



# November Educational Event



Food Intolerance:  
Re-challenging  
our approach





# Snap shot

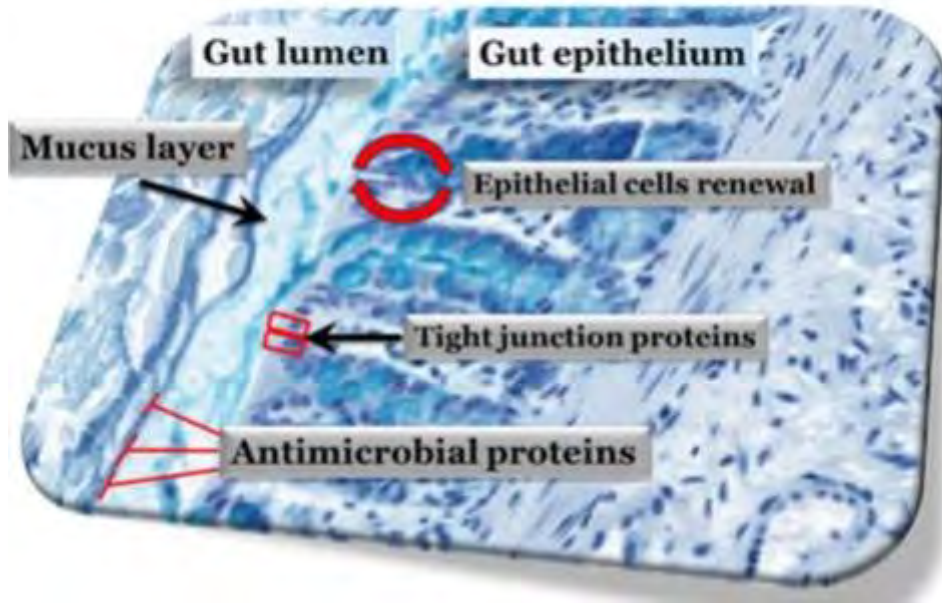
- The importance of function of the gut barrier
- Food allergies and intolerances
- Elimination and rotation eating styles
- Nutritional considerations





# Adverse reactions to food

## The gut barrier function



Food intolerances and food allergies are defined as **“adverse reactions to food”**.

They are a rapidly increasing problem in the western world and according to the World Allergy Organization (WAO) 220-250 million people are affected. The trend continues to rise, especially in children.



# Why do we need a gut barrier?

The intestinal barrier covers a surface of about 400 m<sup>2</sup> and requires approximately 40% of the body's energy expenditure. It prevents against loss of water and electrolytes and entry of antigens and microorganisms into the body, while allowing exchange of molecules between host and environment and absorption of nutrients in the diet.

Specialized adaptations of the mammalian intestinal mucosa fulfil two seemingly opposing functions: firstly to allow a peaceful co-existence with intestinal symbionts without eliciting chronic inflammation and secondly to provide a measured inflammatory and defensive response according to the threat from pathogens.

