanuts
Soy

Nut, Seeds & Oils

NUT, SEEDS & OILS
Nuts
Almonds
Cashews / Pine Nuts
Hazelnuts

Seeds
Sunflower
Sesame

Oils
Canola / Corn
Cottonseed / Grapeseed
Peanut
Safflower
Sunflower

Fruits & Vegetables

FRUITS & VEGETABLES

Melons (Any Kind)

Fruits & Nightshades
Corn
Cucumbers
Eggplant
Peppers
Pumpkin
Squash (Any Kind) / Zucchini
Tomatoes

Sweeteners
Agave
Artificial Sweeteners
Sugar
Sucralose

LOW-LECTIN FOODS

Grains & Animal Foods

GRAINS & GRAIN PRODUCTS
Amaranth
Wild Rice

GRASS-FED ANIMAL FOODS
Grass-Fed Dairy
Grass-Fed Meat

WILD-CAUGHT SEAFOOD

POULTRY
Chicken (Pastured)
Egg Yolk (Omega-rich)
Ostrich
Turkey (Kosher)
Water Fowl

Legumes

THERE ARE
NO
LOW-LECTIN
LEGUMES

The hard lectin in legumes is impervious to soaking, sprouting and cooking.

Nut, Seeds & Oils

NUT, SEEDS & OILS
Nuts
Coconut / Chestnut
Macadamia
Pecans / Pistachios / Walnuts

Seeds
Flax
Hemp
Pumpkin
Chia

Oils
Coconut / Olive / Sesame
Avocado
Macadamia Nut
Red Palm
Rice Bran
Walnut

Fruits & Vegetables

FRUITS & VEGETABLES

Limit these Fruits
Apples
Blueberries / Cherries
Citrus
Kiwi
Nectarines / Peaches
Pomegranates
Raspberries / Strawberries

Unlimited Other Fruits
Unlimited Vegetables

Sweeteners
Monk Fruit (Nutresse)
Jerusalem Artichoke Syrup
Stevia / Xylitol / Erythritol
Yacon

Biological processes mediated by endogenous mammalian lectins[15]

- Cell-cell self recognit
- Cell-extracellular ma (ECM) interactions
- Gamete fertilization
- Embryonic developm
- Cell growth, different signaling, adhesion, a migration
- Apoptosis
- Immunomodulation inflammation
- Host-pathogen inter
- Glycoprotein folding routing
- Mitogenic induction
- Homeostasis

Immune-related functions of lectins

- Defense against invading pathogens
- Directly kill microorganism as part of innate immunity
- Aid dendritic cell and macrophage phagocytosis of invading pathogens
- Direct and Indirect involvement in adaptive immunity

Anti-cancer properties of lectins (under investigation)[16]

In vitro, in vivo, and human case studies demonstrate that certain lectins can

- Bind to cancer cells
- Agglutinate cancer cells
- Have cytotoxic effects in cancer cells
- Inhibit tumor growth
- Trigger cell death
- Inhibit angiogenesis

BMJ VOLUME 318 17 APRIL 1999 www.bmj.com

Do dietary lectins cause disease?

The evidence is suggestive—and raises interesting possibilities for treatment

In 1988 a hospital launched a "l
in its staff canteen at lunc
contained red kidney beans, an
served. At 3 pm one of the custome
trar, vomited in theatre. Over the n
more customers suffered profuse vo
diarrhoea. All had recovered b
pathogens were isolated from the f
contained an abnormally high co
lectin phytohaemagglutinin.[1]

in the past two decades we have realised that many lectins are (*a*) toxic, inflammatory, or both; (*b*) resistant to cooking and digestive enzymes; and (*c*) present in much of our food.[2] It is thus no surprise that they sometimes cause "food poisoning." But the really disturbing finding came with the discovery in 1989 that some food lectins get past the gut wall and deposit themselves in distant organs.[3,4] So do they cause real life diseases?

Lectins/Agglutinins with affinity to specific tissues.

Tissue	Wheat Germ Agglutinin	Soybean Agglutinin	Peanut Agglutinin	Lentil Lectin	Pea Lectin	Bean Agglutinins
Skin	*	*	*	*		*
Buccal mucosa	*	*	*	*		
Stomach	*					
Parietal cells		*	*			
Intestinal brush border	*	*				*
Colonic mucosa	*			*		
Connective tissue	*			*	*	*
Thyroid	*	*		*		*
Cartilage	*	*	*			

Tissue	Wheat Germ Agglutinin	Soybean Agglutinin	Peanut Agglutinin	Lentil Lectin	Pea Lectin	Bean Agglutinins
Liver	*	*	*			*
Pancreas	*					*
Kidney	*			*		*
Prostate	*		*	*		
Skeletal muscle	*	*	*		*	
Cardiac muscle	*	*				
Breast	*	*	*			
Pituitary			*			
Eye	*	*	*		*	*
Brain (myelin)	*			*		*

WGA, wheat germ agglutinin; SBA, soybean agglutinin; PNA, peanut agglutinin; LA, lentil agglutinin; MA, mushroom agglutinin; TA, tomato agglutinin; PA, pea agglutinin; POT.A, potato agglutinin; KBA, kidney bean agglutinin; JBA, jack bean agglutinin. Adapted from: Lambert J, Vojdani A (2017) Correlation of Tissue Antibodies and Food Immune Reactivity in Randomly Selected Patient Specimens. J Clin Cell Immunol 8: 521. doi: 10.4172/2155-9899.1000521.

The Journal of Immunology

Plant Lectins Activate the NLRP3 Inflammasome To Promote Inflammatory Disorders

Plant-derived dietary lectins have been reported to be involved in the pathogenesis of several inflammatory diseases, including inflammatory bowel disease, diabetes, rheumatoid arthritis, and celiac disease, but little is known about the molecular mechanisms underlying lectin-induced inflammation. In this study, we showed that plant lectins can induce caspase-1 activation and IL-1β secretion via the NLRP3 inflammasome. Lectins were internalized and subsequently escaped from the lysosome and then translocated to the endoplasmic reticulum. Endoplasmic reticulum–loaded plant lectins then triggered Ca^{2+} release and mitochondrial damage, and inhibition of Ca^{2+} release and mitochondrial reactive oxygen species by chemical inhibitors significantly suppressed NLRP3 inflammasome activation. In vivo, plant lectin–induced inflammation and tissue damage also depended on the NLRP3 inflammasome. Our findings indicate that plant lectins can act as an exogenous "danger signal" that can activate the NLRP3 inflammasome and suggest that dietary lectins might promote inflammatory diseases via the NLRP3 inflammasome. *The Journal of Immunology*, 2017, 198: 2082–2092.

Adverse reactions to lectins

Pro-inflammatory activity

Lectins stimulate the synthesis of pro-inflammatory cytokines including **IL-1, IL-6 and IL8** in intestinal and immunity cells; induce **NADPH-Oxidase** in neutrophils associated with "respiratory burst" which causes ROS release

Cytotoxicity and excitotoxicity

They are cytotoxic for both normal and cancerous cell lines, are able to induce cell cycle arrest or programmed cell death.

Cardiotoxicity

They enhance the action of **PECAM-1** (platelet endothelial cell adhesion molecule-1) which plays a key role in tissue regeneration

Alteration of endocrine homeostasis

Some lectins have an **insulin-mimetic action**, potentially contributing to **weight gain and insulin resistance;**

are implicated in obesity and leptin resistance by blocking the **hypothalamic receptor** that regulates the sense of satiety.

They stimulate the **Epidermal Growth Factor** which, upregulated, increases the risk of cancer;

interfere with secretion of secretin by the pancreas.

Alteration of the intestinal microbiome

Growth of bacteria, such as Streptoccocus, E. Coli and L. Lactis, increase.

Induction of self-immunity

They amplify the expression of HLA in intestinal cells.

They stimulate the proliferation of T-cells.

They induce thymic atrophy in rats and in humans it has been shown that WGAs induce the development of anti-WGA antibodies that cross-react with other endogenous proteins, contributing to the activation of self-immunity

15 September 1972, Volume 177, Number 4053 SCIENCE

Lectins: Cell-Agglutinating and Sugar-Specific Proteins

Lectins provide new tools for studying polysaccharides, glycoproteins, and cell surfaces, and for cancer research.

Nathan Sharon and Halina Lis

(Altern Ther Health Med. 2015;21(suppl 1):46-51.)

Adverse reactions to lectins

Neurotoxicity

WGA is an excitotoxin and a neurotoxin that crosses the blood-brain barrier through a process called "adsorptive endocytosis"; it has an **affinity for N-acetylneuraminic acid, a component of neuronal membranes in the brain** and for gangliosides that have different roles and whose dysfunction has been implicated in neurodegenerative disorders.

The WGA can attach itself to the myelin sheath and is able to inhibit the nerve growth factor, the maintenance and survival of certain neurons, it binds to N-acetylglucosamine, which is thought to function as an atypical neurotransmitter in nociceptive pathways.

Wheat and soy also contain very high levels of glutamic ac. and Aspartic ac. which makes them all potentially excitotoxic causing excessive activation of CNS cell receptors and secondary damage to the increased membrane permeability for calcium.

These two amino acids can contribute to neurodegenerative conditions such as **multiple sclerosis, Alzheimer's disease, Huntington's disease and other nervous system disorders such as epilepsy, ADHD / ADHD and migraines.**

Increased blood viscosity

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Altern Ther Health Med. 2015;21 Suppl 1:46-51.

Lectins, agglutinins, and their roles in autoimmune reactivities.

Vojdani A.

Abstract

Lectins are carbohydrate-binding proteins present throughout nature that act as agglutinins. Appro some of which may be resistant enough to digestion to enter the circulation. Because of their bindi deficiencies, disrupt digestion, and cause severe intestinal damage when consumed in excess by

(Altern Ther Health Med. 2015;21(suppl 1):46-51.)

Adverse Gut Reactions to Lectins

Researchers propose that lectins interfere with repair mechanisms at the level of the gut epithelial cells, leading to observed gastrointestinal symptoms.

Potential gut-specific adverse effects of lectins if eat in in large quantities

- Affect turnover and loss of epithelial cells
- Damage luminal membranes of the epithelium
- Interfere with digestive/absorptive activities
- Acute nausea, vomiting, diarrhea
- Stimulate shifts in bacterial flora
- Modulate the immune state of the digestive tract
- Interfere with gut hormone secretion
- Serve as potent growth factors for the small intestine (e.g. hyperplasia, hypertrophy)
- Some effects may be beneficial though human research is scarce

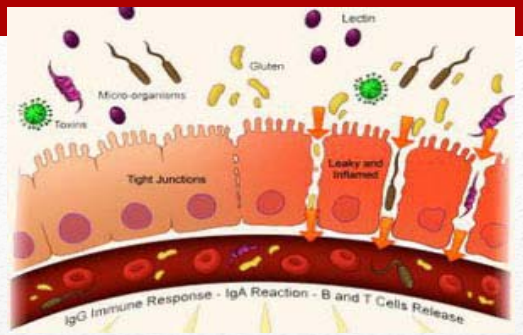
Some suspect that reported adverse reactions to foods in the nightshade family (e.g. tomatoes, potatoes, eggplant, bell pepper) may be due to the presence of lectins. **Some research has extrapolated lectins' affinity for specific carbohydrates to corresponding tissue, suggesting the potential for related adverse reactions.**

According to a toxicology review in the early 2000s, lectins in their active, binding state have the potential to[75]

- Bind to membrane glycosyl groups of cells lining the digestive tract
- Affect turnover and loss of gut epithelial cells
- Damage the luminal membranes of the epithelium
- Interfere with nutrient digestion and absorption
- Stimulate shifts in GI bacterial flora
- Modulate the immune state of the digestive tract
- Systematically disrupt lipid, carbohydrate, and protein metabolism
- Promote enlargement and/or atrophy of key internal organs and tissues
- Alter hormonal and immunological status
- May threaten growth and health of animals consuming them in large amounts
- Are detrimental to numerous insect pests of crop plants

Remember these detrimental effects refer to active lectins that are not broken down or degraded.

Intestinal Damage
Leaky Gut Syndrome



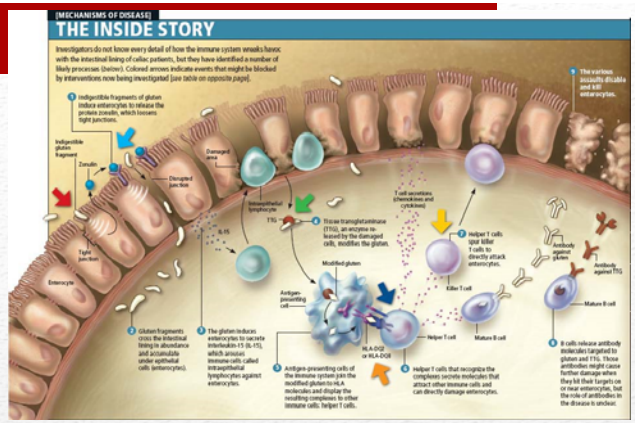
The Leaky Gut Syndrome or Permeable Intestinal Syndrome is a condition that is determined **when the lectins, by binding to the carbohydrates present on the cells of the GI epithelium, cause their death and the loss of intestinal villi and microvilli, reducing the area of absorption of the nutrients.**

Furthermore, lectins **can mimic the effects of epidermal growth factor (EGF) at the cellular level,** suggesting that hyperplasia of the crypt in celiac disease may be due to the growth effects of some lectins.

These proteins cause **cytoskeletal degradation in intestinal cells,** contributing to cell death and increased turnover, **reducing heat shock protein levels** in intestinal epithelial cells, leaving these cells more exposed to the potentially harmful content of the intestinal lumen.

The damage and inflammation caused by lectins determine the dysbiosis of the intestinal flora and the breakage of the tight junctions.

Intestinal Damage
Leaky Gut Syndrome



The gaps **allow the passage to potentially toxic substances** such as undigested food, bacteria and metabolic waste, which should be limited to the digestive tract, to enter the bloodstream inducing inflammation and activation of the self and non-self immune response

Often, the Leaky Gut Syndome is associated with inflammatory bowel diseases such as Crohn's disease and ulcerative colitis or celiac disease, but **even healthy people can have varying degrees of intestinal permeability** leading to a wide variety of symptoms including nausea, vomiting and diarrhea.
The major problem of lectins manifests itself in people with a predisposition to autoimmune diseases or illness already in place.

Lectins are three to four times more likely to pass into the bloodstream through intestinal permeability than other dietary proteins, as they have small dimensions: about 36 kilodalton (the intestine allows the passage of molecules up to the size of 1000 kilodalton)

This demonstrates that maintaining the integrity of the intestinal lining is essential for keeping undigested and partially digested proteins, lectins and environmental toxins out of the bloodstream and thus preventing the activation of self-immunity.

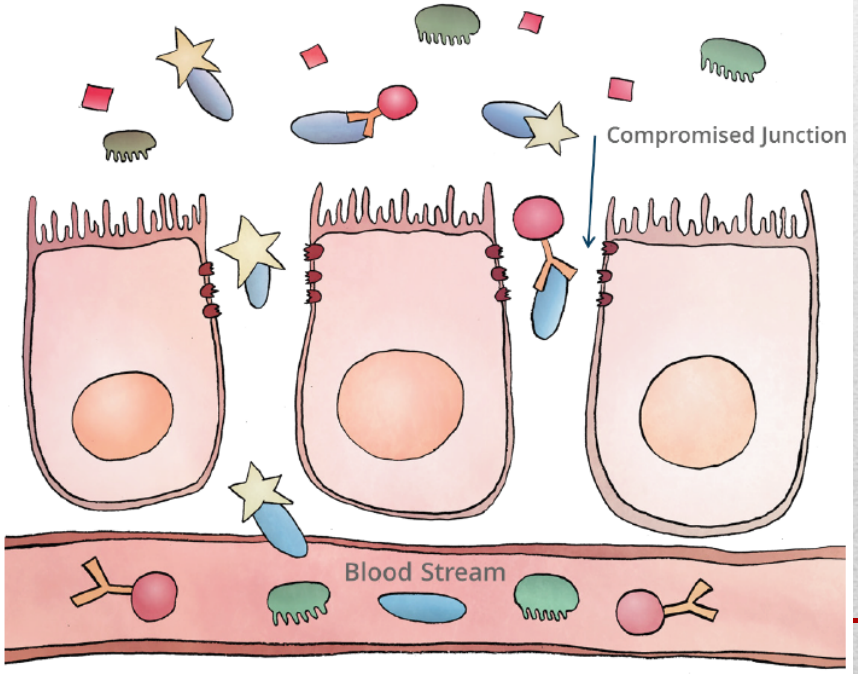
Wheat lectin o WGA

Wheat lectin, or "wheat germ agglutinin" (WGA), is among the most studied lectins and is largely responsible for many of the adverse effects on the body.

The WGA is higher in whole wheat, especially the sprouted one.

Increased Intestinal Permeability

Research demonstrates that WGA can increase intestinal permeability.[92] Researchers theorize that an increase in intestinal permeability will increase passage of potentially harmful compounds such as bacterial toxins or lectins themselves may trigger systemic inflammation and other adverse effects.



92 Dalla Pellegrina C, Perbellini O, Scupoli MT, et al. Effects of wheat germ agglutinin on human gastrointestinal epithelium: insights from an experimental model of immune/epithelial cell interaction. Toxicol Appl Pharmacol. 2009 Jun 1;237(2):146-53. doi: 10.1016/j.taap.2009.03.012. Epub 2009 Mar 28. PubMed PMID: 19332085.

Autoimmunity

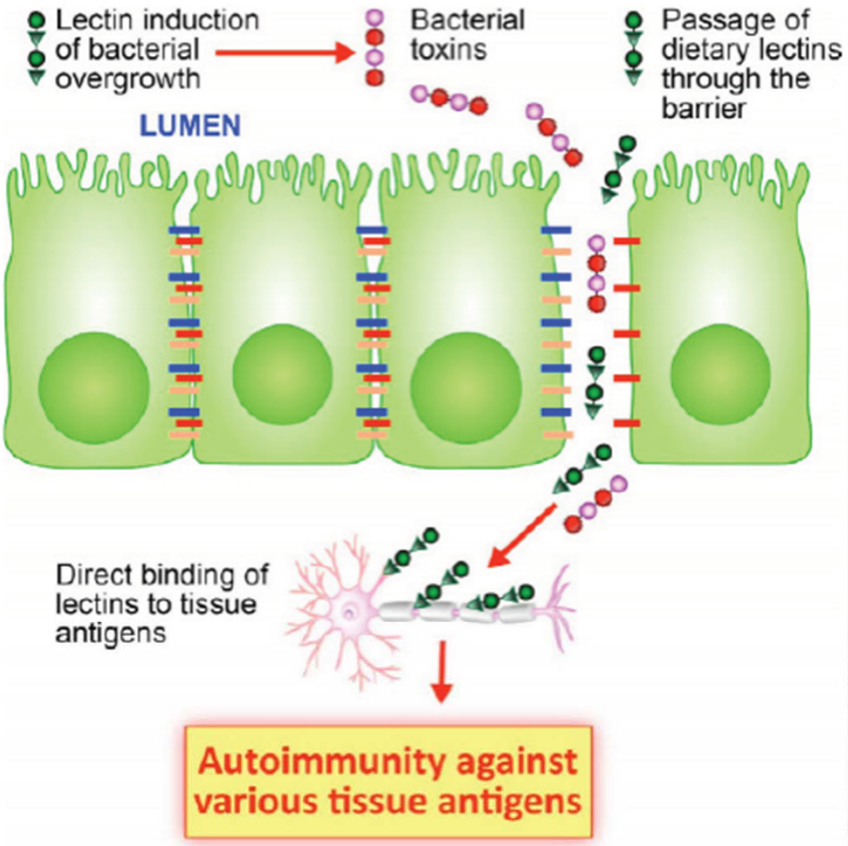


Fig. 26-3. Source: Lambert, J, & Vojdani, A. (2017). Correlation of tissue Antibodies and Food Immune Reactivity in Random Selected Patient Specimens. Journal of Clinical & Cellular Immunology, 8(5). doi:10.4172/2155-9899.1000521. http://pdfs.semanticscholar.org/49a3/897ed9b091a34156b14c8b108cd9af31a4e.pdf Creative Commons License

The proposed link between lectins and autoimmune reactions may lie in **stimulation of class II HLA antigens in tissues such as thyroid and pancreatic** islet cells.

Research suggests that **cytotoxic antibodies associated with insulin-dependent diabetes bind a disaccharide (N-acetyl lactosamine) that also binds tomato, potato, wheat, and peanut lectins**, possibly contributing to autoimmune attack of the islet cells.

A link to **rheumatoid arthritis** may be related to an abnormal IgG molecule that exposes **N-acetylglucosamine** to which certain lectins can bind (e.g. wheat lectin). Indeed, wheat ingestion appears to be a trigger for some with rheumatoid arthritis. Provision of exogenous N-acetylglucosamine may help to block lectin interaction and reduce symptoms.

How can remove lectins from the foods

- **Cooking at high temperatures**
- **Soaking**
- **Sprouting**
- **Fermentation**
- **Remove the peel from fruits and legumes**
- **Remove the seeds**

Raw red beans contain from 20000 to 70000 hau (hemoagglutinant units), cooked contain 200-400 hau

Soaking or sprouting seeds and grains helps eliminate lectins and other anti-nutrients such as phytic acid

Fermenting food can also work, providing good bacteria to digest anti-nutrients

Perspectives

Curr Med Chem. 2017 Nov 17;24(34):3667-3680. doi: 10.2174/0929867324666170523110400.

Lectin-Carbohydrate Interactions: Implications for the Development of New Anticancer Agents.

de Oliveira Figueiroa E[1], Albuquerque da Cunha CR[1], Albuquerque PBS[1], de Paula RA[1], Aranda-Souza MA[1], Alves MS[2], Zagmignan A[2], Carneiro-da-Cunha MG[1], Nascimento da Silva LC[1], Dos Santos Correia MT[1].

⊕ Author information

Abstract

Lectins are a large group of proteins found in animals, plants, fungi, and bacteria that recognize specific carbohydrate targets and play an important role in cell recognition and communication, host-pathogen interactions, embryogenesis, and tissue development. Recently, lectins have emerged as important biomedical tools that have been used in the development of immunomodulatory, antipathogenic, and anticancer agents. Several lectins have been shown to have the ability to discriminate between normal cells and tumor cells as a result of their different glycosylation patterns. Furthermore, the specific binding of lectins to cancer cells has been shown to trigger mechanisms that can promote the death of these abnormal cells. Here, we review the importance of lectins-carbohydrates interactions in cancer therapy and diagnosis. We examine the use of lectins in the modification of nanoparticles (liposomes, solid lipid nanoparticles and other polymers) for anticancer drug delivery. The development of drug delivery systems (liposomes, alginate/chitosan microcapsules, alginate beads) carrying some antitumor lectins is also discussed. In these cases, the processes of cell death induced by these antitumor lectins were also showed (if available). In both cases (lectin-conjugated polymers or encapsulated lectins), these new pharmaceutical preparations showed improved intracellular delivery, bioavailability and targetability leading to enhanced therapeutic index and significantly less side effects.