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

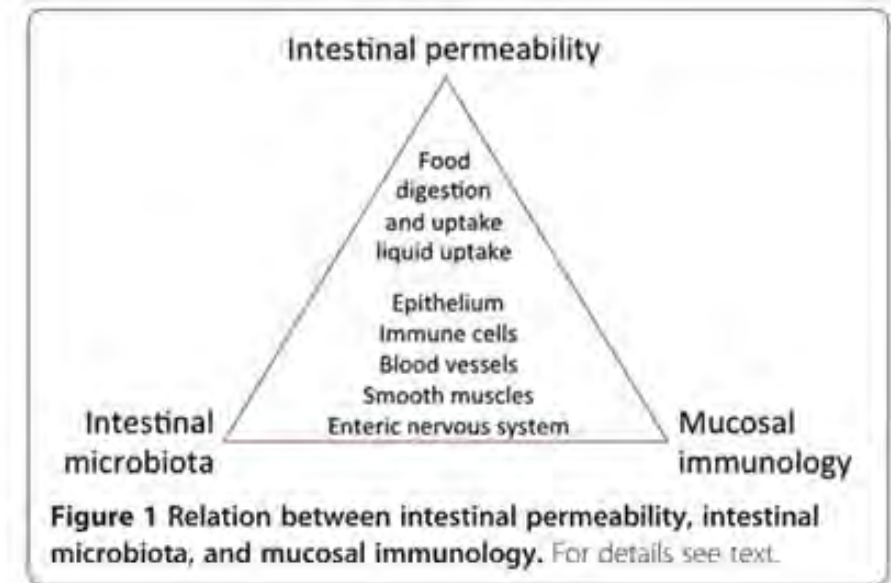


REVIEW

Open Access

## Intestinal permeability – a new target for disease prevention and therapy

Stephan C. Bischoff<sup>1\*</sup>, Giovanni Barbara<sup>2</sup>, Wim Buurman<sup>3</sup>, Theo Ockhuizen<sup>4</sup>, Jörg-Dieter Schulzke<sup>5</sup>, Matteo Serino<sup>6</sup>, Herbert Tilg<sup>7</sup>, Alastair Watson<sup>8</sup> and Jerry M Wells<sup>9</sup>





# Intestinal mucosal membranes

## Table 1 Definitions

<b>Intestinal barrier</b>	<i>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</i>
<b>Intestinal permeability</b>	<i>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</i>
<b>Normal intestinal permeability</b>	<i>is defined as a stable permeability found in healthy individuals with no signs of intoxication, inflammation or impaired intestinal functions</i>
<b>Impaired intestinal permeability</b>	<i>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</i>



# Mucosal gut barrier

- The mucosal barrier the complex structure that separates the internal milieu from the luminal environment.
- The physical barrier includes a cellular component consisting of the vascular endothelium, the epithelial cell lining, and the mucus layer.
- Next to this physical barrier, chemical substances take part in the barrier function as well. They consist of digestive secretions, immune molecules, cell products like cytokines, inflammatory mediators and anti-microbial peptides, mainly produced by Paneth cells in the crypts of the small intestine.
- The intestinal microbiota is involved in metabolic processes and modulates the barrier, but does not represent a barrier function per se. On the other hand, the microbiota contributes to "intestinal health".
- The intestinal wall composed of four layers, the mucosa, the submucosa, the muscularis and the serosa.
- "Intestinal barrier" is a term that has been established more recently by gastroenterologists, immunologists and microbiologists to emphasize the protective component of the gut shielding us against bacterial invasion, or invasion of other microorganisms and their toxins.



# Tight junctions

A single layer of epithelial cells form the main physical barrier between the lumen and mucosal tissues. The paracellular space is sealed by tight junctions (TJ) which regulate the flow of water ions and small molecules through the composition of claudins and other proteins in the junctional complex.

TJ complexes consist of intra-membrane proteins, occludin and different members of the claudin family depending on the tissue and location that interlink within the paracellular space.

Tricullin and occludin as well as a new protein named marvelD3, can be replaced in part by each other, but if all three are down-regulated or lacking, severe leakage occurs.

Claudins are a family of tight junction proteins consisting of sealing molecules and pores facilitating water and electrolyte loss. Zonula occludens proteins (ZO-1, ZO-2 and ZO-3) are important intracellular tight junction proteins, linking the cell cytoskeleton to the transmembrane tight junction proteins.

Whereas occludin and junction adhesion molecule have a regulatory role, claudins are transmembrane proteins mainly responsible for the intestinal barrier function.

A central regulator of this epithelial barrier is the intestinal microbiota.



# Disruptions of the gut barrier

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*Endocrine, Metabolic & Immune Disorders - Drug Targets, 2014, 14, 67-75*

67

## **Abundance and Diversity of GI Microbiota Rather than IgG<sub>4</sub> Levels Correlate with Abdominal Inconvenience and Gut Permeability in Consumers Claiming Food Intolerances**

Berit Hippe<sup>1</sup>, Marlene Remely<sup>1</sup>, Natalie Bartosiewicz<sup>1</sup>, Monika Riedel<sup>2</sup>, Claudia Nichterl<sup>3</sup>, Lulit Schatz<sup>4</sup>, Sandra Pummer<sup>5</sup> and Alexander Haslberger<sup>1,\*</sup>

Food intolerances are an increasing global health problem. Interactions between genetics and environmental changes such as microbial- and stress factors remain poorly understood.