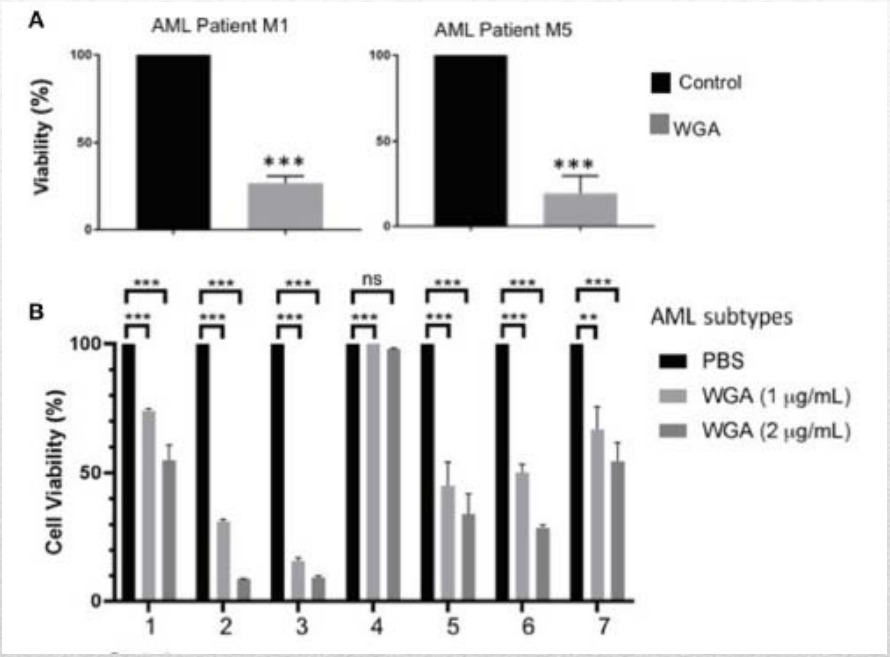
KEYWORDS: Lectins; cancer diagnosis and therapy; cell death; glycosylation; liposomes.; tumor cells

PMID: 28545372 DOI: 10.2174/0929867324666170523110400

[Indexed for MEDLINE]

- Recent studies state that changes in cell surface carbohydrates affect the metastatic behavior of cancer cells.
- Superficial cell carbohydrates influence the interactions of tumor cells with normal cells or with the extracellular matrix during metastatic diffusion and growth. **These interactions can be mediated by the carbohydrates of tumor cells and their binding proteins known as endogenous lectins.**
- Some lectins recognize the "foreing" patterns of carbohydrates on the surface of cells expressed by microorganisms and tumor cells and play a role in innate and adaptive immunity. Lectins have been shown to affect tumor cell survival, adhesion to the endothelium or extracellular matrix, as well as tumor vasculature and other processes that are crucial for metastatic diffusion and growth.
- **Several lectins possess anticancer properties; they are used as therapeutic agents, preferentially binding to tumor cell membranes or their receptors, causing cytotoxicity, apoptosis and inhibition of tumor growth**

Wheat Germ Agglutinin as a Potential Therapeutic Agent for Leukemia



Wheat germ agglutinin (WGA), even at low doses, demonstrated maximum toxicity toward acute myeloid leukemia (AML) cells. Using AML cell lines, we show time- and dose-dependent killing by WGA. We also show that low doses of WGA kills primary patient AML cells, irrespective of subtype, with no significant toxicity to normal cells.

WGA caused AML cell agglutination, but failed to agglutinate RBC's at this dose. WGA, primarily, binds to N-acetyl-D-glucosamine (GlcNAc) and is also reported to interact with sialic-acid-containing glycoconjugates and oligosaccharides.. These data indicate that WGA-induced AML cell death is dependent on both GlcNAc binding and interaction with sialic acids. We did not observe any in vitro or in vivo toxicity of WGA toward normal cells at the concentrations tested. Finally, low doses of WGA injection demonstrated significant in vivo toxicity toward AML cells, using xenograft mouse model. Thus, WGA is a potential candidate for leukemia therapy.

Oligosaccaridi Del Latte Umano

HMOs = Human Milk Oligosaccharides

Human Milk Oligosaccharides

- Sugars
- In high concentrations
- Only in human milk.

Composition

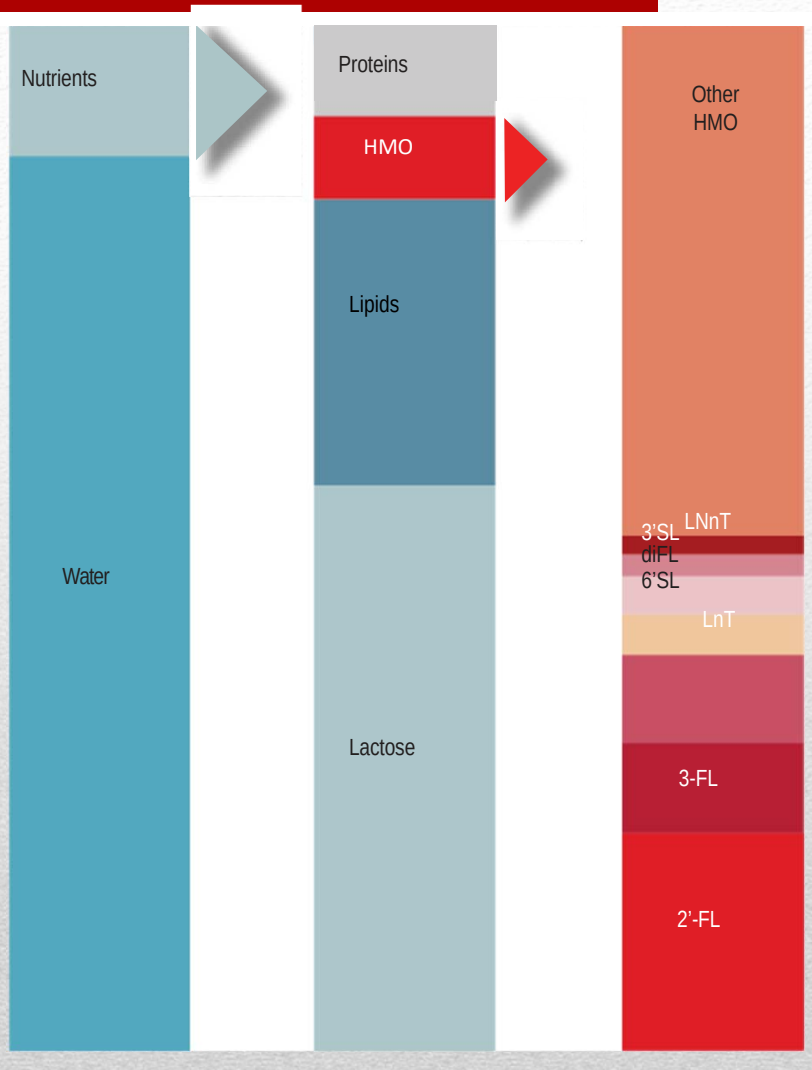
- Specific to each mother
- Varies during the breast feeding period

The dominating oligosaccharide by 80% of the mothers is **2'-fucosyllactose**.

2'-fucosyllactose = fucose + lactose (= glucose + galactose).

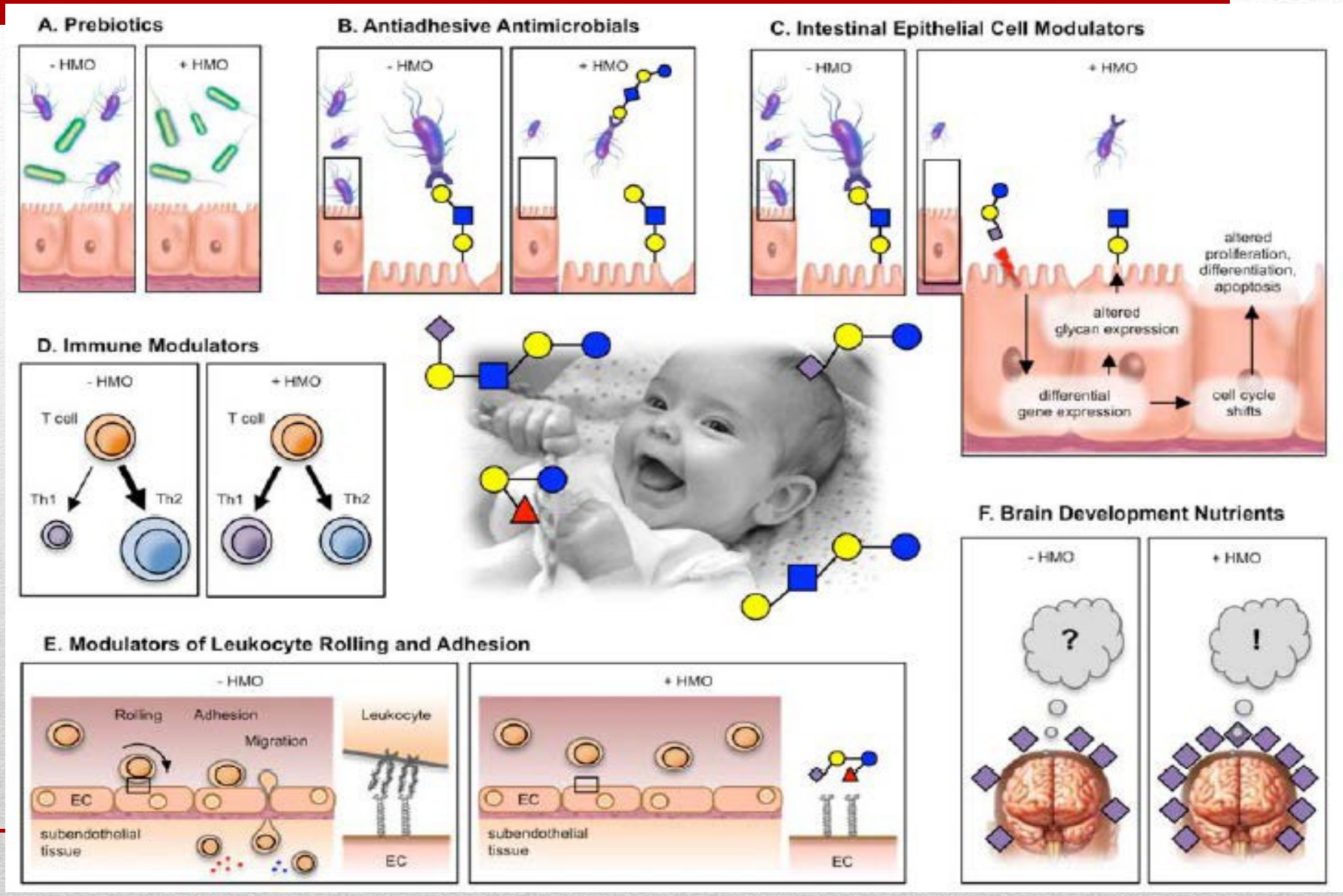
HMOs

- ✓Unique groups of oligosaccharides in human milk.
- ✓Third most important component
- ✓> 200 different oligosaccharides in human milk, **2'-FUCOSYLLACTOSE (2'-FL)** is the most common one - 2,4 g / l.
- ✓ Variation in function of the woman, region and breast feeding phase.



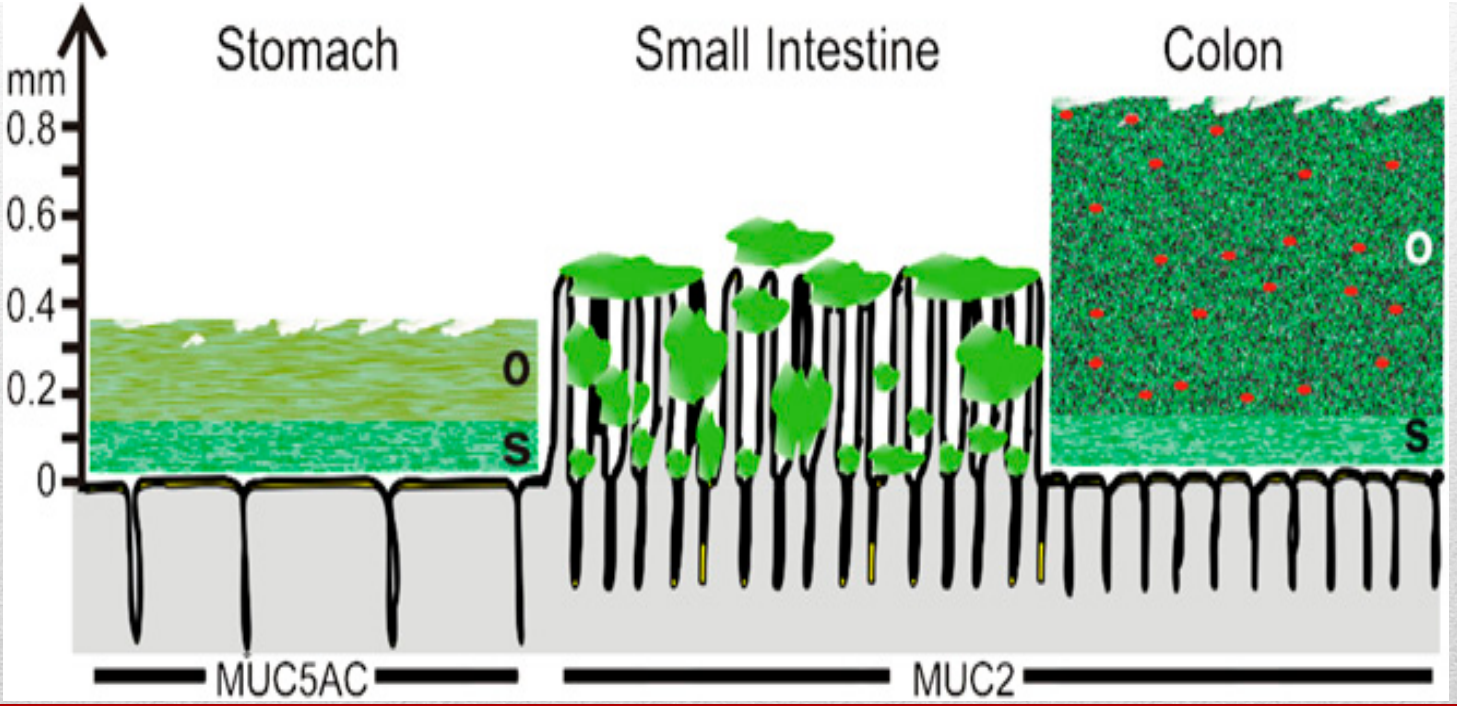
Glycobiology
vol. 22 no. 9 pp. 1147–1162, 2012
doi:10.1093/glycob/cws074 Advance Access publication on April 18, 2012

Human milk oligosaccharides: Every baby needs a sugar mama

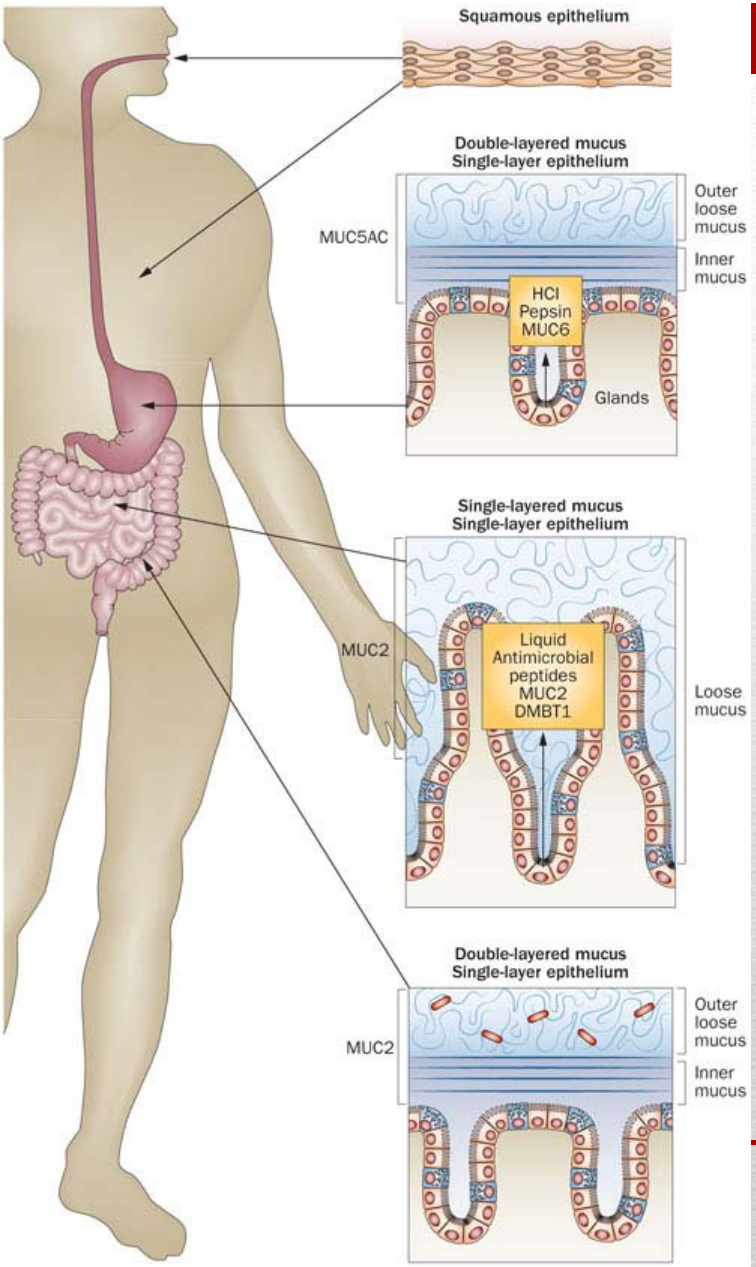


Johansson MEV Et al., PNAS 2010

LO STRATO DI MUCO HA UN RUOLO IMPORTANTE NEL MANTENIMENTO DELLA FUNZIONE DI BARRIERA INTESTINALE



Mucus thickness is maintained by a balance between synthesis, secretion, and degradation, modulated by the microbial glycosidases and proteases and the mechanical shear forces of peristalsis



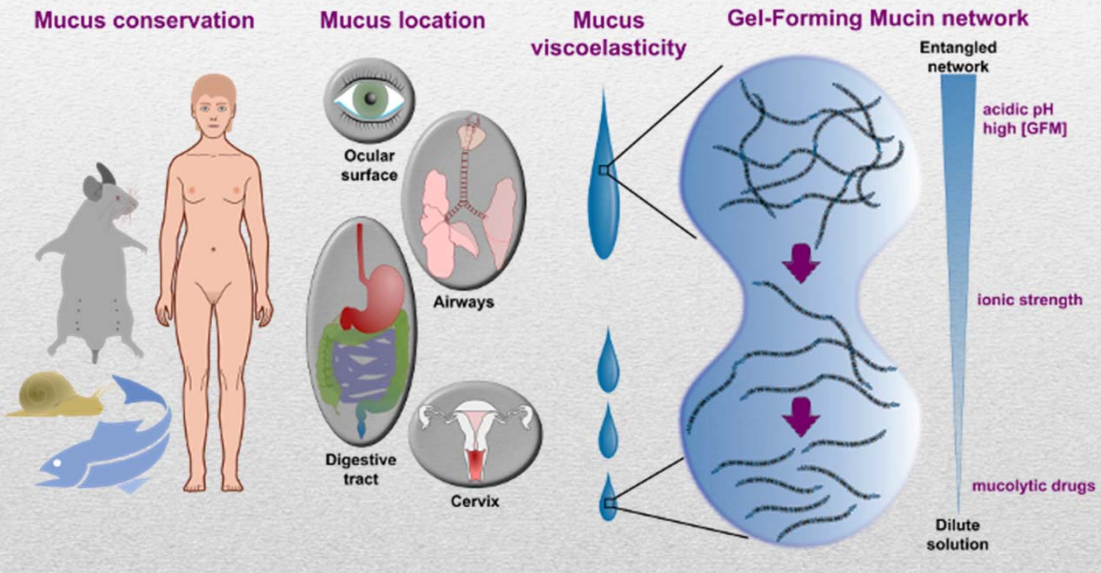
MUCUS & DIGESTIVE SYSTEM

The mucus **becomes thicker and evolves from the small intestine to the large intestine**.

Stomach and **large intestine** consist of **two layers**, an inner solid mucus and an outer loose mucus.

However, **the small intestine** consists of only loose mucus

MUCUS & MUCINS



The **gel-forming mucins** : well conserved during the evolution

- Secreted at the surface,
- Forming a gel in contact with water
- Giving the gel specific physical and chemical properties.

Mucins form **an entire network**

How tighter the network, how thicker and more sticky the mucus becomes.