The present pilot study analyses forty participants, under consultation of nutritional health professionals, for gastrointestinal discomfort and claimed food intolerances.





# Disruptions of the gut barrier

Experimental data showed that disruption of the peaceful co-existence with intestinal symbionts at early life, and possibly even later in life, results in severe immunodeficiency and risk of disease.

Many factors can alter intestinal permeability such as gut microbiota modifications, mucus layer alterations, and epithelial damage, resulting in translocation of luminal content to the inner layers of the intestinal wall.

Moreover, lifestyle and dietetic factors like alcohol and energy-dense food can increase intestinal permeability such as alcohol and energy-dense Western style diet.

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# Permeability and food processing

Increased passage of glycated compounds into the systemic circulation is expected to induce at least two pathological situations: allergies and metabolic disorders.

Exposure of intestinal CaCO<sub>2</sub> cells to methylglyoxal or glyoxal, two potent glycating metabolites, in vitro is followed by increased IL-6 and IL-8 formation, which amplify the effects of TNF- $\alpha$  and IL-1 $\beta$ .

Some data suggest that AGEs may cause intestinal inflammation on their own. IL-9 has been reported to play a particularly important role in allergy by mediating the mast cell response.

IL-9 deficient mice do not develop anaphylaxis, whereas IL-9 overexpression does produce anaphylaxis

## BRINGING IDEAS TOGETHER

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### POSSIBLE LINKS BETWEEN INTESTINAL PERMEABILITY AND FOOD PROCESSING: A POTENTIAL THERAPEUTIC NICHE FOR GLUTAMINE

Jean Robert Rapin,<sup>1,2,3</sup> Nicolas Wiernsperger<sup>1,2,3</sup>

doi: [10.1590/S1807-59322010000600012](https://doi.org/10.1590/S1807-59322010000600012)

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Rapin JR, Wiernsperger N. Possible links between intestinal permeability and food processing: a potential therapeutic niche for glutamine. Clinics. 2010;65(6):635-43.



# Food allergies and intolerances

- In a recent study released by the Center for Disease Control (2013), it was reported that between the years of 1997 and 2011, food allergies among children increased 50%.
- The number of food allergies is increasing, but the cause is unknown.
- The rate of anaphylaxis reactions after exposure to food is increasing, as well.
- Food allergy conditions are a complex diagnosis; each individual is affected differently.
- It is also a difficult area of epidemiological, toxicological, or medicinal research because many food allergies are self-reported without qualifying or quantifying metrics (such as pathology, symptom, or biomarker identification).

Journal of Environmental Science and Public Health  
doi: 10.26502/JESPH.003

**fortune**  
Journals

Volume 1, Issue 1

Review Article

## Environmental Factors Contribute to the Onset of Food Allergies

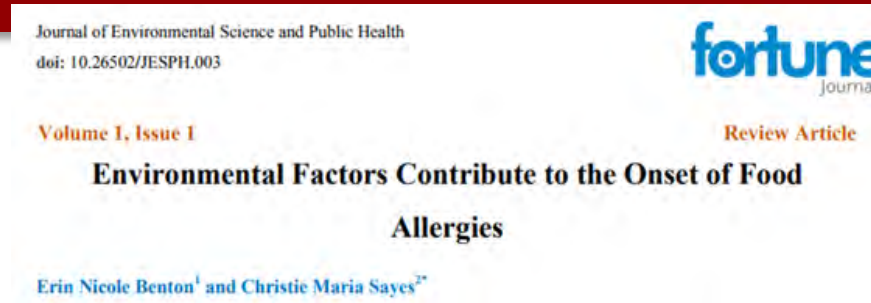
Erin Nicole Benton<sup>1</sup> and Christie Maria Sayes<sup>2\*</sup>



**Figure 1:** The progression of food allergy diagnosis. This figure shows the possible interactions a body can have to an allergen. The three stages are: no sensitivity to the food, food sensitivity, and food allergy.