STRUTTURA DELLE MUCINE

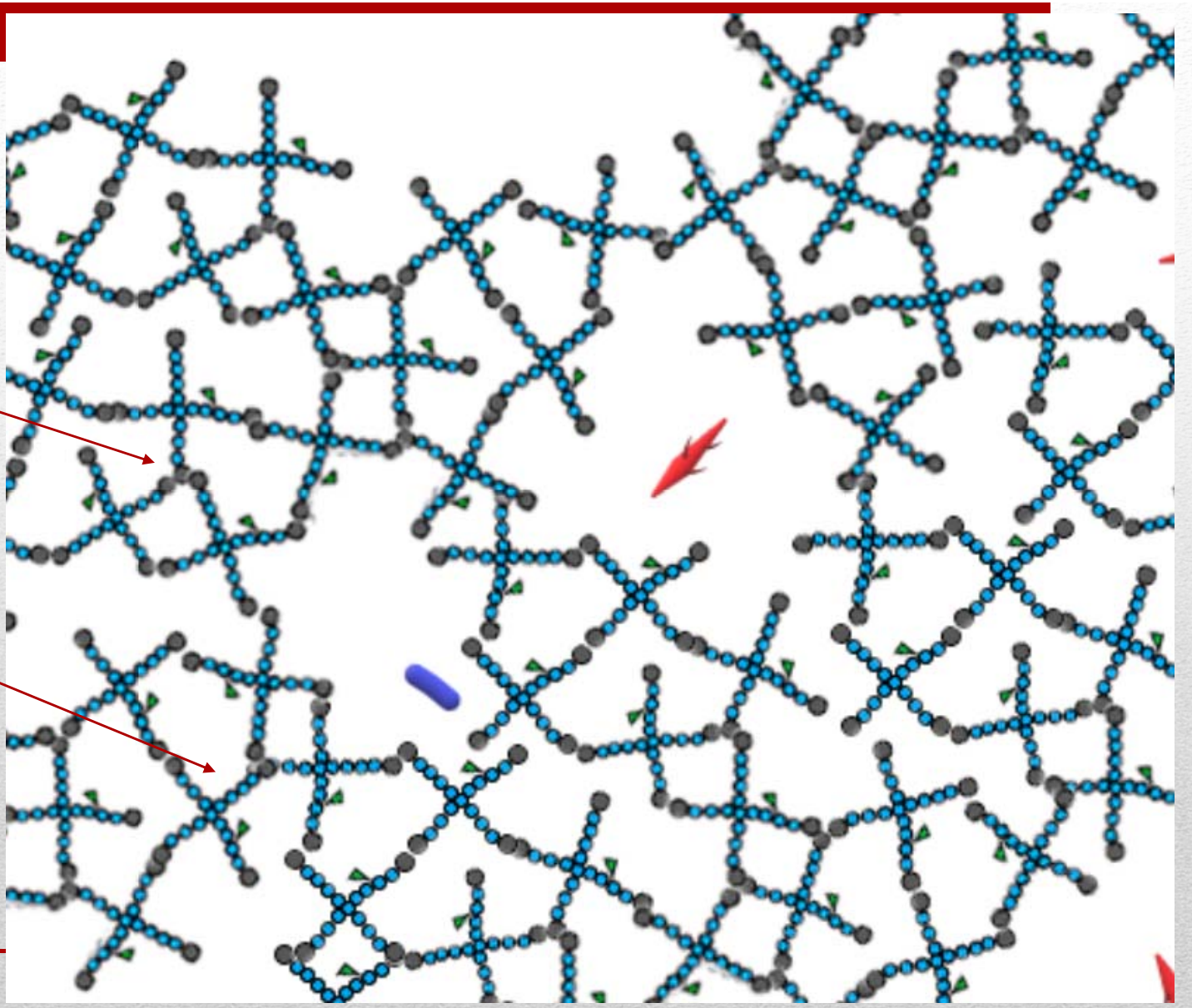
Domini ricchi di cisteina che creano ponti disolfuro e la struttura tridimensionale delle mucine

Domini ricchi di serina e treonina che servono da siti per la glicosilazione

Residi di Fucosio

Bifidobatterio

Patogeno



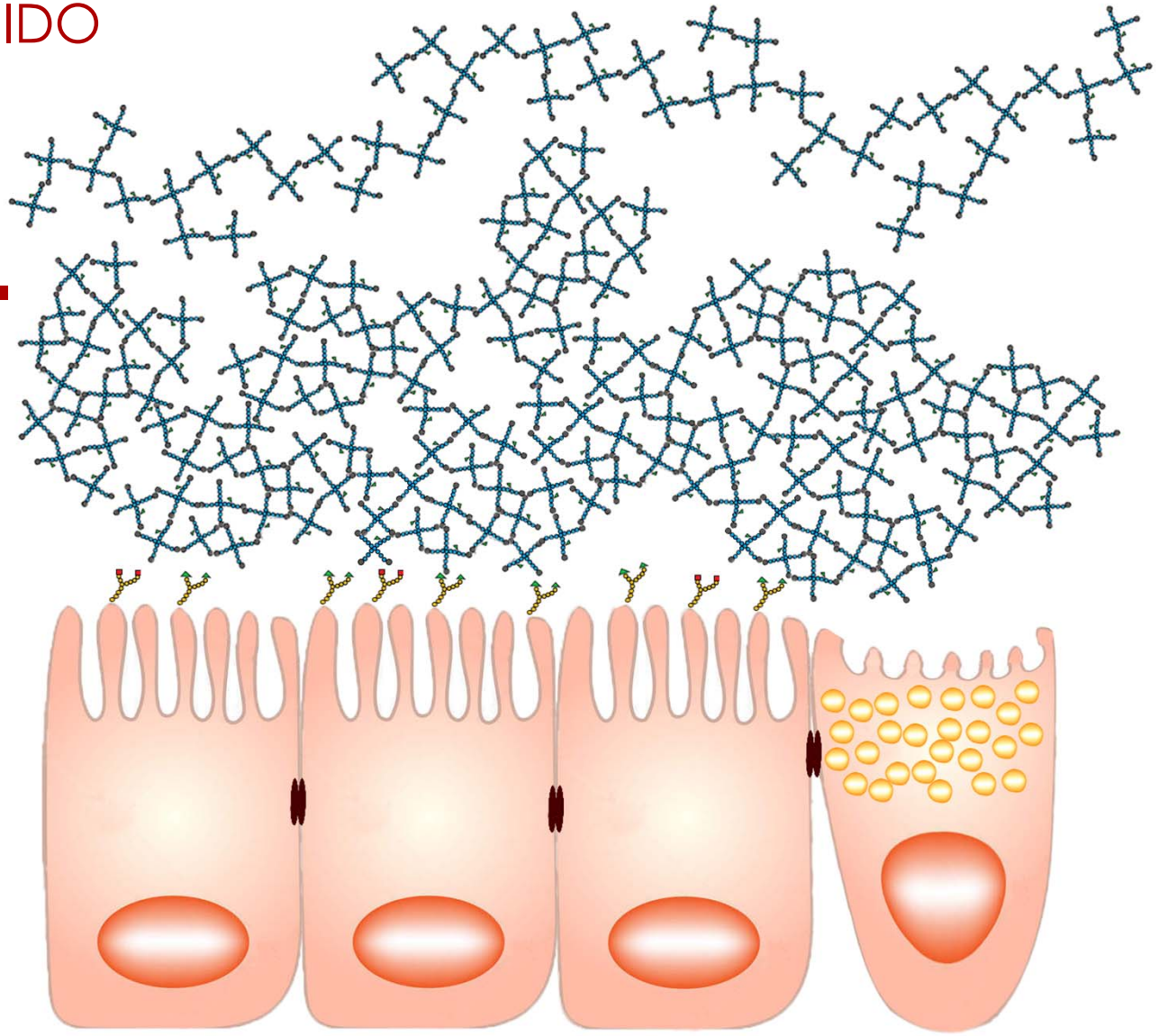
UN SECONDO STRATO PIÙ FLUIDO SUL LATO LUMINALE

Strato di muco fluido sul lato luminale

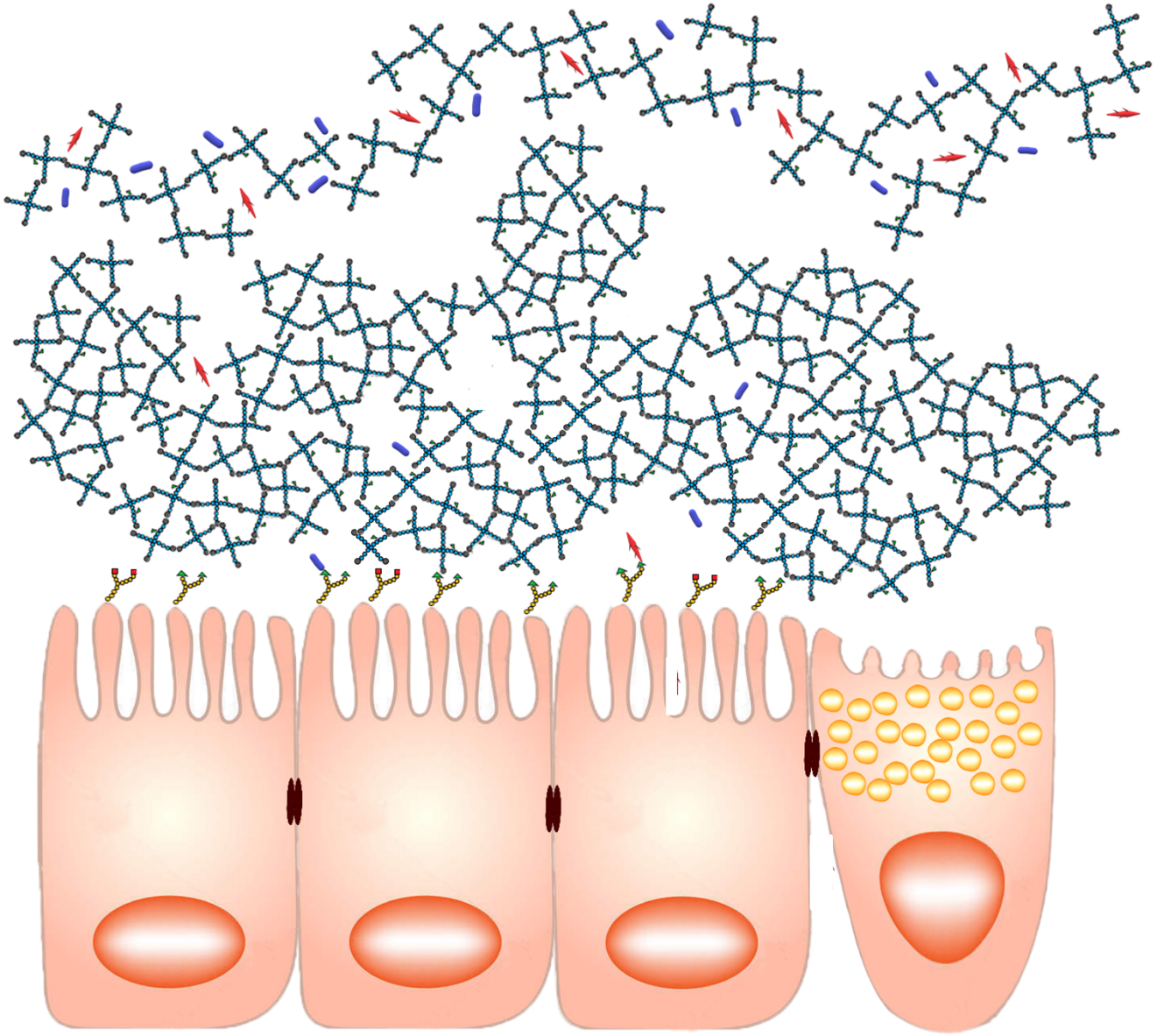
Strato di muco compatto sul lato endoteliale

Enterociti

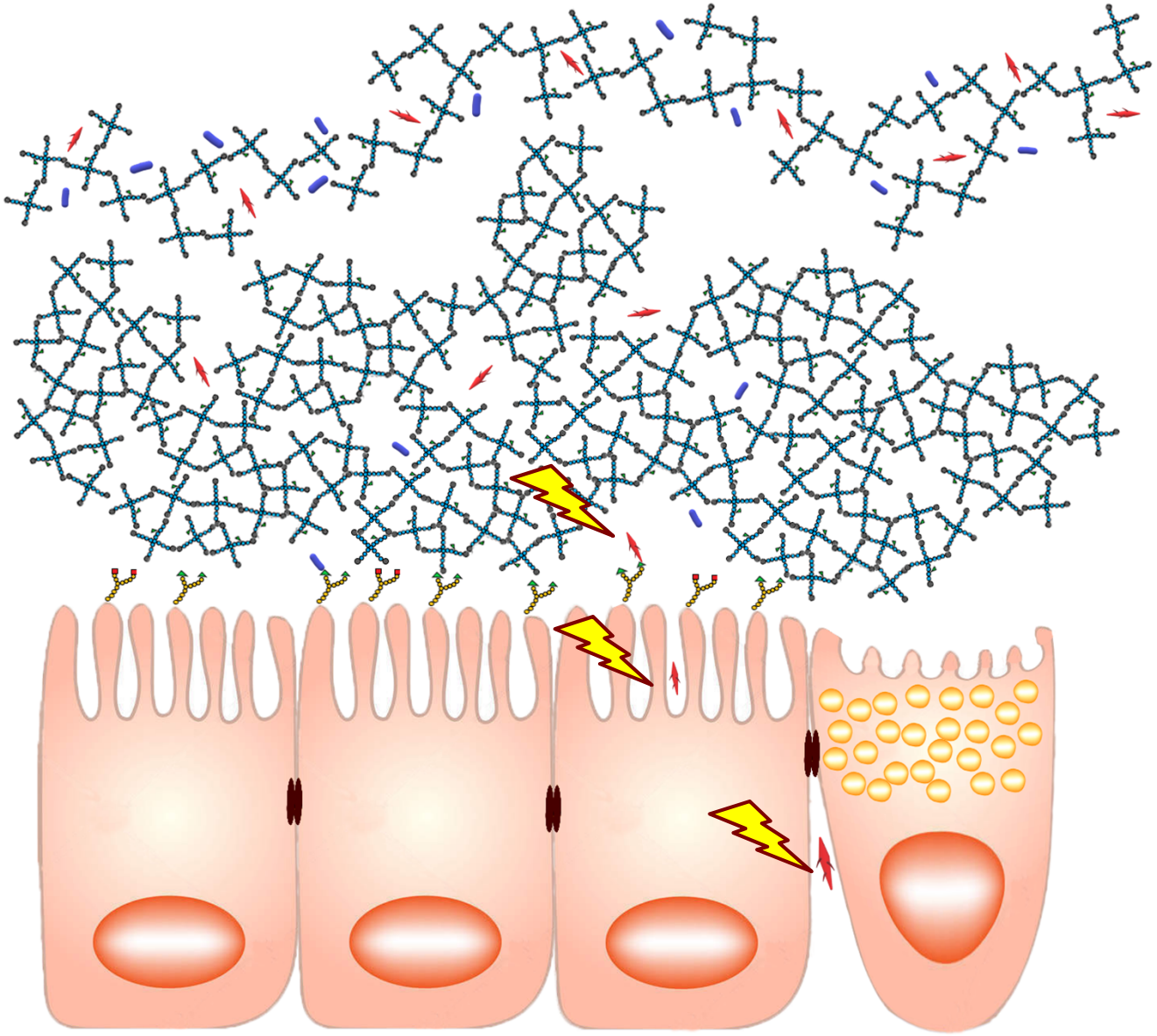
Zona sotto endoteliale



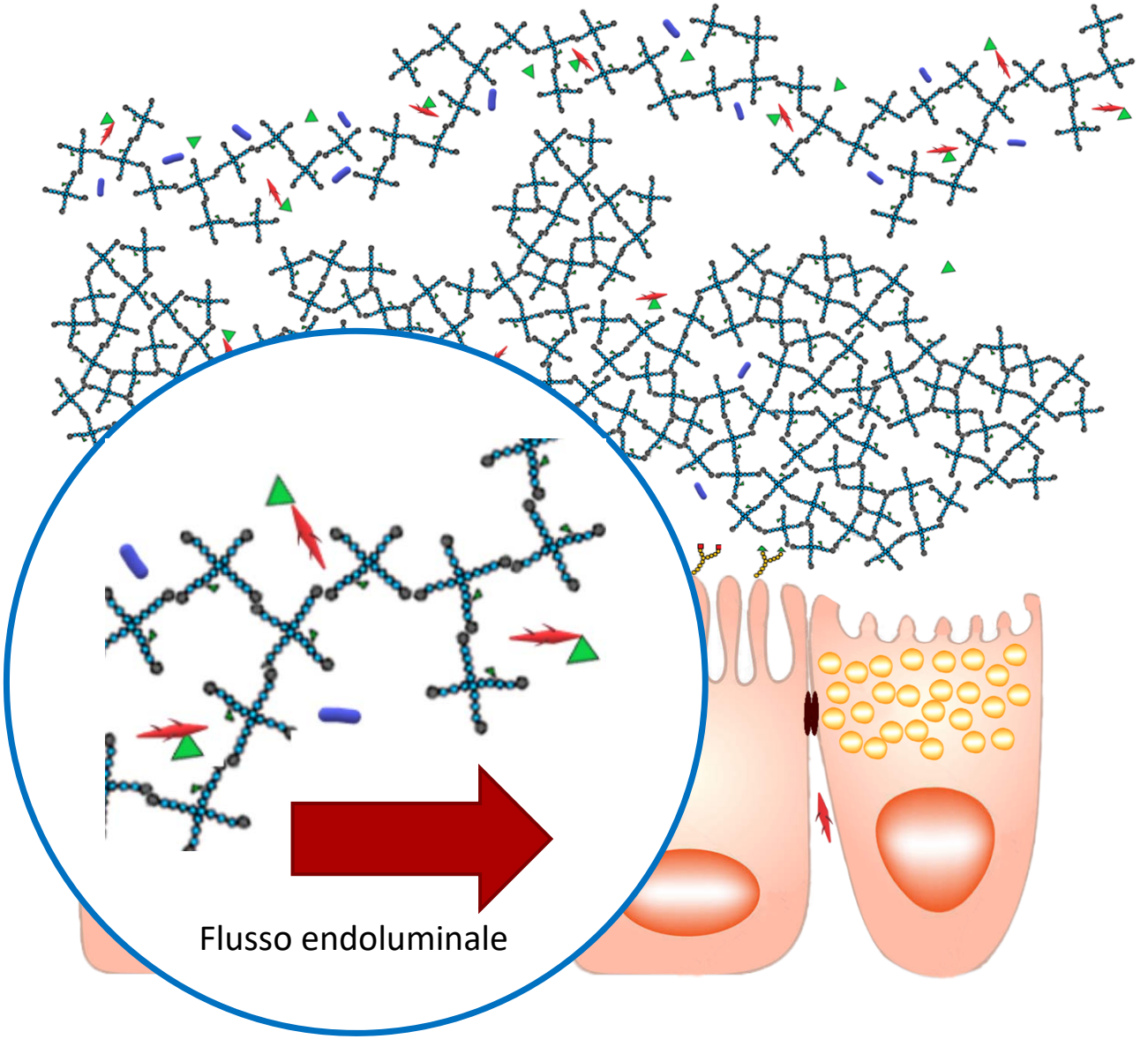
IN STATO DI EUBIOSI
IL MICROBIOTA COLONIZZA LO STRATO
DI MUCO FLUIDO
E RARAMENTE RAGGIUNGE GLI STATI PROFONDI
E GLI ENTEROCITI



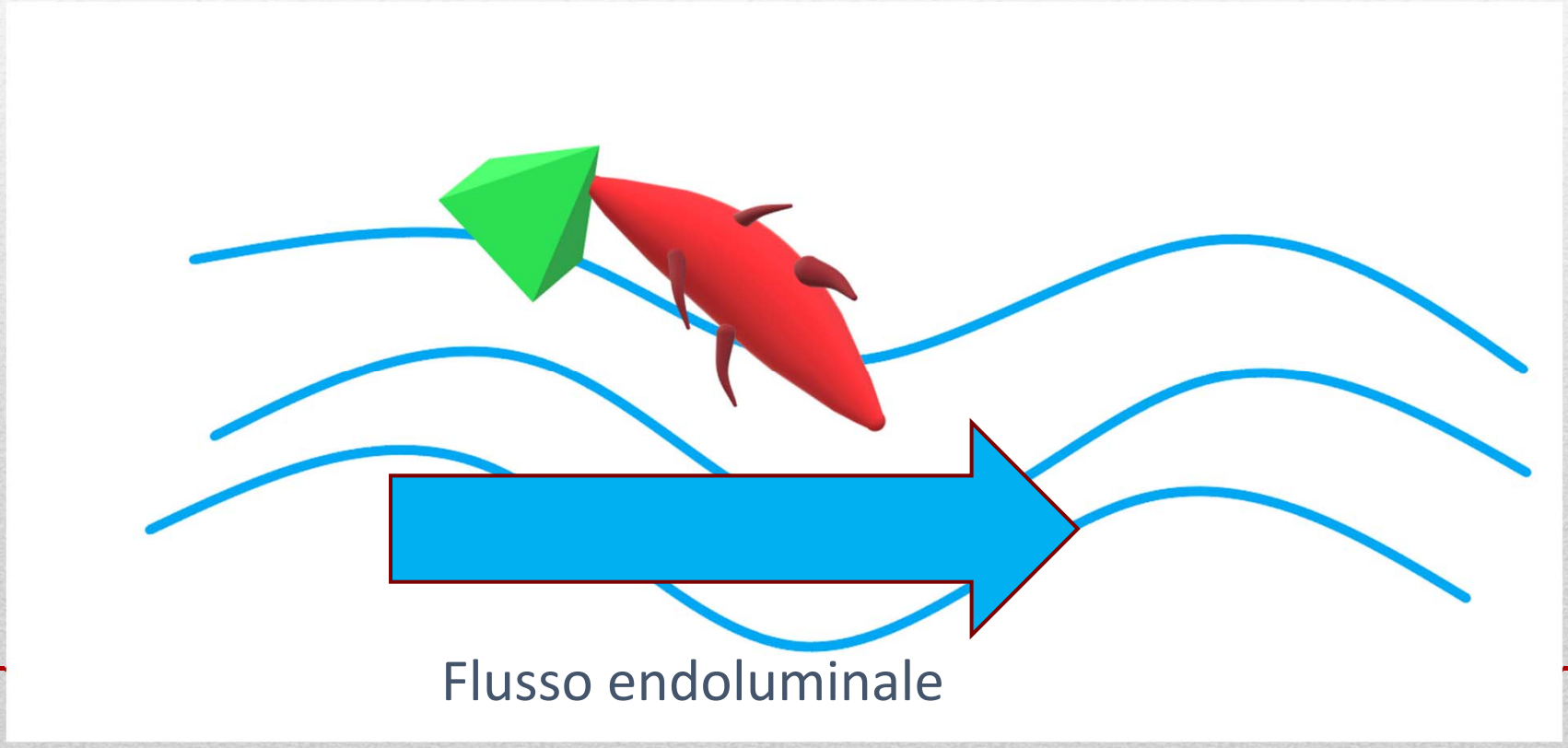
IN STATO DI DISBIOSI IL MICROBIOTA COLONIZZA LO STRATO DI MUCO SPESSO, RAGGIUNGE GLI ENTEROCITI, LA ZONA SOTTOENDOTELIALE RICHIAMANDO I MACROFAGI E ATTIVANDO LA RISPOSTA IMMUNITARIA



L'integrazione con HMO fornisce siti di adesione liberi che funzionano come "esche per i patogeni"



I patogeni legati al fucosio libero vengono trascinati dalla corrente endoluminale nel cosidetto “effetto Wash-out”