# Food allergies and intolerances



- While no literature has yet to prove causation, a few articles have proposed possible correlations. Within the environmental construct of food and food delivery, the individual's culture often promotes specific allergic reactions; if a food is not eaten in the population, then tolerance to the food is never developed, thus can result in a food allergy.
- Researchers know that the environment plays a role in the development of food allergies, but few have studies have found concrete evidence to support the role that the environment plays. Some possible roles the environment contributes to food allergies include: traffic pollution, animal exposure, farm environment, smoking, and air pollution.
- Any allergy has the potential to triggers a life threatening immune response. A sensitivity (also referred to as an intolerance) is generally not life threatening, but does result from the inability to metabolize or digest a food completely.
- The majority of studies that focus on food allergies tend to avoid the more mild and less complex food intolerances or sensitivities.
- There evidence to suggest, however, that some food sensitivities can lead to food allergies over time.



# IgE vs IgG mediated responses?

Among the food intolerances, an IgE-mediated allergy is well understood. Also mechanisms of lactose intolerance, histamine intolerance, and fructose intolerance are well described.

In contrast many aspects in the area of non IgE-mediated intolerances remain poorly understood.

IgG1 is formed as the initial response after contact with a new food antigen.

With further exposure to the antigen, a change in the formation of IgG4 antibodies seems to take place.

Following this change the amount of IgG4 rises from 3% up to 50%.

High IgG4 concentrations may indicate an intense conflict of the immune system with food antigens.

The synthesized IgG4 antibodies are suspected to sensitise cells, but may also block the IgE mediated allergic response.

Hippe, Berit, et al. "Abundance and diversity of GI microbiota rather than IgG4 levels correlate with abdominal inconvenience and gut permeability in consumers claiming food intolerances." *Endocrine, Metabolic & Immune Disorders-Drug Targets (Formerly Current Drug Targets-Immune, Endocrine & Metabolic Disorders)* 14.1 (2014): 67-75.



# IgG food sensitivities

- IgG antibodies are associated with delayed hypersensitivity reactions, which are the most common—and sometimes the most difficult to detect— type of food reaction.
- These delayed or “hidden” food reactions can cause a variety of chronic symptoms. Since IgG reactions occur several hours or even days later, there may be no obvious association between consuming a food and an adverse reaction.
- Food IgG levels increase in response to the presence of the food antigens that penetrate a weakened intestinal barrier and enter the bloodstream, particularly with commonly eaten foods (e.g., corn, wheat, dairy, and egg).



# Key points to remember

- If you were not consuming a tested food, the test probably will not show a positive reaction.
- If you are already on an elimination diet due to known food reactions, a negative result on an IgG food antibody profile does not necessarily mean you can freely eat the food without experiencing symptoms
- Complete elimination of all highly reactive foods for one month, and rotation of ones with low levels, can relieve symptoms related to this type of food reaction.



# Elimination of Foods

1. All foods classed as +2 or higher on your lab report should be eliminated for 4 weeks.
2. After 4 weeks, reintroduce each food one-at-a-time and wait one week before introducing the next food.
3. Record the date and time each food is eaten and any reactions or symptoms that occur.
4. If no reactions occur after 72 hours, add the food into the rotation diet. If adverse reactions are experienced, continue to eliminate the food and try to reintroduce it again in 2-4 weeks.
5. All foods that are categorised as mild should be eaten only once every four days.





# Elimination and detoxification

- Although there are currently no proven methods to overcome a diagnosed food allergy, there are some potential ways to overcome a sensitivity related food illness.
- The first step includes completely eliminating the food from the diet, avoidance of the trigger response.
- The second step includes biochemical restoration.
- This is the body repairing itself since it is no longer experiencing illness.
- The third and final step is elimination of bioaccumulated toxicant load.