MUCO INTESTINALE

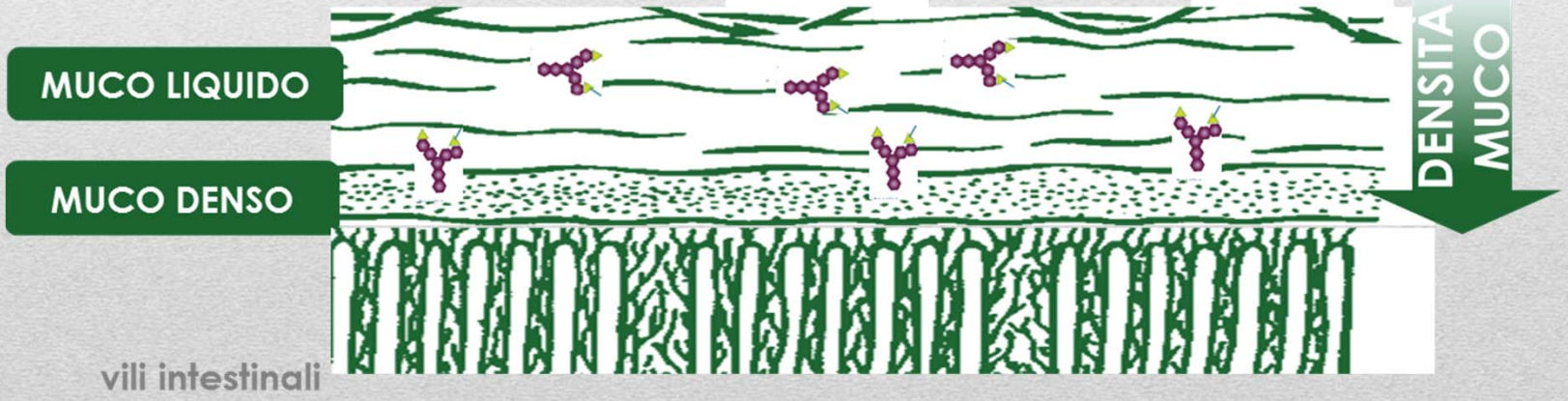
Copre e protegge la mucosa intestinale

Elemento fondamentale per l'aumento della DENSITÀ del MUCO

L-TREONINA amminoacido essenziale

FUCOSIO

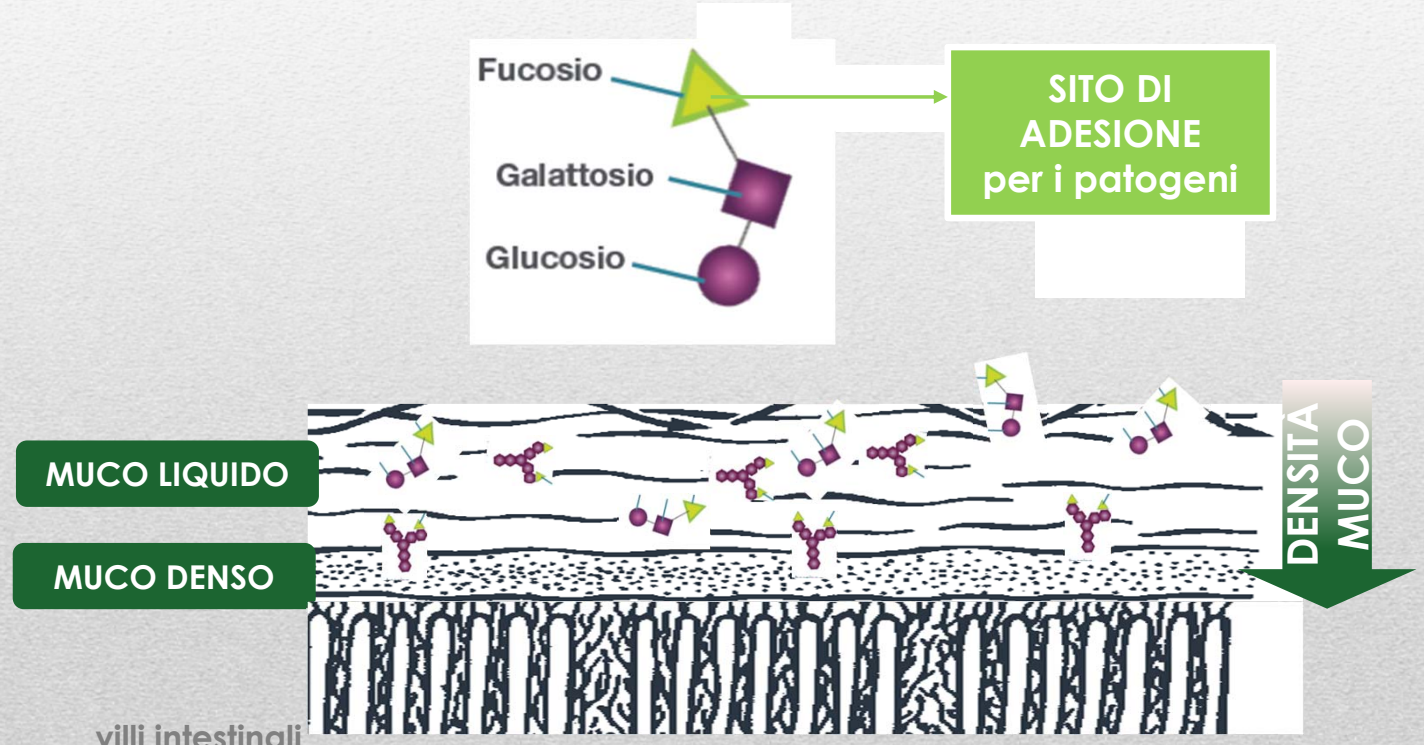
SITO DI ADESIONE per i patogeni



MUCO INTESTINALE

Copre e protegge la mucosa intestinale

HMO MIMA L'AZIONE DELLE MUCINE INTESTINALI POTENZIANDO L'EFFETTO WASH-OUT



ANTIMICROBIAL / ANTI-ADHESIVE EFFECTS OF HMOS

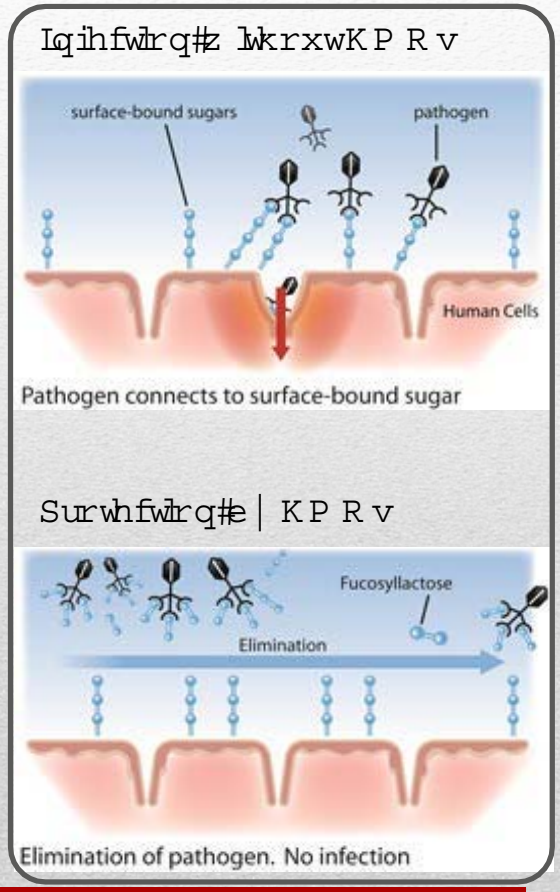
Efficient protective system against pathogens - virus, bacteria and toxins :

- HMOs are similar to glycans (mostly used by pathogens for cell adherence and cell infection)

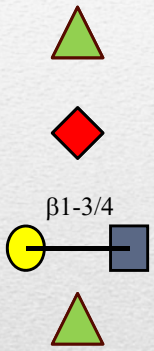
Decoy for pathogens

- Will use them as receptors (will not attach to the human cells)
- HMOs attached to pathogens → elimination

Scientifically well described and proven



ANTIMICROBIAL / ANTI-ADHESIVE EFFECTS OF HMOs



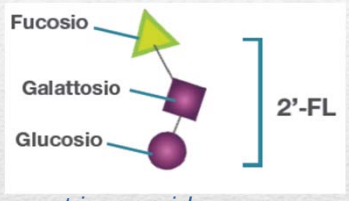
Receptors	Microorganisms
Mannose-containing glycoproteins	*Escherichia coli* (type 1 fimbriae)
Fucosylated oligosaccharides	*E. coli* (heat-stable enterotoxin)
Fucosylated tetra- and pentasaccharides	*E. coli*
Sialyl(α2-3)lactose and glycoproteins	*E. coli* (S-fimbriae)
Sialyl(α2-3)galactosides in mucins	*E. coli* (S-fimbriae)
Neutral oligosaccharides (LNT, neo-LNT)	*Streptococcus pneumoniae*
Gal(ß1-4)GlcNAc or Gal(ß1-3)GlcNAc	*Pseudomonas aeruginosa*
Fucα1-2Gal epitopes	*Candida albicans*
Sialyl-lactose	*Helicobacter pylori*
Sialyl-lactose	*Streptococcus sanguis*
Sialyl-lactose and sialylated glycoproteins	*H. pylori*
Sialylated glycoproteins (α2-3-linked)	*Mycoplasma pneumoniae*
Sialylated poly-*N*-acetyllactosamine	*M. pneumoniae*
Sialylated (α2-3)poly-*N*-acetylactosaminoglycans	*Streptococcus suis*
Sialyl(α2-6)lactose	Influenzavirus A
Sialyl(α2-3)lactose	Influenzavirus B
9-O-Ac-of-NeuAc(α2-3)R	Influenzavirus C

Kunz C *et al.* (2000) *Ann Rev Nutr* 20:699-722

RINFORZARE LE MUCOSE

FONTE DI FUCOSIO

2'-fucosillattosio



trisaccaride

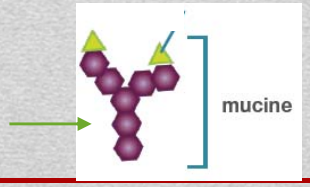
- ✓ Oligosaccaride più rappresentato nel latte materno

  = *HMO (Human Milk Oligosaccharides)*

NATURALE **SICURO**

MATTONE DELLE MUCINE

L-treonina



- ✓ Amminoacido essenziale
- ✓ Mattone indispensabile delle mucine

OPEN ACCESS Freely available online

PLOS | ONE

Fucosylated but Not Sialylated Milk Oligosaccharides Diminish Colon Motor Contractions

John Bienenstock[1,3*], Rachael H. Buck[2], Hawley Linke[2], Paul Forsythe[4,5], Andrew M. Stanisz[1], Wolfgang A. Kunze[1,6,7]

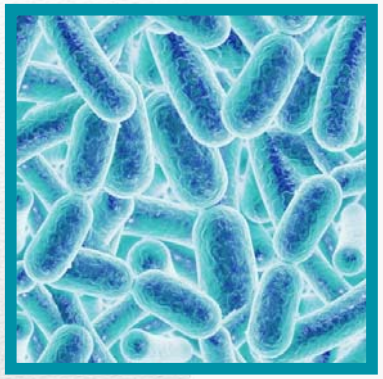
1 McMaster Brain-Body Institute at St Joseph's Healthcare, Hamilton, Ontario, Canada, **2** Abbott Nutrition, a Division of Abbott Laboratories, Columbus, Ohio, United States of America, **3** Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario, Canada, **4** Department of Medicine, McMaster University, Hamilton, Ontario, Canada, **5** Firestone Institute for Respiratory Health, Hamilton, Ontario, Canada, **6** Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Ontario, Canada, **7** Farncombe Family Digestive Health Institute, Hamilton, Ontario, Canada

Abstract

Human milk oligosaccharides (HMO) are being studied by different groups exploring a broad range of potential beneficial effects to the breastfed infant. Many of these effects have been attributed to a growth promotion effect on certain gut organisms such as bifidobacteria. Additionally, evidence indicates that HMO are able to directly promote positive changes in gut epithelium and immune responses under certain conditions. This study utilizes a standardized *ex vivo* murine colon preparation to examine the effects of sialylated, fucosylated and other HMO on gut motor contractions. Only the fucosylated molecules, 2'FL and 3'FL, decreased contractility in a concentration dependent fashion. On the basis of IC_{50} determinations 3'FL was greater than 2 times more effective than 2'FL. The HMO 3'SL and 6'SL, lacto-N-neotetraose (LNnT), and galactooligosaccharides (GOS) elicited no effects. Lactose was used as a negative control. Fucosylation seems to underlie this functional regulation of gut contractility by oligosaccharides, and L-fucose, while it was also capable of reducing contractility, was substantially less effective than 3'FL and 2'FL. These results suggest that specific HMO are unlikely to be having these effects via bifidogenesis, but though direct action on neuronally dependent gut migrating motor complexes is likely and fucosylation is important in providing this function, we cannot conclusively shown that this is not indirectly mediated. Furthermore they support the possibility that fucosylated sugars and fucose might be useful as therapeutic or preventative adjuncts in disorders of gut motility, and possibly also have beneficial central nervous system effects.

Citation: Bienenstock J, Buck RH, Linke H, Forsythe P, Stanisz AM, et al. (2013) Fucosylated but Not Sialylated Milk Oligosaccharides Diminish Colon Motor Contractions. PLoS ONE 8(10): e76236. doi:10.1371/journal.pone.0076236

PREBIOTIC EFFECTS OF HMOs

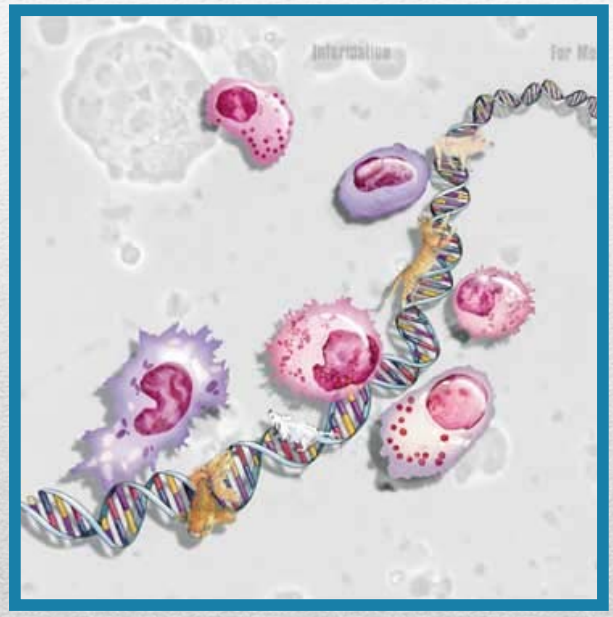


HMOs may indirectly **increase the production of SCFA**, such as n-butyrate; this effect is mediated by bifidobacteria.

Plaza-Diaz J. et al. (2018) Nutrients 10,1038

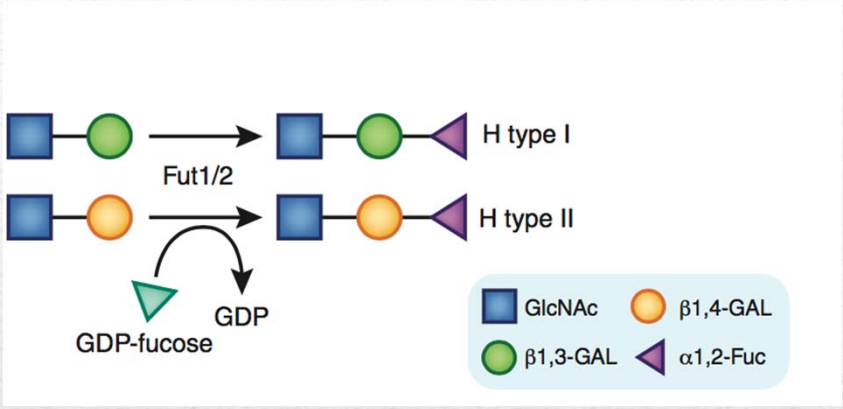
MODULATING EFFECT OF IMMUNITY AND INFLAMMATION

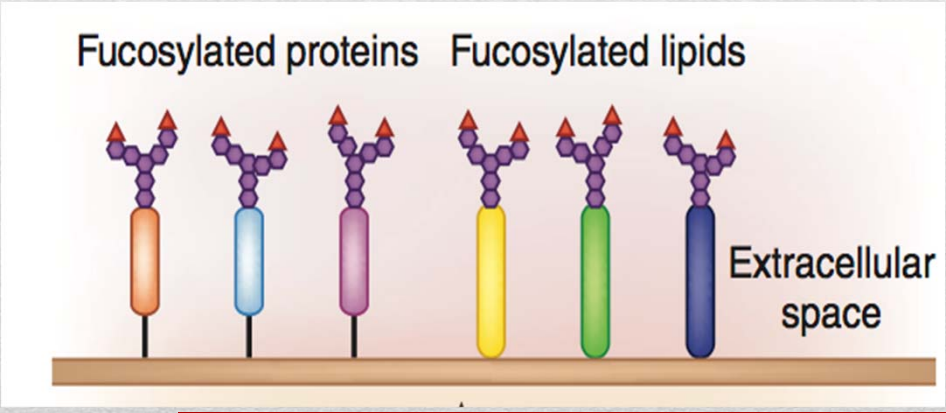
- Modification of the microbiota composition : has a direct impact on the immune system
- **HMOs modulate directly the immune and inflammatory response**
- They can work locally, on the cells of the lymphoid tissues linked to the mucous membranes, or at a systemic level.
- 1% of the HMOs (2'-FL included) are absorbed and enter the systemic pathways (they are found in the urine).



Plaza-Diaz J. et al. (2018) Nutrients 10,1038

FUCOSYL TRANSFERASE 2 (FUT 2)





Galactoside 2-alpha-L-fucosyltransferases:

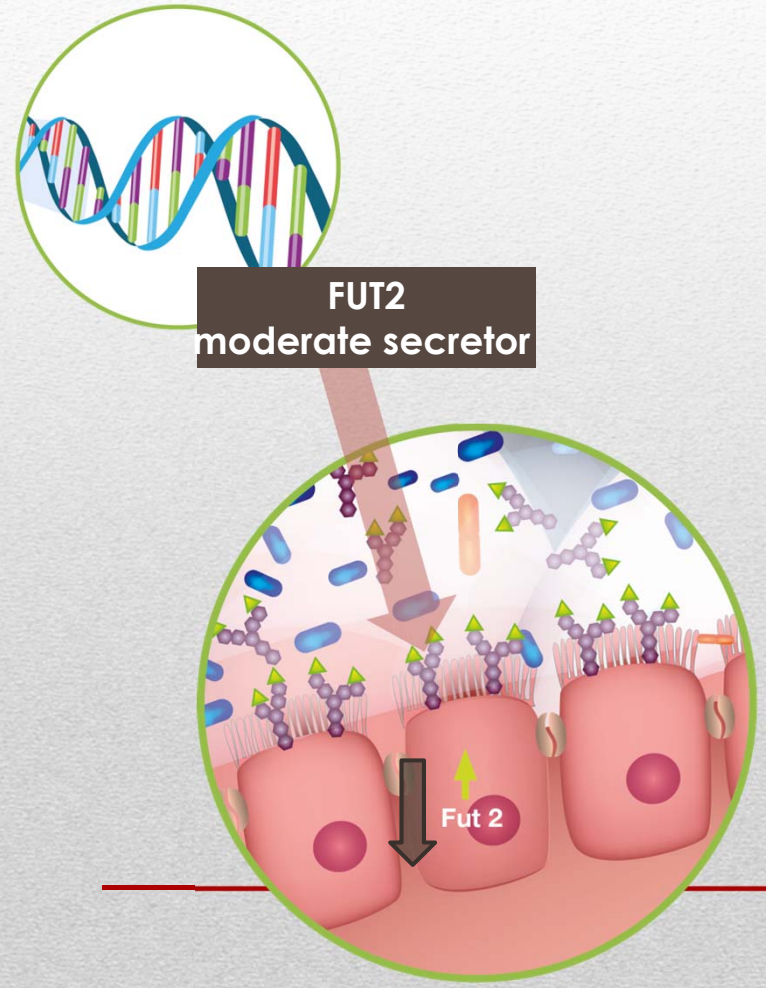
Enzymes attaching a fucosyl group to the sugar chains of the mucins are **fucosyl transferases** (FUT).

Until now, 13 fucosyl transferase genes were identified in the human genome.

In the human gut, they are called fucosyl transferase 1 and 2 = FUT 1 and FUT 2.

Fucosylation on enterocytes is specifically regulated by FUT2.

FUT 2-POLYMORPHISM



Non-secretor polymorphism affects 20% of the Caucasians, **with a defect FUT2**

(non-sense mutation – causing a stop codon – in the FUT2 gene).

There also seems to be a **moderate secretor polymorphism,** with **less functional FUT2** (mutation of the FUT2 gene modifying an amino acid) ➔ less abundant fucosylated glycans.

As for many enzymes, we expect that FUT2 becomes less efficient over the years.

Possible association with the decrease of bifidobacteria in seniors?

IL POLIMORFISMO DEL FUT2

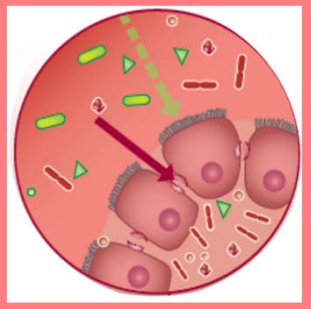
20% della popolazione produce un enzima non funzionante*

=

GENE FUT2

=

MUCOSA COMPROMESSA



SQUILIBRIO DEL MICROBIOTA INTESTINALE

Meteorismo, gonfiori, diarrea/stitichezza, pesantezza, dispepsia, reflusso, alitosi, ecc.

MAGGIOR RISCHIO DI PATOLOGIE e DISTURBI FUNZIONALI

(disbiosi intestinale)

Candidosi croniche, Celiachia, Colangite sclerosante, Diabete di tipo 1, Infezioni del tratto urinario, Enterocolite necrosante, MICI (malattia di Crohn)

Rinforzare la mucosa intestinale durante ogni terapia probiotica

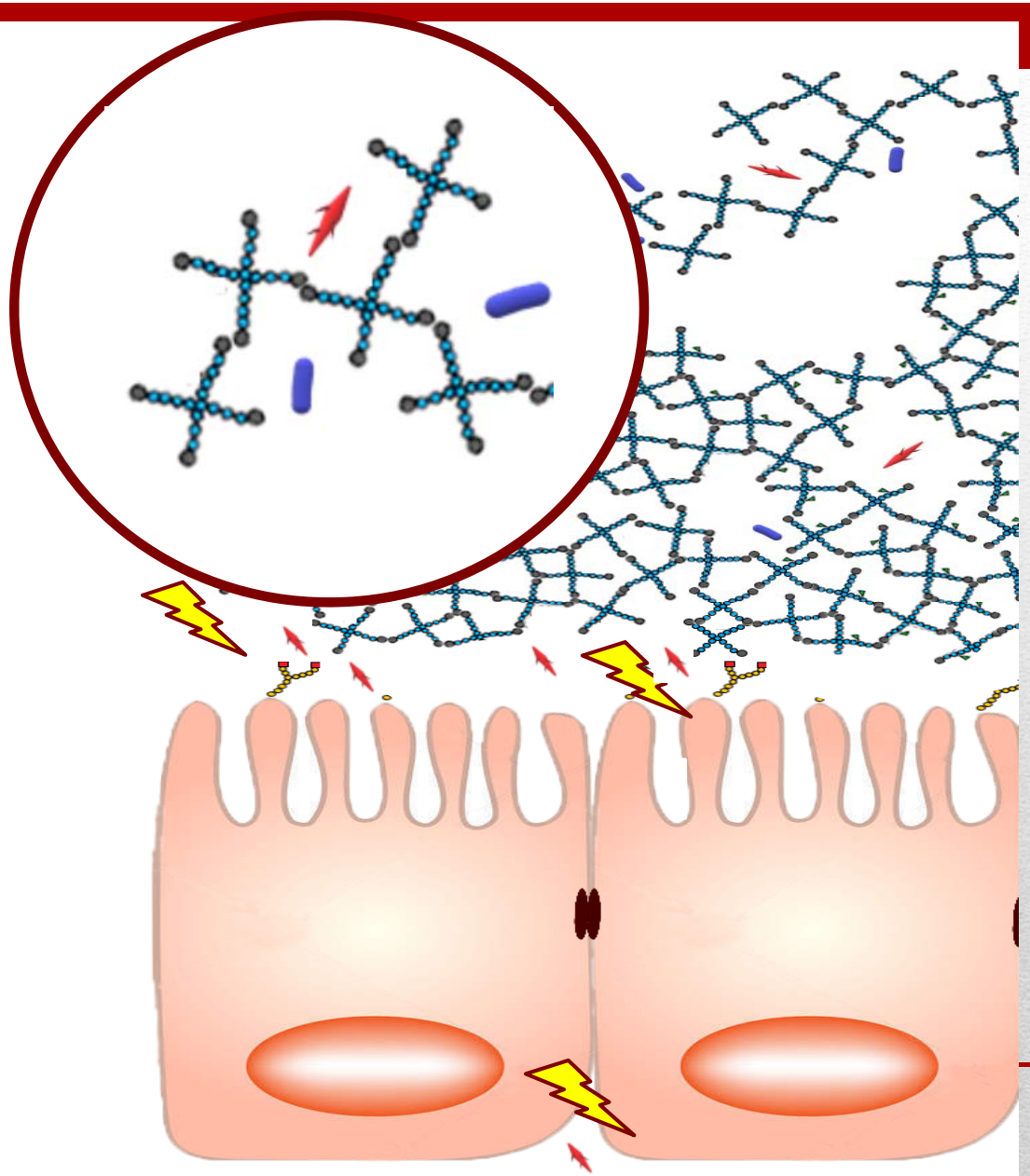
*A genome-wide association meta-analysis of diarrheal disease in young children identifies FUT2 & provides plausible biological pathways M Bustamante et al. Human Molecular Genetics, 2016, Vol. 25

Fucosyltransferase 2: a genetic risk factor for primary sclerosing cholangitis and Crohn's disease--a comprehensive review. Maroni L et al. Clin Rev Allergy Immunol. 2015 Jun;48(2-3):182-91.

Fucosyltransferase 2 non-secretor and low secretor status predicts severe outcomes in premature infants Ardythe L. Morrow et al. Pediatr. 2011 May ; 158(5): 745–751.

FUT2 Nonfunctional Variant: A "Missing Link" Between Genes and Environment in Type 1 Diabetes? Ping Yang et al. Diabetes, vol. 60, November 2011

Nei soggetti con **polimorfismo limitante del FUT2** mancano i siti di adesione fucosilati nel muco fluido e i batteri raggiungono più facilmente gli strati profondi



OPEN ACCESS Freely available online

PLoS one

Secretor Genotype (*FUT2* gene) Is Strongly Associated with the Composition of *Bifidobacteria* in the Human Intestine

Pirjo Wacklin*, Harri Mäkivuokko, Noora Alakulppi, Janne Nikkilä, Heli Tenkanen, Jarkko Räbinä, Jukka Partanen, Kari Aranko, Jaana Mättö

Finnish Red Cross Blood Service, Helsinki, Finland

Bifidobacterial diversity, abundance and richness are significantly reduced in samples of non-secretor individuals as compared with those from the secretor individuals.

Non-secretor individuals lacked or were rarely colonized by several genotypes related to *B. bifidum*, *B. adolescente and B. catenulatum / pseudocatenulatum*.

In contrast to bifidobacteria, several bacterial genotypes were more common and the abundance of dominant bacteria was higher in the non-secretor individuals than in the secretor individuals.

We showed that **the diversity and the composition of the bifidobacterial population is strongly associated with the secretor / non-secretor status**, which consequently appears to be one of the host genetic determinant for the composition of the intestinal microbiota.

Effects of *FUT2-gene* non-sense polymorphism in pathophysiological disorders

Condition	Disease or pathology	Evaluation	Polymorphism(s)	Ref(s).
Inflammation	Crohn's disease	Susceptible	rs281379, rs601338, rs602662	69,70
	Chronic pancreatitis		–	71
	Primary sclerosing cholangitis		rs281379, rs601338, rs602662	72
	Acute uncomplicated pyelonephritis		–	73
	Type I diabetes		rs601338	74
	Psoriasis		rs1047781	75
	Behçet's disease		rs632111, rs601338	76
Infection	*Candida albicans*	Susceptible	–	61
	Neisseria meningitidis		–	59
	Streptococcus pneumoniae		–	59
	Haemophilus influenza		–	60
	Urinary tract infection		–	62
	Pathogenic *Escherichia coli*		–	63
	Bacteremia and infection after hematopoietic stem cell transplantation		rs601338	86
Infection	*Helicobacter pylori*	Resistant	rs601338	84,85
	Norovirus		rs601338	86,88
	Rotavirus		rs601338	87,88,89

Diabetes. 2011 Nov;60(11):2685-7. doi: 10.2337/db11-1104.

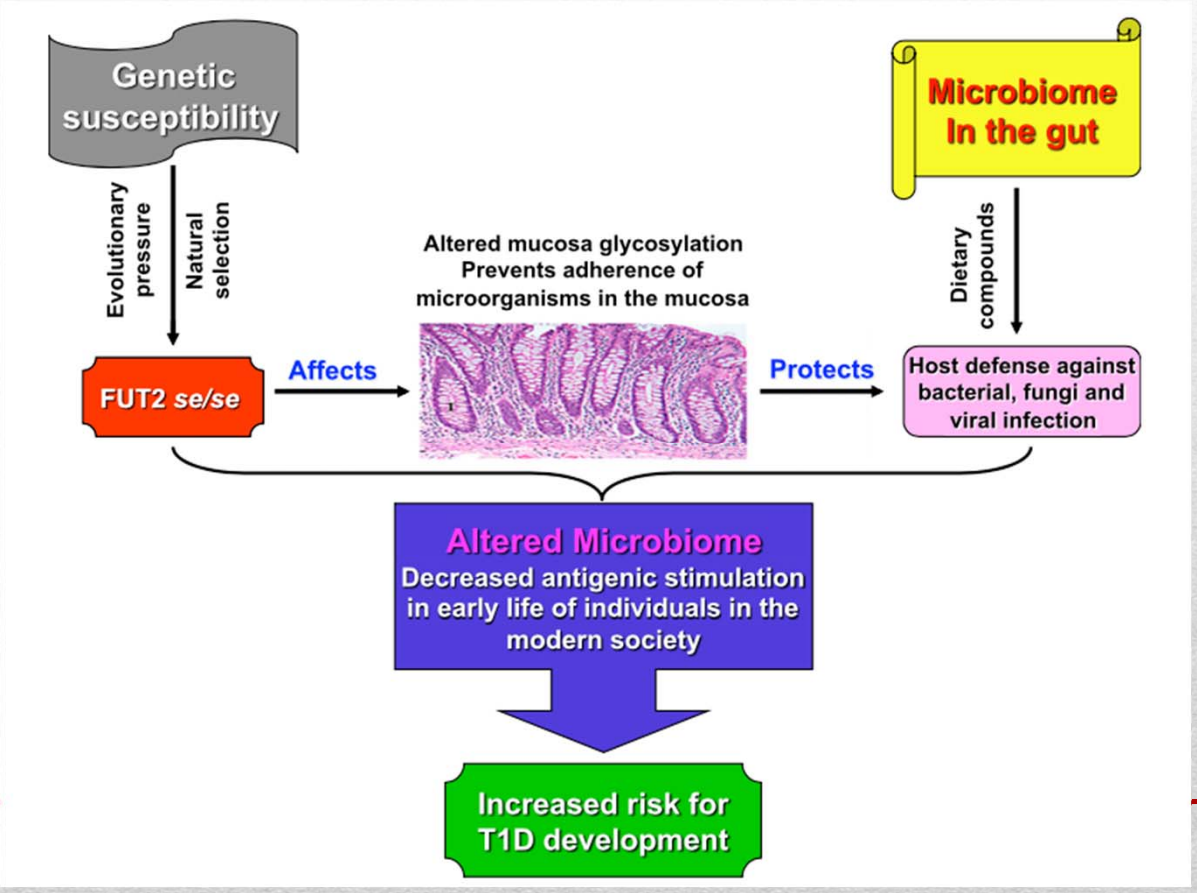
FUT2 nonfunctional variant: a "missing link" between genes and environment in type 1 diabetes?

Yang P[1], Li HL, Wang CY.

Author information

Comment on
FUT2 nonsecretor status links type 1 diabetes susceptibility and resistance to infection. [Diabetes. 2011]

PMID: 22025775 PMCID: PMC3198105 DOI: 10.2337/db11-1104



Clin Rev Allergy Immunol. 2015 Jun;48(2-3):182-91. doi: 10.1007/s12016-014-8423-1.

Fucosyltransferase 2: a genetic risk factor for primary sclerosing cholangitis and Crohn's disease--a comprehensive review.

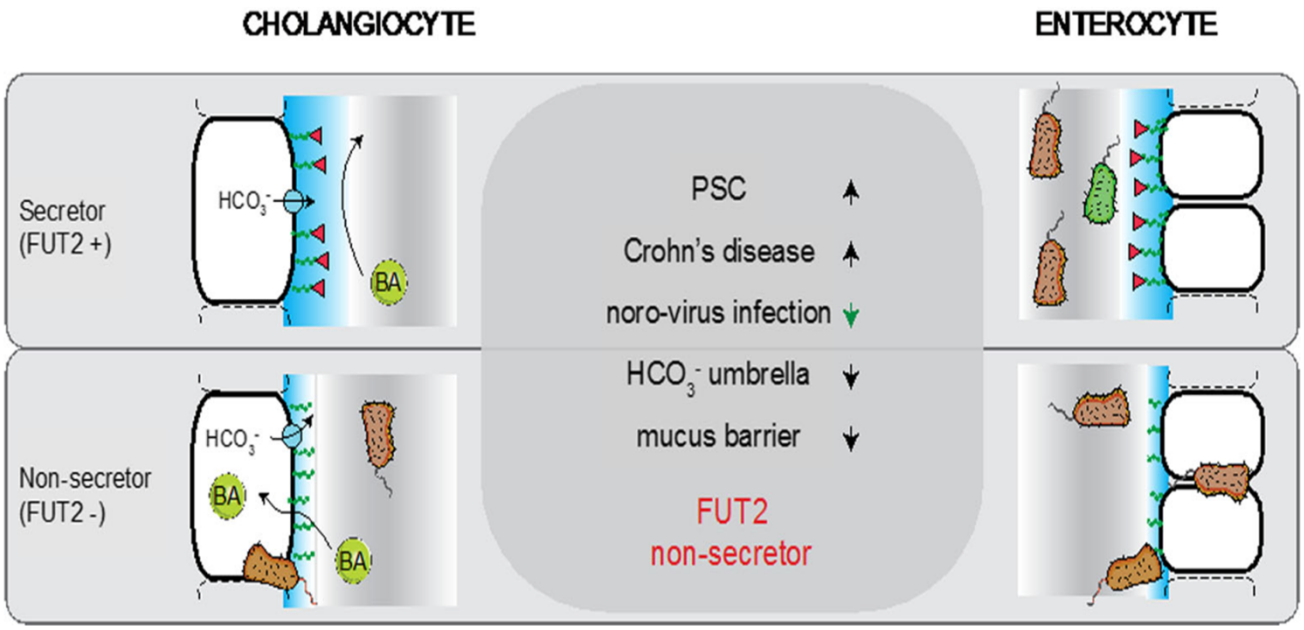


Fig. 1 FUT2 in cholangiocytes and enterocytes (schematic overview). FUT2-positive individuals (FUT2+; secretors; *top part* of the figure) have fucose moieties at the cell surface of cholangiocytes (*left*) and enterocytes (*right*), whereas non-secretor (FUT2-) individuals lack this fucosylation. This results in differences in the mucus layer in epithelia and possibly alteration in barrier function and pathogen adhesion. In the liver, the constitution and thickness of the mucus layer will affect the diffusion rate of HCO_3^-, secreted by cholangiocytes, and thus the local pH. Increased pH in close proximity of the cell surface (biliary HCO_3^- umbrella) results in more deprotonated, charged bile salts which do not enter the cell in a carrier-independent fashion. FUT2-negative individuals might have an altered (thinner) mucus layer, rendering the cholangiocytes more susceptible to bile acid-induced cell damage

Nat Immunol. 2016 Oct 19;17(11):1244-1251. doi: 10.1038/ni.3587.

Epithelial glycosylation in gut homeostasis and inflammation.

Goto Y[1,2], Uematsu S[2,3], Kiyono H[2,4,5].

Intestinal epithelial cells apically express glycans, especially a1,2-fucosyl linkages, which work as a biological interface for the host-microbe interaction.

Emerging studies have shown that **epithelial a1,2-fucosylation is regulated by microbes and by immune cells of the mucosa**.

Dysregulation of the gene encoding fucosyl transferase 2 (FUT2), an enzyme governing epithelial a1,2-fucosylation, is associated with various disorders, including infections and chronic inflammatory diseases.

This suggests a **critical role for an interaction between microbes, epithelial cells and GALT, mediated via glycan residues.**

fucose and Fut2 gene expression as an example, we describe how epithelial glycosylation is controlled by immune cells and luminal microbes. We also address the pathophysiological contribution of epithelial α1,2-fucosylation to pathogenic and commensal microbes as well as the potential of α1,2-fucose and its regulatory pathway as previously unexploited targets in the development of new therapeutic approaches for human diseases.

The human milk oligosaccharide 2′-fucosyllactose modulates CD14 expression in human enterocytes, thereby attenuating LPS-induced inflammation

YingYing He,[1,2] ShuBai Liu,[3] David E Kling,[2] Serena Leone,[2] Nathan T Lawlor,[2] Yi Huang,[2] Samuel B Feinberg,[2] David R Hill,[2] David S Newburg[1,2]

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2014-307544).

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ABSTRACT

Background A major cause of enteric infection, Gram-negative pathogenic bacteria activate mucosal inflammation through lipopolysaccharide (LPS) binding to intestinal toll-like receptor 4 (TLR4). Breast feeding lowers risk of disease, and human milk modulates inflammation.

Objective This study tested whether human milk oligosaccharides (HMOSs) influence pathogenic *Escherichia coli*-induced interleukin (IL)-8 release by intestinal epithelial cells (IECs), identified specific proinflammatory signalling molecules modulated by HMOSs, specified the active HMOS and determined its

2′-fucosyllactose (2′-FL), at milk concentrations, displayed equivalent ability as total HMOSs to suppress CD14 expression, and protected AIEC-infected mice.

Conclusions HMOSs and 2′-FL directly inhibit LPS-mediated inflammation during ETEC invasion of T84 and H4 IECs through attenuation of CD14 induction. CD14 expression mediates LPS-TLR4 stimulation of portions of the 'macrophage migration inhibitory factors' inflammatory pathway via suppressors of cytokine signalling 2/signal transducer and activator of transcription 3/NF-κB. HMOS direct inhibition of inflammation supports its functioning as an innate immune system whereby the mother protects her vulnerable neonate through her milk. 2′-FL, a principal HMOS, quenches inflammatory signalling.

Significance of this study

What is already known on this subject?

- Major causes of enteric infection, Gram-negative bacteria, activate mucosal inflammation through lipopolysaccharide (LPS) binding to intestinal toll-like receptor 4 (TLR4).
- Breast feeding lowers risk of disease, and human milk modulates inflammation.
- Oligosaccharides are collectively the third largest components of human milk

How might it impact on clinical practice in the foreseeable future?

- 2′-FL directly attenuating inflammation further confirms HMOSs as an innate immune system of human milk whereby the mother protects her vulnerable neonate; this supports universal breast feeding as a standard of care.
- 2′-FL may represent a novel oral prophylactic and therapeutic agent to quench mucosal inflammation associated with diverse inflammatory disorders of the mucosa.

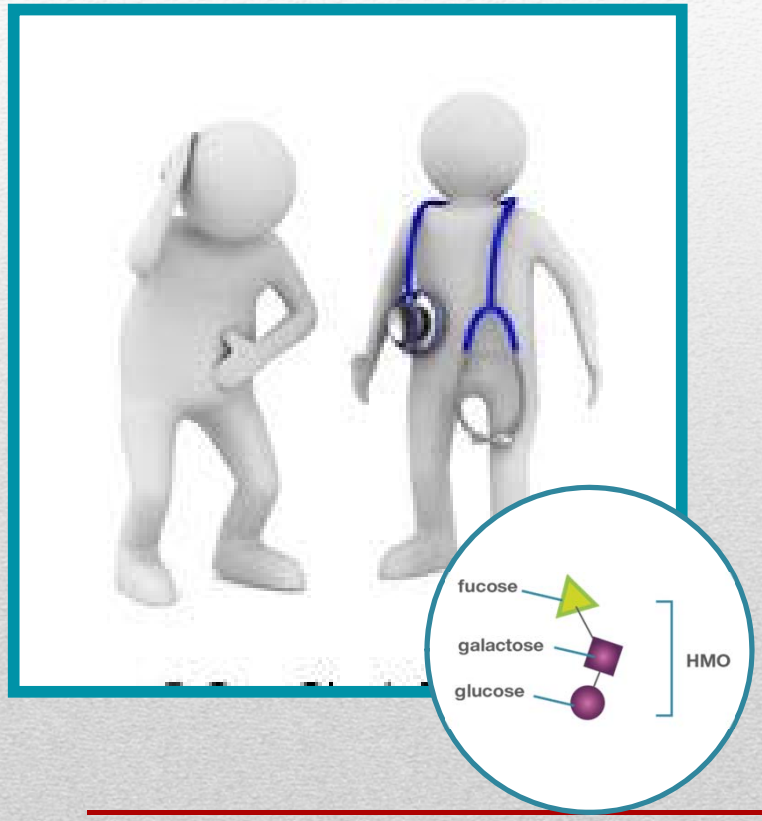
How might it impact on clinical practice in the near future?

Directly attenuating inflammation further confirms 2'-FL HMOs as an innate immune system of breast milk whereby mother protects the vulnerable neonate; this supports universal breast feeding as a standard of care.

2'-FL may present a novel oral prophylactic and therapeutic agent to quench mucosal inflammation associated with diverse inflammatory disorders of the mucosa.

2'-FL SECURITY

2'-FL is **completely safe.**



- For people with intestinal **dysbiosis** and/or **candidosis**, **chronic vaginal infections, urinary tract infections** or patients with **Crohn's disease**.
- For those not responding to probiotics.

Recommended to start with a supplementation of 2'-FL (250 mg) and to adapt in function of the clinical response (double or x 4).

- Tested in clinical trials up to 20g /day

SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 29 June 2015

PUBLISHED: 20 July 2015

doi:10.2903/j.efsa.2015.4184

Safety of 2'-*O*-fucosyllactose as a novel food ingredient pursuant to Regulation (EC) No 258/97

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)

Abstract

Following a request from the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on 2'-*O*-fucosyllactose as a novel food ingredient (NFI) submitted pursuant to Regulation (EC) No 258/97 of the European Parliament and of the Council, taking into account the comments and objections of a scientific nature raised by Member States. 2'-*O*-fucosyllactose (2'-FL) is a synthetic trisaccharide, which is intended to be used in infant and follow-on formulae, foods for special medical purposes for infants and young children, and other foods for infants and young children, as well as in foods or food supplements for adults. The information provided on the potential mutagenicity of 2'-FL does not raise safety concerns as regards the genotoxicity of this NFI. Based on the observations from a sub-chronic 90-day toxicity study in rats, the Panel considers that the no observed adverse effect level is 2 000 mg/kg body weight per day. The applicant provided a double-blind, randomised, controlled clinical trial on the effects of 2′-FL consumed in combination with another oligosaccharide (lacto-*N*-neotetraose (LNnT)) in infants. The Panel concludes that 2′-FL is safe for infants (up to one year of age) when added to infant and follow-on formulae, in combination with LNnT, at concentrations up to 1.2 g/L of 2′-FL and up to 0.6 g/L of LNnT, at a ratio of 2:1 in the reconstituted formulae; is safe for young children (older than one year of age) when added to follow-on and young-child formulae, at concentrations up to 1.2 g/L of 2′-FL (alone or in combination with LNnT, at concentrations up to 0.6 g/L, at a ratio of 2:1). The Panel also concludes that 2′-FL is safe when added to other foods at the uses and use levels proposed by the applicant.