Journal of Environmental Science and Public Health

doi: 10.26502/JESPH.003



Volume 1, Issue 1

Review Article

## Environmental Factors Contribute to the Onset of Food Allergies

Erin Nicole Benton<sup>1</sup> and Christie Maria Sayes<sup>2\*</sup>





# Rotation style eating plan

## How to Use a Rotation eating plan

- If you have multiple food allergies, one way that may help is to “rotate” your foods, or eat a rotation diet. A rotation diet is a system of controlling food allergies by eating biologically related foods on the same day and then waiting at least four days before eating them again.
- Rotation diets may help to prevent the development of allergies to new foods. Any food, if eaten repetitively, can cause food allergies in allergy-prone individuals or people with intestinal permeability.
- A common occurrence when an individual finds out they have a food intolerance or sensitivity is to permanently eliminate the foods. As a result the new foods that take predominance can become new intolerances in years to come. This is not rectifying the underlying problem.
- A rotation diet allows you to eat foods to which you have a mild or borderline allergy and which you might not tolerate if you ate them often. Sometimes your reaction to borderline foods may depend on your stress level, other illness or infection, lack of adequate rest, or the season of the year.
- The rotations style eating plan is not a long term treatment. After removing high allergen foods for a certain time frame it can be advised to add them back into the diet in moderation and on a rotated schedule. Treating the root causes of your food allergies can may lead to improvement in your ability to tolerate foods.
- A rotation diet alone is not “the answer” to food intolerances, it is however a tool that can be utilised to help support our patients while we are helping to balance their health.





# Rotation Diet

1. Your rotation diet is divided into 4 days. Do not include any foods that showed moderate or severe reactions.
2. Start with Day 1 and after Day 4, go back to the Day 1 column for Day 5, and so on.
3. Consume a variety of foods including vegetables, fruits, and protein-rich foods daily for optimal nutrition.
4. Following this diet will assure that no one food is eaten more often than once every four days, which prevents food addictions and reactions.
5. Once you have reintroduced the moderate and severely reactive foods without experiencing any adverse reactions, you may incorporate them into one of the four days of your rotation diet.



# Why rotation?

*Generally, rotation dieting greatly enhances a person's awareness of what foods his/her body does and doesn't handle well, again resulting in one being less likely to keep overstimulating her/his immune system.*

*Also helps to reduce local inflammation of the mucous membranes and gap junctions.*

## Food group information?

Rotation style eating plans are aimed at rotating foods to decrease the load or burden on the immune system, while providing optimal nutrient quantities and diversity

When we eliminate favourite foods from the diet, we sometimes compensate by over-eating a substitute for a food we are missing. This can cause new food allergies or sensitivities to surface.



# Advantages of a rotational eating plan

## Advantages of the Four Day Rotation Diet

- By allowing the body's immune system to recover from the effects of a challenging food, current food allergies begin to mitigate.
- Helps to reduce the chance of developing new/additional allergies
- Encourages diet diversity by providing a wide range of nutritional choices.
- Discourages the over-indulgence of one food to compensate for the removal of another.
- Aids in identifying foods that could be causing problems.