ANDIDNOTIZIE
RIVISTA DELL'ASSOCIAZIONE NAZIONALE DIETISTI
ANNO VENTINOVESIMO
SECONDO NUMERO
PERIODICO TRIMESTRALE
II TRIMESTRE 2019

ANDID ASSOCIAZIONE NAZIONALE DIETISTI
Member of EFAD - ICDA
AS AND

HUMAN MILK OLIGOSACCHARIDES (HMO), DAL LATTE MATERNO UNO STRAORDINARO SEGRETO DI SALUTE PER OGNI ETÀ

Dott. Maurizio Salamone *Direzione scientifica Metagenics Italia srl*

HMO NEL LATTE MATERNO

Il latte materno è un tessuto vivente straordinario che cambia la sua composizione nel corso dell'allattamento per venire incontro alle esigenze del lattante.
Queste esigenze varino ben oltre il semplice aspetto nutritivo. Il latte materno contiene anche cellule e citochine immunitarie, fattori di crescita e di regolazione genica.
Dal punto di vista quantitativo la classe di sostanze più presenti dopo l'acqua e il lattosio sono dei piccoli oligosaccaridi denominati HMO (Human Milk Oligosaccharides); ne troviamo da 5 a 15 g/L nel colostro e nel latte materno maturo.[1-3]
Nel latte materno umano troviamo circa 150-200 differenti HMO mentre nel latte bovino solo una trentina[1-4]. Solo l'1-2% di queste brevi catene di zuccheri è assorbito dal lattante, che non possiede il corredo enzimatico per digerirli, e arriva alla circolazione sistemica. Il resto prosegue il suo percorso fino al colon e viene metabolizzato dal microbiota intestinale.[3-6]
Anche se la quota di assorbimento sistemico è molto ridotta sembrerebbe che possa svolgere un'azione neurotrofica promuovendo fattori di regolazione come BDNF. Anche la presenza di metaboliti degli HMO nell'apparato escretore potrebbe avere un qualche ruolo nella modulazione del microbiota genito-urinario del neonato.

STRUTTURA DEGLI HMO

Gli HMOs sono delle **sostanze bioattive naturali sintetizzate dalla ghiandola mammaria umana**. La loro complessa struttura consiste essenzialmente di 5 mattoni fondamentali differentemente legati fra di loro: glucosio, galatosio, N-acetilglucosamina, fucosio e acido sialico. Lo zucchero fucosio è anche una molecola insolita poiché ha una configurazione L, mentre le altre molecole di zuccheri dell'organismo hanno una configurazione D.
Fondamentalmente gli **HMO si basano su una struttura essenziale di lattosio differentemente decorate nelle posizioni terminali**. Sono possibili anche strutture elongate o ramificate in vario modo a creare una varietà di HMOs con differente architettura e peso molecolare.[1-3]
Gli HMO fucosilati sono risultati la componente più cospicua (circa il 77% degli HMO), mentre gli HMO siallati rappresentano circa il 16% degli HMO totali. Gli HMO fucosilati sono molecole neutre, mentre gli HMOs siallati sono molecole acide.
Per semplificare possiamo classificare gli HMO in base allo zucchero terminale in HMOs fucosilati come il 2'FL, non fucosilati come LNnT e HMO siallati come ad esempio il 3'SL.[1-3]
Il 2F' lattosio rappresenta il singolo HMO più rappresentato in assoluto nel latte materno **(Fig.1)** con una percentuale di oltre il 60% di tutti gli HMO materni.[1-3]

(Fig.1)

RUOLO BIOLOGICO

Per lungo tempo gli scienziati si sono interrogati sul significato biologico di questi oligosaccardidi vista la loro non-digeribilità per il neonato. Ma da sempre è risaputo che **l'allattamento al seno si associa ad un ridotto rischio di disturbi gastrointestinali e infezioni nel lattante e nelle fasi successive della vita**.[7-13] Forse **gli HMO sono in parte responsabili di questo effetto protettivo** visto che il latte materno ha evidenza di supportare le difese immunitarie del bambino.[6, 13-16]
Il tipo di zucchero terminale condiziona il tipo di patogeni o tossine che vi possono aderire. Esiste infatti una specificità di legame di tipo lectina-glicano.
I ricercatori hanno scoperto che il tipo e la quantità di HMO nel latte materno si correla a antigeni materni del Gruppo ABO e di Lewis.[16]

GENETICA DEGLI HMO: SECRETORI E NON SECRETORI

L'abbondanza relativa di HMO fucosilati dipende dall'attività di transferasi che glicosilano il lattosio o le mucine transmembranarie. **Queste fucosiltransferatsi sono codificate da geni come FUT2**. Circa l'80% delle donne italiane sono **soggetti secretori** ovvero in grado di produrre e secernere nel latte materno una grande abbondanza di 2'FL e altri HMO.[16-18]
Il polimorfismo limitante della FUT2 non ha implicazioni solo nel sesso femminile (legato alla produzione del latte materno). Un polimorfismo **FUT2 non secretore** sia nel maschio che nella femmina **porterà anche a minore fucosilazione delle mucine transmembranarie intestinali con effetti negativi sull'equilibrio del microbiota e sulla maturazione del sistema immunitario**.

EFFETTI BENEFICI DEGLI HMO

Gli effetti benefici degli HMO possono essere raggruppati in 2 classi **(Fig.2)**:
- Effetti legati all'azione prebiotica
- Effetti specifici immunomodulatori e regolatori[19,20]

Effetti legati all'azione prebiotica

Attraverso meccanismi di modulazione prebiotica gli HMO:
- **Esercitano una pressione selettiva sull'equilibrio microbico favorendo batteri benefici (azione bifidogenica) e sfavoriscono i patobionti opportunisti**[3,21,22]
- **Favoriscono la produzione di SCFA**

Effetti specifici immunomodulatori e regolatori

Gli HMOs sono in grado di apportare benefici che vanno ben oltre l'azione prebiotica e che si esplicano attraverso meccanismi specifici:

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J Nutr. 1994 Dec;124(12):2358-64.

Oligosaccharides from human milk block binding and activity of the Escherichia coli heat-stable enterotoxin (STa) in T84 intestinal cells.

Crane JK[1], Azar SS, Stam A, Newburg DS.

Author information

Abstract

Enterotoxin-producing Escherichia coli are major causes of pediatric diarrhea in developing countries. The heat-stable enterotoxin of Escherichia coli (STa) causes diarrhea by virtue of its ability to bind to and stimulate intestinal membrane-bound guanylate cyclase, generating cyclic GMP (cGMP). Previous work showed that a fucosylated oligosaccharide fraction of human milk was able to protect suckling mice from the secretory effects of STa, but the mechanism of the protection could not be determined. Oligosaccharide fractions from human milk were tested for their ability to block the biochemical effects of STa in T84 cells, a human colon carcinoma line responsive to the toxin. Total and fucosylated oligosaccharide fractions were found to inhibit STa-stimulated

These findings demonstrate the **protective activity of HMOs against an enterotoxin** that is stable is by the heath of **E.Coli** in a human cell line and prove that the biochemical step blocked by oligosaccharides is STa mediated stimulation of guanylate cyclase.

This represents a novel mechanism by which HMOs protect against diarrhea.

Eur J Nutr. 2017 Apr;56(3):1293-1301. doi: 10.1007/s00394-016-1180-6. Epub 2016 Feb 24.

FUT2-dependent breast milk oligosaccharides and allergy at 2 and 5 years of age in infants with high hereditary allergy risk.

Sprenger N[1], Odenwald H[2,3,4], Kukkonen AK[5], Kuitunen M[6], Savilahti E[6], Kunz C[7].

Author information

Abstract

PURPOSE: Manifestation of allergic disease depends on genetic predisposition, diet and commensal microbiota. Genetic polymorphism of mothers determines their breast milk glycan composition. One major determinant is the fucosyltransferase 2 (FUT2, secretor gene) that was shown to be linked to commensal microbiota establishment. We studied whether FUT2-dependent breast milk oligosaccharides are associated with allergic disease in breast-fed infants later in life.

METHODS: We analyzed FUT2-dependent oligosaccharides in breast milk samples of mothers (n = 266) from the placebo group of a randomized placebo-controlled trial of prebiotics and probiotics as preventive against allergic disease in infants with high allergy risk (trial registry number: NCT00298337). Using logistic regression models, we studied associations between FUT2-dependent breast milk oligosaccharides and incidence of allergic disease at 2 and 5 years of age.

RESULTS: At 2 years, but not at 5 years of age, we observed a presumed lower incidence ($p < 0.1$) for IgE-associated eczema manifestation in C-section-born infants who were fed breast milk containing FUT2-dependent oligosaccharides. By logistic regression, we observed a similar relation ($p < 0.1$) between presence of FUT2-dependent breast milk oligosaccharides and IgE-associated disease and IgE-associated eczema in C-section-born infants only. When testing with the levels of breast milk oligosaccharide 2'-fucosyllactose as proxy for FUT2 activity, we

The data indicate that infants born by C-section and having a hereditary risk for allergies might have **a lower risk to manifest IgE associated eczema** at 2 years, but not 5 years of age, when fed **breast milk with FUT2-dependent milk oligosaccharides**.

Further studies with larger cohorts and especially randomized controlled intervention trials are required to build on these preliminary observations.

Diabet Med. 2017 Apr;34(4):586-589. doi: 10.1111/dme.13288. Epub 2016 Dec 15.

FUT2 non-secretor status is associated with Type 1 diabetes susceptibility in Japanese children.

Ihara K[1,2], Fukano C[1], Ayabe T[3], Fukami M[3], Ogata T[3,4], Kawamura T[5], Urakami T[6], Kikuchi N[7], Yokota I[8,9], Takemoto K[10,11], Mukai T[12,13], Nishii A[14], Kikuchi T[15,16], Mori T[17,18], Shimura N[19], Sasaki G[20], Kizu R[21], Takubo N[22,23], Soneda S[24], Fujisawa T[25], Takaya R[26], Kizaki Z[27], Kanzaki S[28], Hanaki K[29], Matsuura N[30,31], Kasahara Y[32], Kosaka K[33], Takahashi T[34], Minamitani K[35], Matsuo S[36], Mochizuki H[37], Kobayashi K[38], Koike A[39], Horikawa R[40], Teno S[41], Tsubouchi K[42], Mochizuki T[43,44], Igarashi Y[45], Amemiya S[15], Sugihara S[46]; Japanese Study Group of Insulin Therapy for Childhood and Adolescent Diabetes (JSGIT).

⊕ Author information

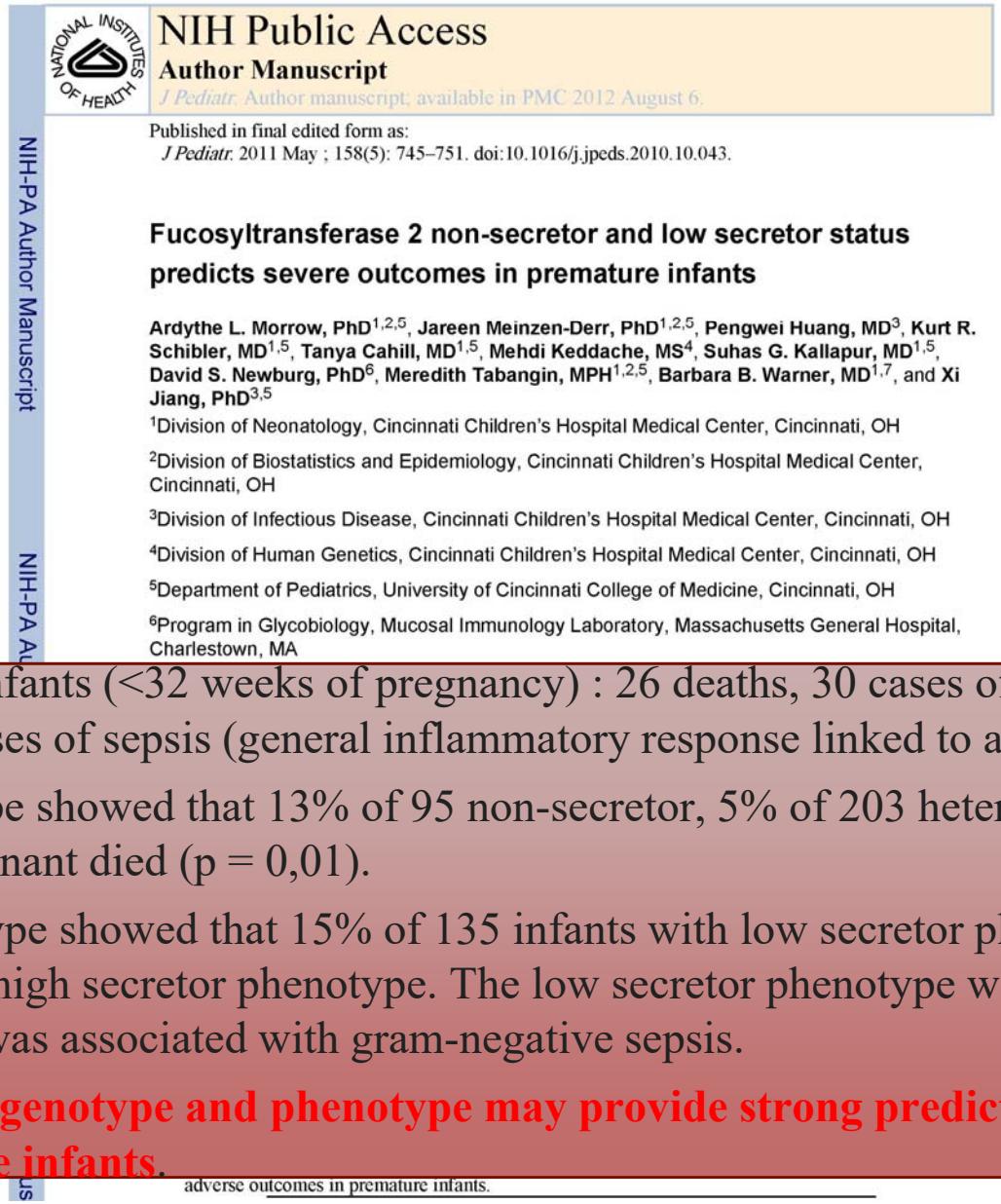
Abstract

AIM: To examine the contribution of the FUT2 gene and ABO blood type to the development of Type 1 diabetes in Japanese children.

METHODS: We analysed FUT2 variants and ABO genotypes in a total of 531 Japanese children diagnosed with Type 1 diabetes and 448 control subjects. The possible association of FUT2 variants and ABO genotypes with the onset of Type 1 diabetes was statistically examined.

RESULTS: The se2 genotype of the FUT2 gene was found to confer susceptibility to Type 1 diabetes in a recessive effects model.

CONCLUSIONS: **The FUT2 gene contributed to the development of Type 1 diabetes** in the present cohort of Japanese children.



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Author Manuscript
J Pediatr. Author manuscript; available in PMC 2012 August 6.

Published in final edited form as:
J Pediatr. 2011 May ; 158(5): 745–751. doi:10.1016/j.jpeds.2010.10.043.

Fucosyltransferase 2 non-secretor and low secretor status predicts severe outcomes in premature infants

Ardythe L. Morrow, PhD[1,2,5], Jareen Meinzen-Derr, PhD[1,2,5], Pengwei Huang, MD[3], Kurt R. Schibler, MD[1,5], Tanya Cahill, MD[1,5], Mehdi Keddache, MS[4], Suhas G. Kallapur, MD[1,5], David S. Newburg, PhD[6], Meredith Tabangin, MPH[1,2,5], Barbara B. Warner, MD[1,7], and Xi Jiang, PhD[3,5]

[1]Division of Neonatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

[2]Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

[3]Division of Infectious Disease, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

[4]Division of Human Genetics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

[5]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH

[6]Program in Glycobiology, Mucosal Immunology Laboratory, Massachusetts General Hospital, Charlestown, MA

There were 410 study infants (<32 weeks of pregnancy) : 26 deaths, 30 cases of NEC (necrotizing enterocolitis) and 96 cases of sepsis (general inflammatory response linked to a severe infection).

The analysis by genotype showed that 13% of 95 non-secretor, 5% of 203 heterozygotes and 2% of 96 infants who were secretor dominant died (p = 0,01).

The analysis by phenotype showed that 15% of 135 infants with low secretor phenotype died, compared with 2% of 248 infants with high secretor phenotype. The low secretor phenotype was associated with NEC and the non-secretor genotype was associated with gram-negative sepsis.

Conclusions – **secretor genotype and phenotype may provide strong predictive biomarkers of adverse outcomes in premature infants**.

adverse outcomes in premature infants.

Effetti benefici

- Regolano l'adesione cellulare
- Regolano la sintesi delle glicoproteine
- Regolano i livelli di proteine plasmatiche
- Hanno un importante ruolo sul sistema immunitario innato
- Possono avere proprietà antimicrobiche

Effetti avversi

- Attività pro-infiammatoria
- Induzione dell'auto-immunità
- Interferenza con l'espressione genica
- Neurotossicità
- Cardiotossicità
- Citotossicità e eccitotossicità
- Aumento della viscosità del sangue
- Alterazione dell'omeostasi endocrina
- Leaky Gut Syndrome
- Alterazione del microbiota intestinale

Conclusioni

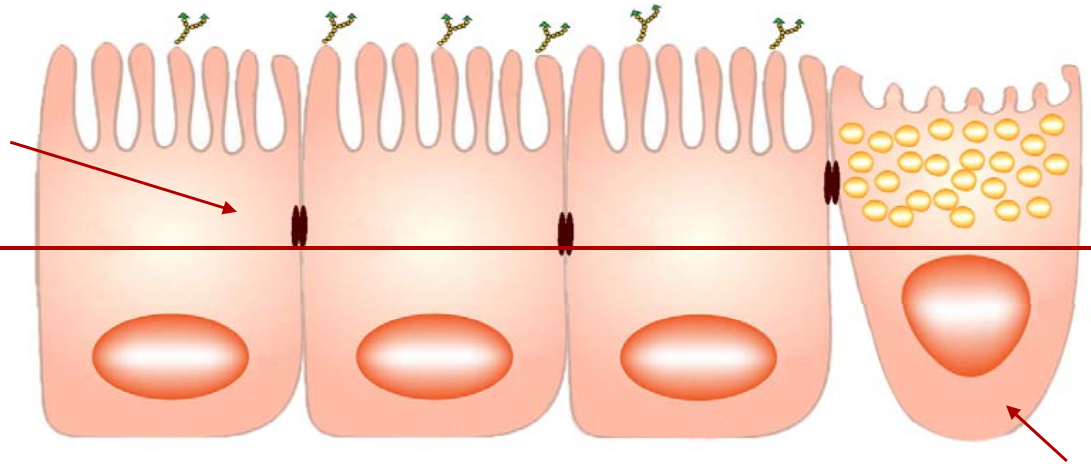
- Le lectine sono sono **carbohydrate-binding proteins** of non-immune temperament, ubiquitarie, considerate **antinutrienti**

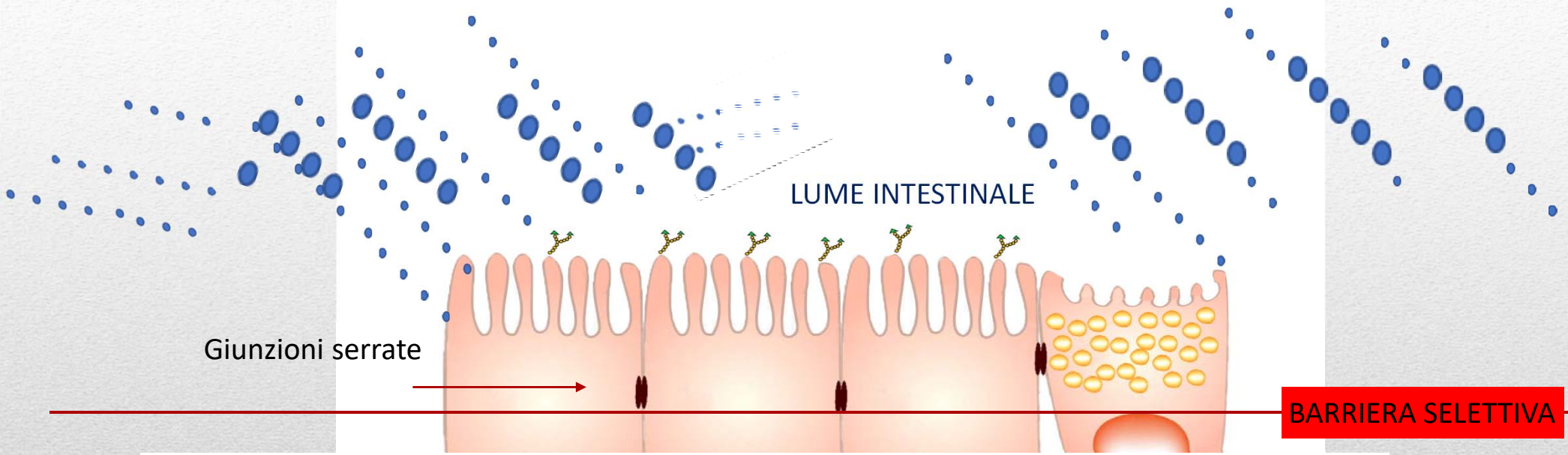
- Hanno un importante ruolo nel **sistema immunitario innato** e la capacità di regolare l'adesione cellulare, la sintesi delle glicoproteine e i livelli di proteine plasmatiche

- In elevate concentrazioni risultano dannose per l'organismo contribuendo all'insorgenza della **Leaky Gut Syndome**, all'attivazione dell'**auto-immunità** e alla manifestazione di patologie autoimmune quali **diabete mellito tipo1**, **artrite reumatoide**, **celiachia**, **nefropatia IgA** ecc.

- Modifiche dei carboidrati della superficie cellulare incidono sul comportamento metastatico delle cellule tumorali, pertanto diverse lectine possono essere utilizzate come agenti terapeutici, legandosi preferenzialmente alle membrane delle cellule tumorali o ai loro recettori, causando citotossicità, apoptosi e **inibizione della crescita tumorale**

L'ENDOTELIO INTESTINALE CREA UNA BARRIERA SELETTIVA TRA L'AMBIENTE LUMINALE E L'INTERNO GRAZIE A UN SISTEMA DI GIUNZIONI STRETTE (TIGHT JUNCTIONS)





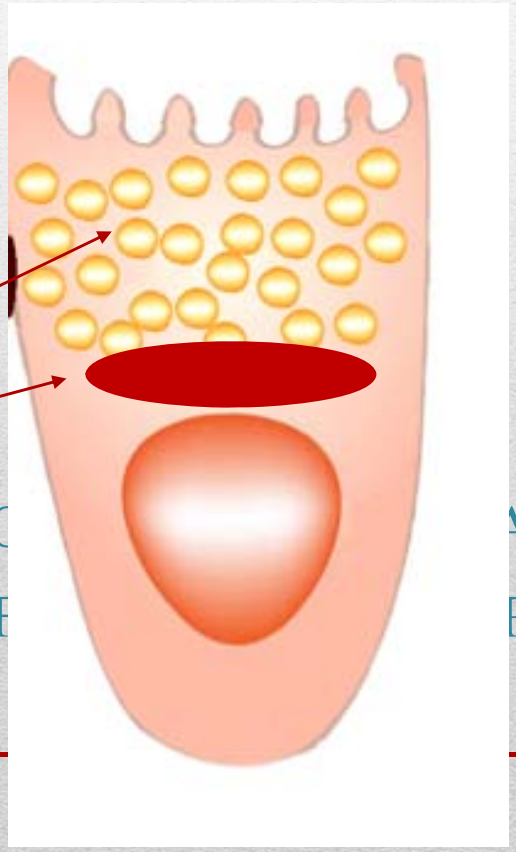
GLI ORGANISMI DEL MICROBIOTA DEVONO ESSERE COMPARTIMENTATI NEL LUME CON ACCESSO LIMITATO ALLA SUPERFICE DELL'ENDOTELIO

e o goblet cell

Forma caliciforme

Vescicole di esocitosi piene di mucine

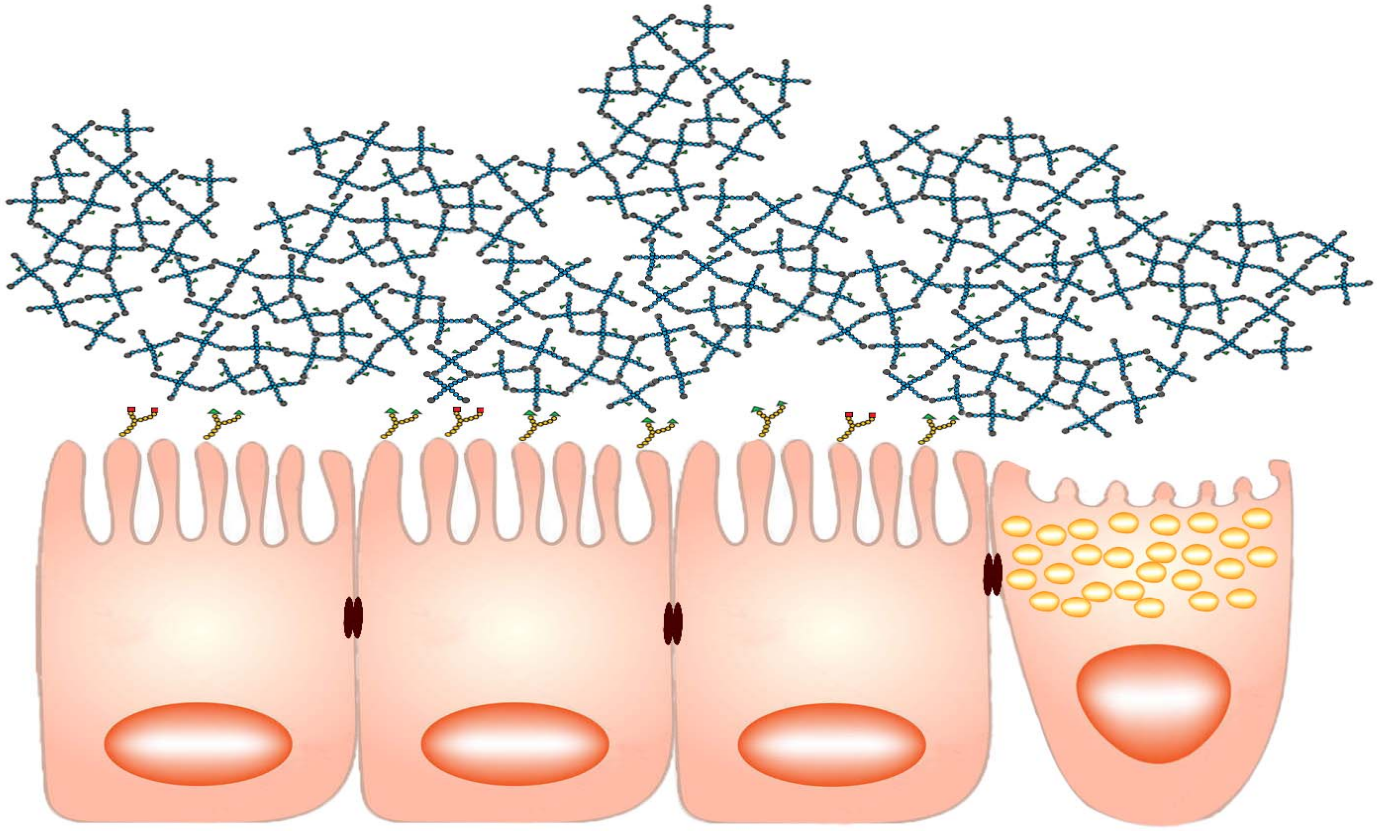
Grande apparato del Golgi



UN ALTRO ELEMENTO DELL'ENDO ALE È LA CELLULA MUCIPARA CALICI RNE GRANDE QUANTITÀ DI MUCINE

LE MUCINE FORMANO UN PRIMO STRATO PROSSIMO ALL'ENDOTELIO SPESSO E POCO COLONIZZATO DAI BATTERI

Strato di muco compatto sul lato luminale endoteliale



Enterociti

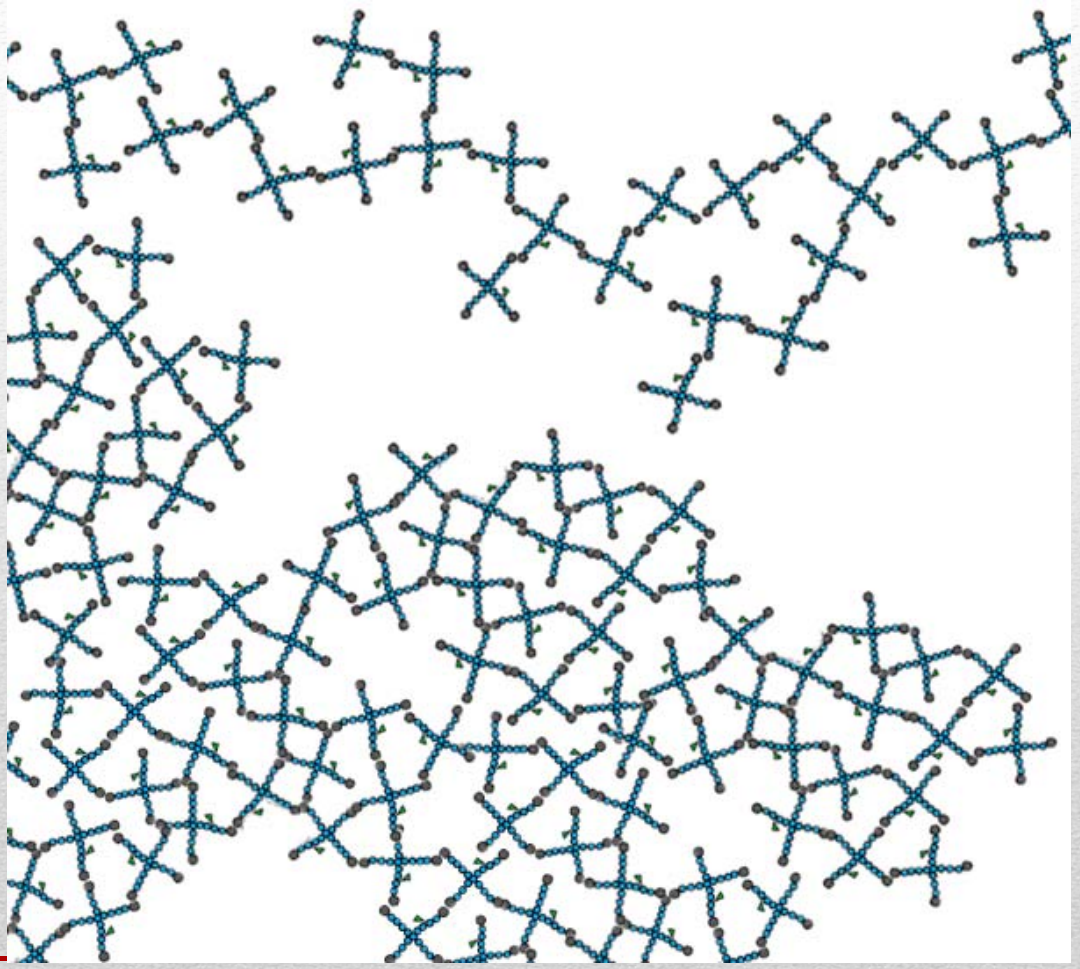
Zona sotto endoteliale

DIFFERENTE DENSITÀ DEL MUCO

Strato di muco fluido
sul lato luminale

Strato di muco compatto
sul lato endoteliale

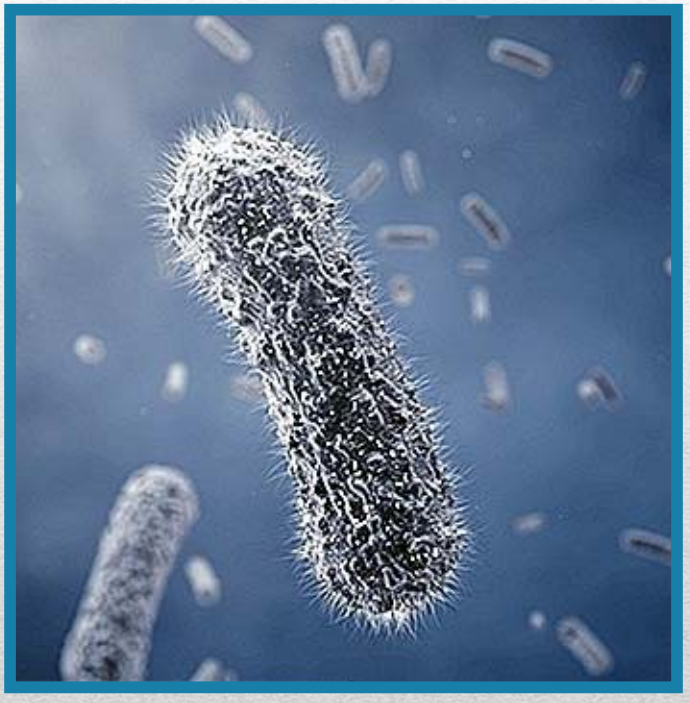
Il muco più fluido ha una struttura meno densa di mucine e un maggiore contenuto d'acqua



ANTIMICROBIAL / ANTI-ADHESIVE EFFECTS OF HMOS

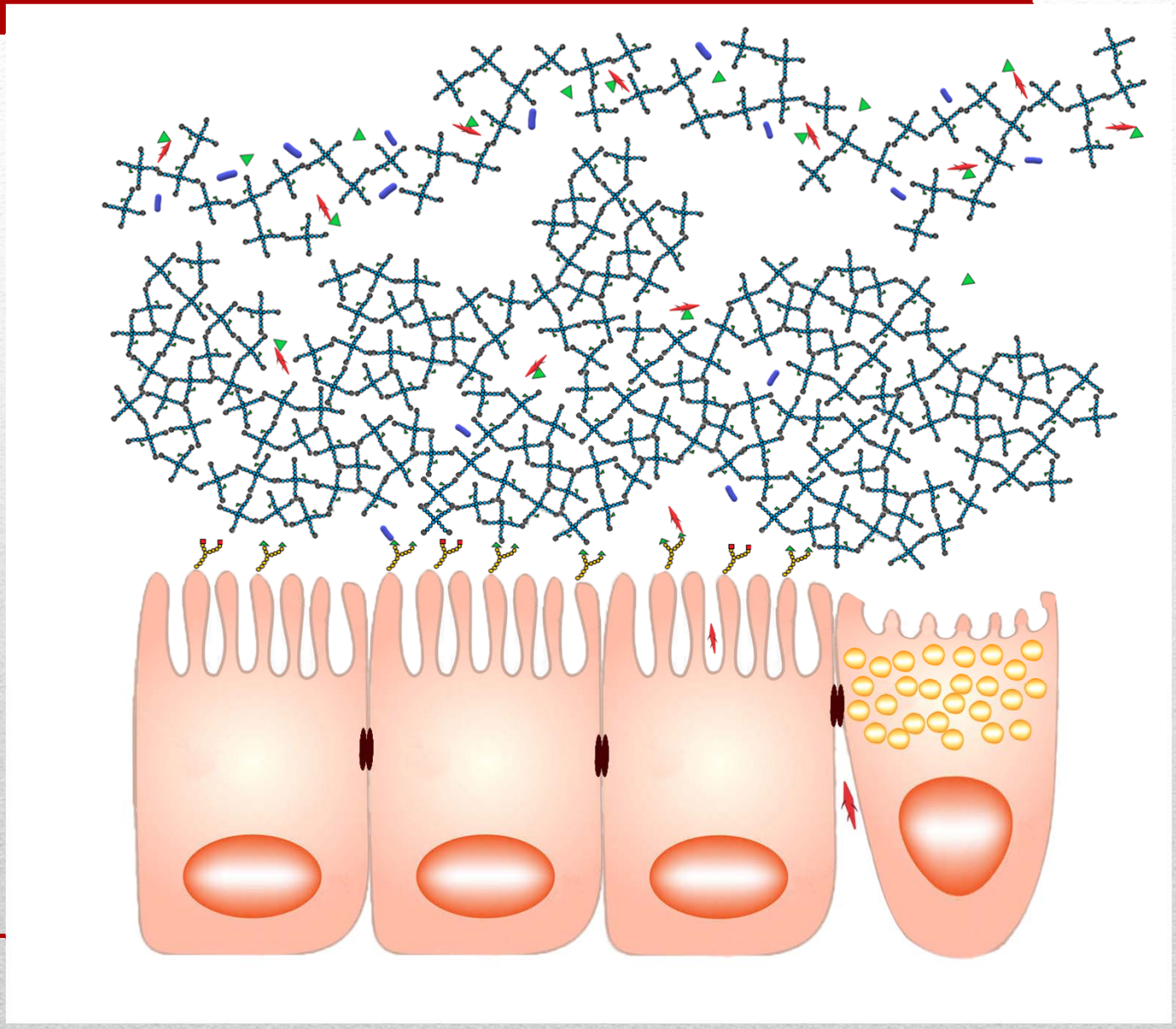
Glycans at the cell surface do not only serve as a target for the adhesion of pathogens, but also for microbial toxins.

The **by the entero-toxinogenic E. Coli induced toxin** is also inhibited by 2-fucosyl oligosaccharides.



Castanys-Munoz et al. Nutrition Reviews 71 (12) : 773-789 / Crane, J.K. et al. J. Nutr. 1994, 124, 2358–2364.

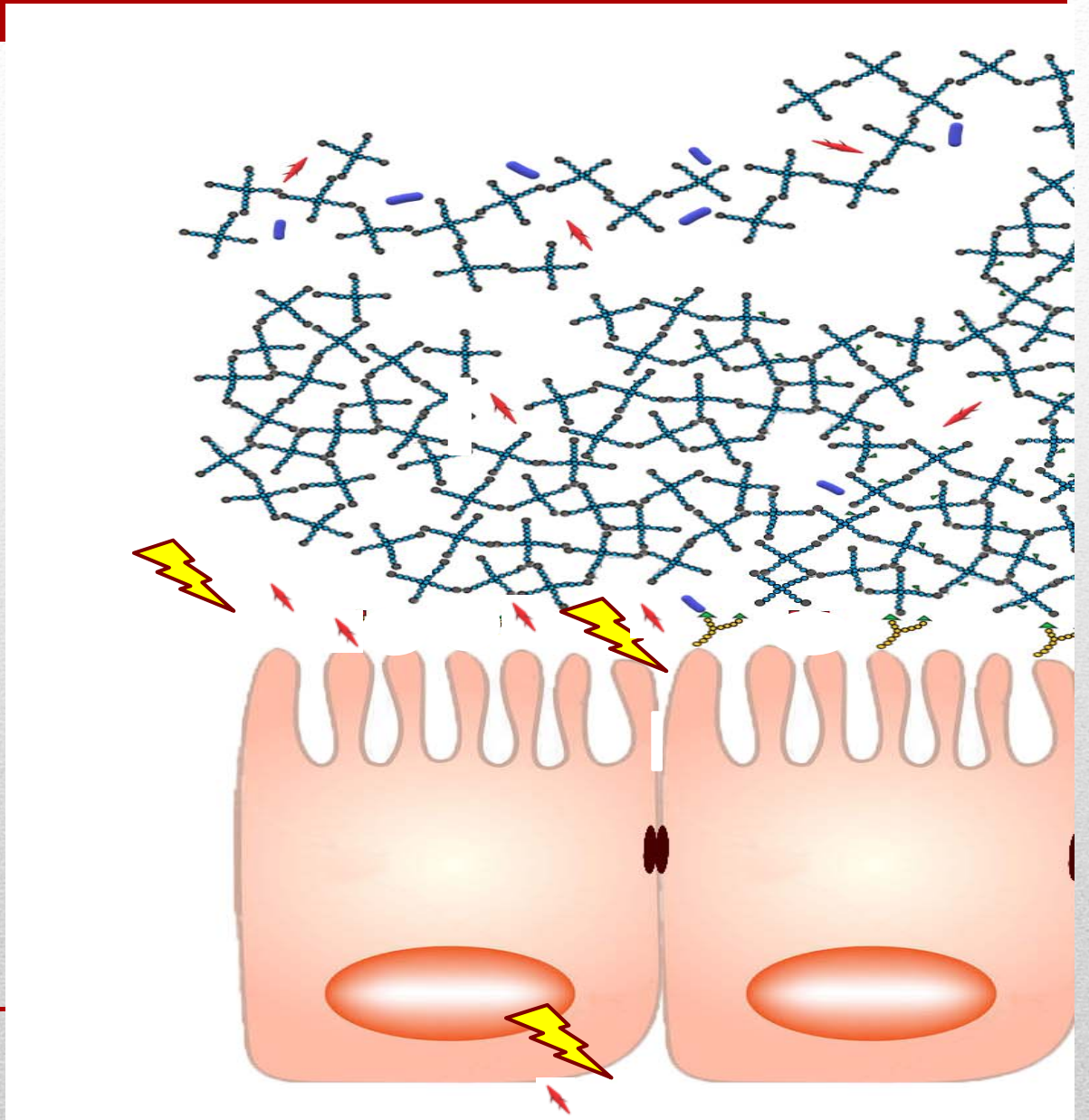
L'integrazione con HMO fornisce siti di adesione liberi che funzionano come "esche per i patogeni"



FUCOSYL TRANSFERASE 2 (FUT 2)

The importance of polymorphism identification in preventive and curative medicine

Nei soggetti con **polimorfismo limitante del FUT2** mancano i siti di adesione fucosilati nel muco fluido e i batteri raggiungono più facilmente gli strati profondi



OXFORD

Human Molecular Genetics, 2016, Vol. 25, No. 18 4127–4142

doi: 10.1093/hmg/ddw264
Advance Access Publication Date: 23 August 2016
Association Studies Article

ASSOCIATION STUDIES ARTICLE

A genome-wide association meta-analysis of diarrhoeal disease in young children identifies *FUT2* locus and provides plausible biological pathways

Mariona Bustamante[1,2,3,4,*,†], Marie Standl[5,†], Quique Bassat[6,7],

Abstract

More than a million childhood diarrhoeal episodes occur worldwide each year, and in developed countries a considerable part of them are caused by viral infections. In this study, we aimed to search for genetic variants associated with diarrhoeal disease in young children by meta-analyzing genome-wide association studies, and to elucidate plausible biological mechanisms. The study was conducted in the context of the Early Genetics and Lifecourse Epidemiology (EAGLE) consortium. Data about diarrhoeal disease in two time windows (around 1 year of age and around 2 years of age) was obtained via parental questionnaires, doctor interviews or medical records. Standard quality control and statistical tests were applied to the 1000 Genomes imputed genotypic data. The meta-analysis ($N = 5758$) followed by replication ($N = 3784$) identified a genome-wide significant association between rs8111874 and diarrhoea at age 1 year. Conditional analysis suggested that the causal variant could be rs601338 (W154X) in the *FUT2* gene. Children with the A allele, which results in a truncated FUT2 protein, had lower risk of diarrhoea. FUT2 participates in the production of histo-blood group antigens and has previously been implicated in the susceptibility to infections, including *Rotavirus* and *Norovirus*. Gene-set enrichment analysis suggested pathways related to the histo-blood group antigen production, and the regulation of ion transport and blood pressure. Among others, the gastrointestinal tract, and the immune and neuro-secretory systems were detected as relevant organs. In summary, this genome-wide association meta-analysis suggests the implication of the *FUT2* gene in diarrhoeal disease in young children from the general population.

This genome-wide association meta-analysis suggests the **implication of the FUT2 gene in diarrhoeal diseases in young children from the general population.**

Human Molecular Genetics, 2010, Vol. 19, No. 17 **3468–3476**
doi:10.1093/hmg/ddq248
Advance Access published on June 22, 2010

Fucosyltransferase 2 (FUT2) non-secretor status is associated with Crohn's disease

Dermot P.B. McGovern[1,2,*], Michelle R. Jones[3], Kent D. Taylor[2], Kristin Marciante[4], Xiaofei Yan[2], Marla Dubinsky[1], Andy Ippoliti[1], Eric Vasiliauskas[1], Dror Berel[1], Carrie Derkowski[1], Deb Dutridge[2], International IBD Genetics Consortium, Phil Fleshner[1], David Q. Shih[1], Gil Melmed[1], Emebet Mengesha[2], Lily King[2], Sheila Pressman[2], Talin Haritunians[2], Xiuqing Guo[2], Stephan R. Targan[1] and Jerome I. Rotter[2]

[1]Inflammatory Bowel and Immunobiology Research Institute, [2]Medical Genetics Institute and [3]Endocrinology, Diabetes & Metabolism, Cedars-Sinai Medical Center, Los Angeles, CA, USA and [4]Cardiovascular Health Research Unit, Department of Internal Medicine, University of Washington, Seattle, WA, USA

Received January 19, 2010; Revised June 3, 2010; Accepted June 10, 2010

Genetic variation in both innate and adaptive immune systems is associated with Crohn's disease (CD) susceptibility, but much of the heritability to CD remains unknown. We performed a genome-wide association

We demonstrated replication in an independent cohort of 1174 Crohn Disease cases and 357 controls between the **four primary FUT2 single nucleotide polymorphisms** (SNP) and CD, and even their association with FUT2.

Further evidence of the relevance of this locus to the CD pathogenesis was demonstrated by the **association of the original four SNPs and CD** in the recently published CD GWAS meta-analysis.

These findings strongly implicate **this locus in CD susceptibility and highlight the role of the mucus layer in the development of CD**.

Clin Rev Allergy Immunol. 2015 Jun;48(2-3):182-91. doi: 10.1007/s12016-014-8423-1.

Fucosyltransferase 2: a genetic risk factor for primary sclerosing cholangitis and Crohn's disease--a comprehensive review.

Maroni L[1], van de Graaf SF, Hohenester SD, Oude Elferink RP, Beuers U.

Author information

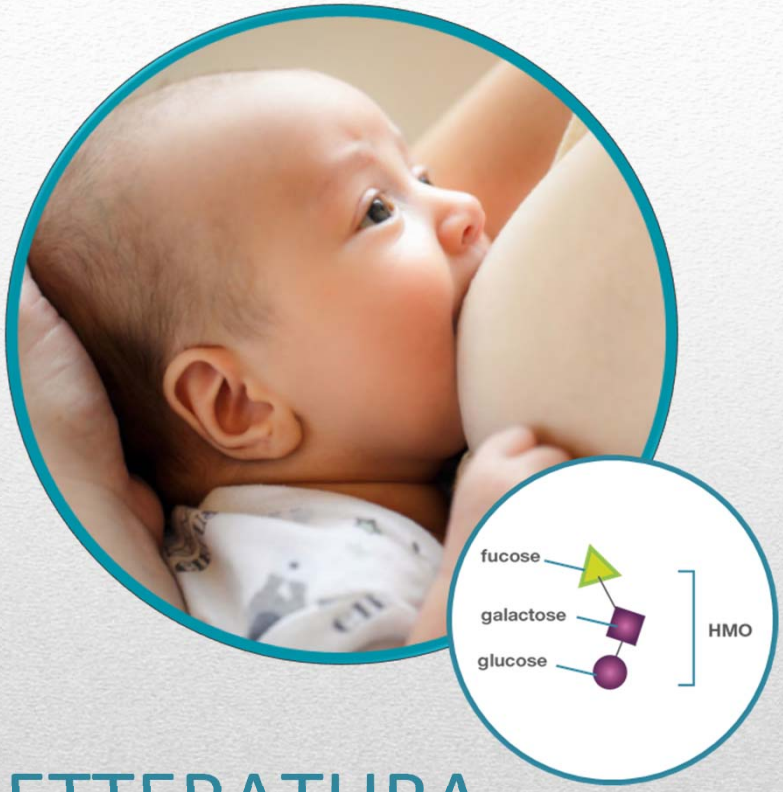
In recent years, genome-wide association studies (GWAS) identified inactivating variants at the FUT2 locus to be associated with primary sclerosing cholangitis (PSC), Crohn's disease (CD) and biochemical markers of biliary damage.

These associations are intriguing given the important role of fucosylated glycans in host-microbe interactions and membrane stability.

Non-secretors have a reduced fecal content of Bifidobacteria. The intestinal bacterial composition of CD patients resembles the one of non secretors, with an increase in Firmicutes and decreases in Proteobacteria and Actinobacteria.

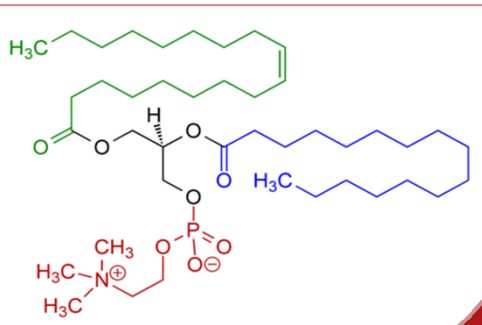
Non-secretor individuals lack fucosylated glycans at the surface of the biliary epithelium and display a different bacterial composition compared to secretors. Notably; an intact biliary epithelial glycocalix is relevant for the protection against toxic effects of hydrophobic bile salt monomers.

Here the biology of FUT2 will be discussed as well as the hypotheses **to explain the role of FUT2 in the physiopathology of PSC and Crohn's disease**.



SELEZIONE DELLA LETTERATURA SCIENTIFICA RILEVANTE

What are lectins?



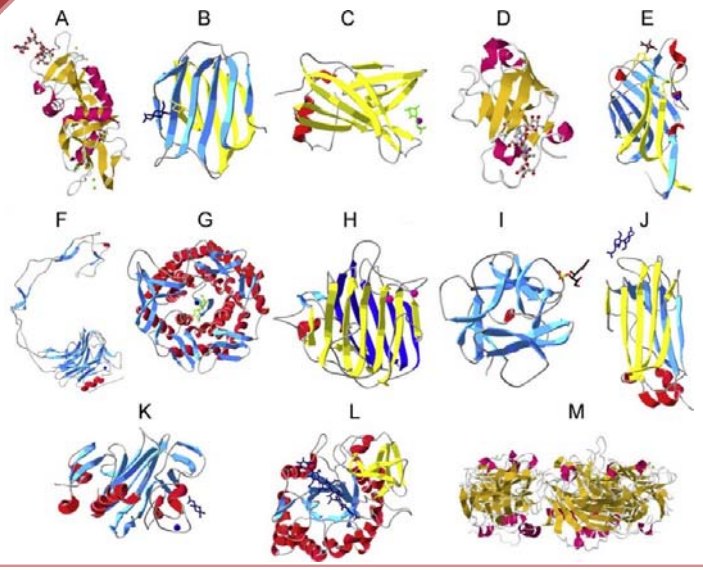
Lectins are omnipresent proteins that play a vital function in the plants resistance against insect pests and have been found to be deadly to viruses, bacteria, fungi, insects, and prominent animals.

Lectins are sugar-binding proteins that are extremely specific for their sugar molecules.

They are carbohydrate-binding proteins of nonimmune

Temperament.

They are considered **anti-nutrients** as they reduce nutrient absorption (Calcium, iron, phosphorus, zinc).



Plant Signaling & Behavior 8:12, e26595; December 2013;

Hindawi Publishing Corporation
Gastroenterology Research and Practice
Volume 2017, Article ID 4148651, 6 pages
http://dx.doi.org/10.1155/2017/4148651

Research Article

Association of Fucosyltransferase 2 Gene Polymorphisms with Inflammatory Bowel Disease in Patients from Southeast China

Hao Wu,[1,2] Liang Sun,[2] Dao-po Lin,[2] Xiao-xiao Shao,[2] Sheng-long Xia,[2] and Ming Lv[1]

[1] *Qilu Hospital, Shandong University, Ji'nan, Shandong 250012, China*
[2] *Department of Gastroenterology, The Second Affiliated Hospital, Wenzhou Medical University, Wenzhou, China*

Correspondence should be addressed to Ming Lv; lvming@sdu.edu.cn

Received 24 October 2016; Accepted 14 December 2016; Published 12 January 2017

Academic Editor: Paolo Gionchetti

Aims. Fucosyltransferase 2 (*FUT2*) gene potentially affects the constituent of intestinal microbiota, which play a crucial role in the pathogenesis of inflammatory bowel disease (IBD). This study investigated the association of *FUT2* gene polymorphisms with

Fucosyltransferase 2 gene (FUT2) potentially affects the constituent of the intestinal microbiota which play a crucial role in the pathogenesis of inflammatory bowel disease.

Results: The frequency of the allele and the FUT2-genotype did not differ between ulcerative colitis patients and controls. The **polymorphisms and FUT2 gene haplotypes are significantly associated with the susceptibility to CD.**

Br J Nutr. 2000 Mar;83(3):207-17.

Modulation of immune function by dietary lectins in rheumatoid arthritis.

Cordain L[1], Toohey L, Smith MJ, Hickey MS.

Author information

Abstract

Despite the almost universal clinical observation that inflammation of the gut is frequently associated with inflammation of the joints and vice versa, the nature of this relationship remains elusive. In the present review, we provide evidence for how the interaction of dietary lectins with enterocytes and lymphocytes may facilitate the translocation of both dietary and gut-derived pathogenic antigens to peripheral tissues, which in turn causes persistent peripheral antigenic stimulation. In genetically susceptible individuals, this antigenic stimulation may ultimately result in the expression of overt rheumatoid arthritis (RA) via molecular mimicry, a process whereby foreign peptides, similar in structure to endogenous peptides, may cause antibodies or T-lymphocytes to cross-react with both foreign and endogenous peptides and thereby break immunological tolerance. By eliminating dietary elements, particularly lectins, which adversely influence both enterocyte and lymphocyte structure and function, it is proposed that the peripheral antigenic stimulus (both pathogenic and dietary) will be reduced and thereby result in a diminution of disease symptoms in certain patients with RA.

PMID: 10884708

[Indexed for MEDLINE]

Pediatr Allergy Immunol. 1995 May;6(2):98-102.

Elevated levels of serum antibodies to the lectin wheat germ agglutinin in celiac children lend support to the gluten-lectin theory of celiac disease.

Fälth-Magnusson K[1], Magnusson KE.

Author information

Abstract

Lectins recognize carbohydrate moities of glycoproteins and glycolipids, and can elicit several biological effects, including cell agglutination, cell activation and mitogenesis. According to the gluten-lectin theory, celiac lesions represent a response to a toxic lectin, putatively wheat germ agglutinin (WGA). In this study we compared the serum antibody levels IgA, IgG and IgM to WGA and to gliadin in children under investigation for celiac disease (CD), as compared to reference children. We found that the levels of IgA and IgG to WGA as well as gliadin were significantly higher in celiac children on a gluten-containing diet, compared to children on gluten-free diet and reference children. These findings lend support to the concept that WGA is a biologically significant component of gluten. Since WGA can mimic the effects of epidermal growth factor (EGF) at the cellular level, we hypothesize that the crypt hyperplasia seen in celiac children could be due to a mitogenic response induced by WGA.

PMID: 7581728

[Indexed for MEDLINE]

Contrazioni motorie gastrointestinali

Diversi HMO hanno un pronunciato effetto sulle contrazioni motorie gastrointestinali, come indicato da un modello di peristalsi di colon murino in vitro.

Il 2'-fucosillattosio (2'-FL) e 3'-fuco- sillattosio (3'-FL) hanno ridotto la contrattilità in modo concentrazione-dipendente.

Il fucosio e le molecole fucosilate hanno avuto l'effetto immediato di ridurre la contrattilità del muscolo liscio del colon **entro 5-10 minuti dall'applicazione**.

È improbabile che questi effetti degli HMO avvengano mediante stimolazione dei bifidobatteri, ma piuttosto tramite azione diretta su complessi motori neurone-dipendenti.

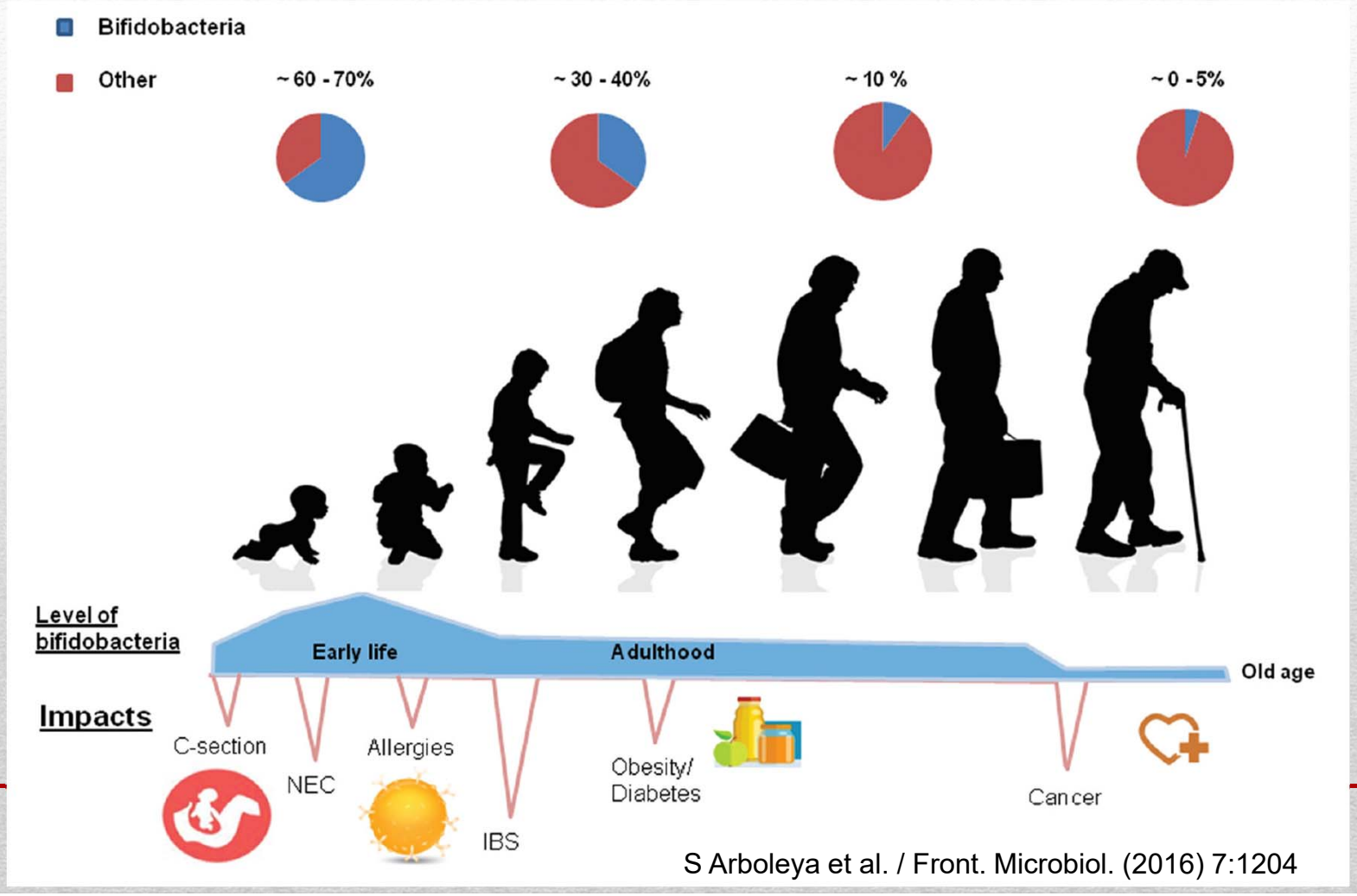
Questi risultati suggeriscono una specifica interazione di fucosio e/o HMO fucosilati con i recettori dei tessuti che, a loro volta, regolano la motilità intestinale e possono anche dimostrare attività anti-nocicettiva.

Queste osservazioni supportano l'ipotesi che gli HMO fucosilati possano essere utili come supporto terapeutico o preventivo nelle patologie di motilità intestinale e dolore intestinale e possano inoltre, anche avere effetti benefici sul sistema nervoso centrale.

Bienenstock J, Buck RH, Linke H et al (2013) Fucosylated but not sialylated milk oligosaccharides diminish colon motor con-tractions. PLoS ONE 8:e76236

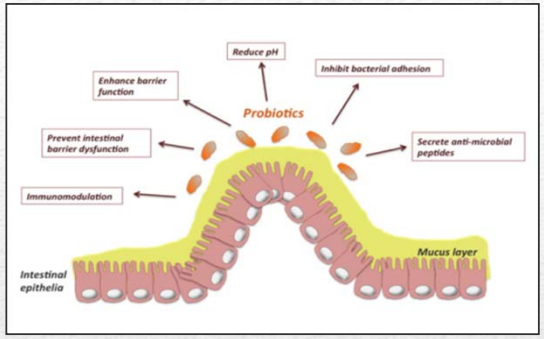
Gut Bifidobacteria Populations in Human Health and Aging

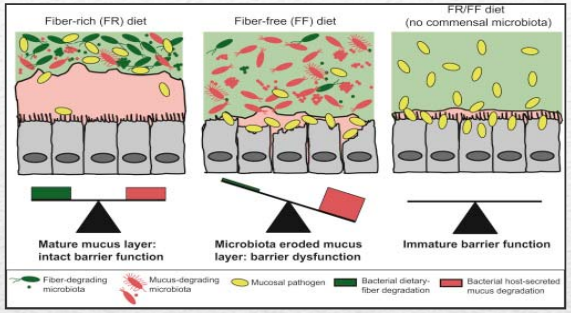
*Silvia Arboleya[1,2], Claire Watkins[1,2,3], Catherine Stanton[1,2] and R. Paul Ross[1,2,4]**



S Arboleya et al. / Front. Microbiol. (2016) 7:1204

Strategies for microbiota modulation in the adults





- Nutrition
- Pro-/prebiotics
- Mucus production and mucin glycan modification
- Fecal transplantation

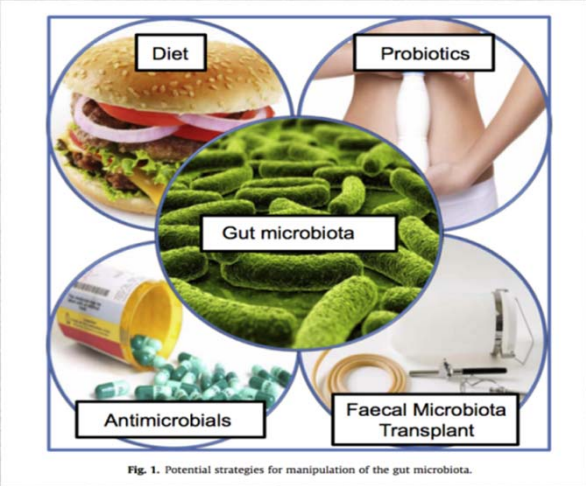
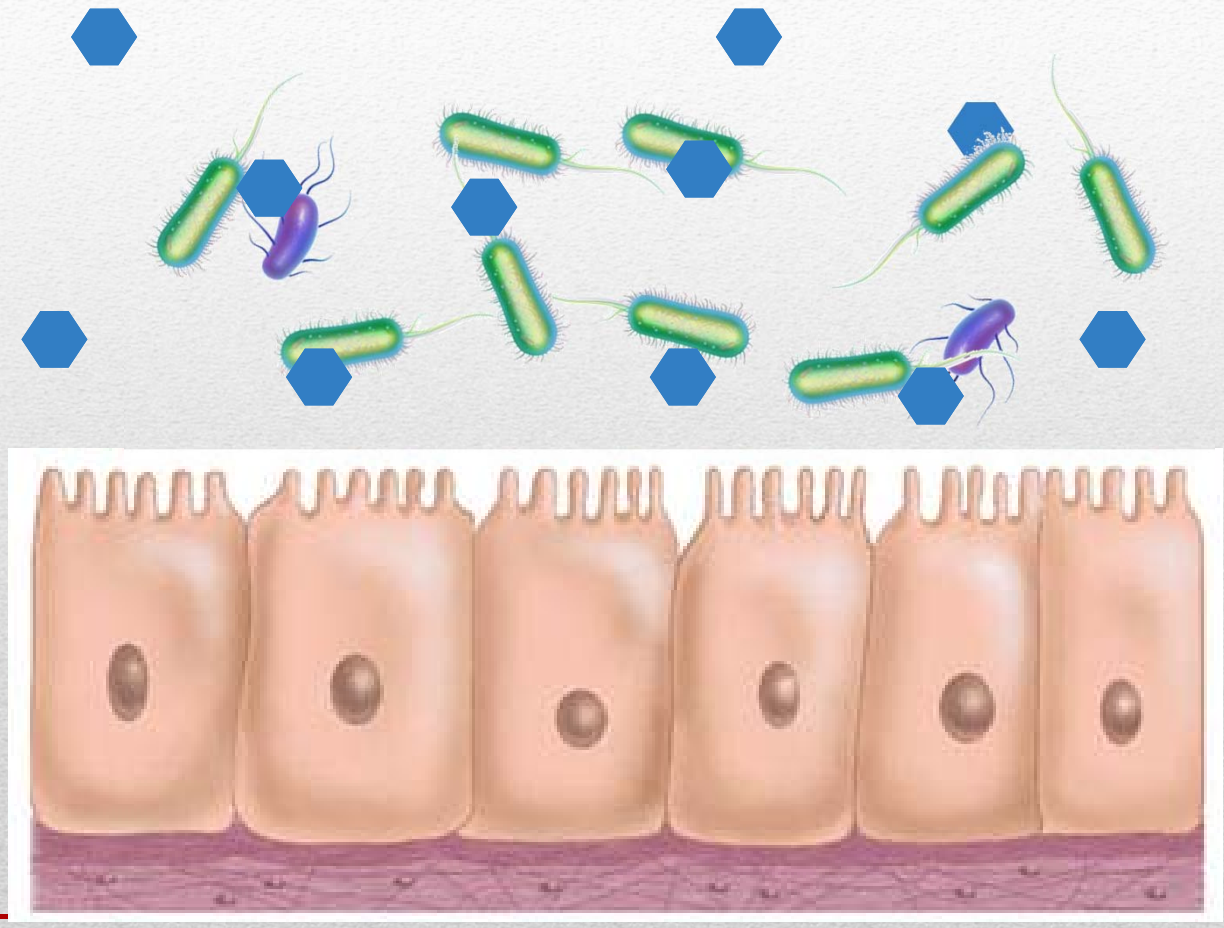


Fig. 1. Potential strategies for manipulation of the gut microbiota.

Walsh et al, 2014

PREBIOTIC EFFECTS OF HMOs

- Very bifidogenic
- Get untouched in the colon (no production of fucosidases in humans)
- Used as substrate by the bacteria of the microbiota
- Improve the variability and balance of the microbiota



Ward RE et al. (2006) Appl Environ Microbiol 72:4497-9 / Sela DA et al. (2008) PNAS 105:18964-9

ANTIMICROBIAL / ANTI-ADHESIVE EFFECTS OF HMOS

Annu Rev Nutr. 2000;20:699-722.

Oligosaccharides in human milk: structural, functional, and metabolic aspects.

Kunz C[1], Rudloff S, Baier W, Klein N, Strobel S.

Author information

Abstract

The similarities between epithelial cell surfaces and human milk oligosaccharides strengthen the idea that specific interactions of those oligosaccharides with pathogenic microorganisms do occur preventing the attachment of microbes to epithelial cells.

HMOs may act as soluble receptors for different pathogens, thus increasing the resistance of breast-fed infants.

oligosaccharides in the gastrointestinal tract. How far are oligosaccharides degraded by intestinal enzymes and does oligosaccharide processing (e.g. degradation, synthesis, and elongation of core structures) occur in intestinal epithelial cells? Further research on HMOs is certainly needed to increase our knowledge of infant nutrition as it is affected by complex oligosaccharides.