Food Group	Day 1	Day 2	Day 3	Day 4
<b>Primary Protein</b>	<b>Bird:</b> chicken, turkey, duck, pheasant, all types of eggs <b>Ovis:</b> lamb, mutton, sheep <b>Legume:</b> tolu	<b>Swine:</b> pork, ham, bacon <b>Crustacean:</b> crab, shrimp, lobster, crayfish <b>Mollusk:</b> snail, squid, clam, oyster, scallop	<b>Fish:</b> saltwater, freshwater	<b>Bovine:</b> beef/bison, beef/bison products, milk and dairy products, such as butter, cheese, ice cream
<b>Vegetables</b>	<b>Parsley:</b> carrots, celery, parsley, parsnips, fennel <b>Sedge:</b> water chestnuts <b>Legume:</b> green beans, peas, navy beans, etc. <b>Goosefoot:</b> spinach, beet, chard, beetroot, sugar beet	<b>Morning Glory:</b> sweet potato, yam <b>Gourd:</b> cucumber, squashes, pumpkin, casaba, zucchini, marrow <b>Fungi:</b> mushrooms, truffle <b>Grass:</b> bamboo shoots, corn	<b>Mustard:</b> broccoli, Brussels sprouts, cabbage, kale, watercress, turnip, cauliflower, radish, mustard greens <b>Algae:</b> dulse, kelp <b>Olive:</b> green, black	<b>Nightshade:</b> eggplant, hot peppers, tomato, potato, bell peppers <b>Lily:</b> asparagus, chives, garlic, leek, onion <b>Aster:</b> endive, artichoke, Jerusalem artichoke, lettuce, escarole, chicory, stevia <b>Mallow:</b> okra
<b>Fruit</b>	<b>Laurel:</b> avocado <b>Banana:</b> banana, plantain <b>Palm:</b> coconut, date, sago <b>Pineapple:</b> pineapple <b>Mulberry:</b> figs, breadfruit <b>Pomegranate:</b> pomegranate	<b>Cashew:</b> mango <b>Citrus:</b> orange, grapefruit, lemon, lime, kumquat, tangerine, tangelo <b>Grape:</b> grape, raisins, wine, wine vinegar <b>Rose Berries:</b> blackberry, raspberry, strawberry <b>Gourd:</b> cantaloupe, honeydew, melons, watermelon	<b>Heath:</b> blueberry, cranberry <b>Rose Pomes:</b> apple, apple cider vinegar, pear, quince, loquat <b>Papaya:</b> papaya <b>Soapberry:</b> lichi <b>Honeysuckle:</b> elderberry <b>Ebony:</b> persimmons <b>Actinidiaceae:</b> kiwi <b>Myrtle:</b> guava	<b>Plum:</b> apricot, cherry, peach, plum, nectarine, prune, chokecherry <b>Saxifrage:</b> currant, gooseberry <b>Ebony:</b> persimmons <b>Custard Apple:</b> custard apple, paw-paw
<b>Nuts/Seeds</b>	<b>Sapucaya:</b> brazil nut <b>Pedalium:</b> sesame seeds, tahini	<b>Birch:</b> hazelnut <b>Cashew:</b> pistachio, cashew <b>Gourd:</b> pumpkin seeds	<b>Walnut:</b> walnut, pecan, butternut <b>Beech:</b> chestnut	<b>Conifer:</b> pine nut <b>Protea:</b> macadamia <b>Aster:</b> sunflower seed <b>Rose Stone:</b> almond
<b>Grains</b>	<b>Buckwheat:</b> buckwheat flour <b>Legume:</b> chickpeas, lentil flour, carob, soy (soy milk/ tofu), sprouts <b>Arum:</b> arrow root <b>Goosefoot:</b> quinoa	<b>Ginger:</b> east India arrowroot starch <b>Grass:</b> corn starch, popcorn, oats, rice, wild rice, millet, sorghum, corn meal	<b>Spurge:</b> cassava flour, tapioca starch <b>Amaranth:</b> amaranth seeds and flour	<b>Nightshade:</b> potato flour <b>Composite:</b> artichoke flour <b>Grain:</b> spelt, bulgar, rye, barley, kamut, wheat (durham, selemon, graham)
<b>Oils</b>	<b>Bird:</b> bird fat <b>Legume:</b> soy oil, peanut oil <b>Pedalium:</b> sesame oil <b>Palm:</b> coconut oil	<b>Grass:</b> corn oil <b>Flax:</b> flaxseed oil	<b>Olive:</b> olive oil <b>Walnut:</b> walnut oil <b>Mustard:</b> canola oil	<b>Aster:</b> sunflower oil, safflower oil <b>Mallow:</b> cotton seed oil <b>Bovine:</b> butter <b>Rose stone:</b> apricot and almond oil
<b>Seasoning &amp; Condiments</b>	<b>Laurel:</b> cinnamon, bay leaf <b>Poppy:</b> poppy seed <b>Pepper:</b> peppercorns, pepper <b>Parsley:</b> dill, caraway, celery seed, coriander, cumin, parsley <b>Legume:</b> fenugreek, clover honey, licorice, carob	<b>Citrus:</b> orange blossom honey <b>Ginger:</b> ginger, cardamom, turmeric <b>Grass:</b> corn syrup, corn sugar, rice sweetener <b>Fungi:</b> baker's and brewer's yeast <b>Tea:</b> black and green	<b>Mint:</b> mint, basil, oregano, rosemary, sage, summer, savory, thyme <b>Myrtle:</b> allspice, clove, paprika, pimiento <b>Orchid:</b> vanilla <b>Mustard:</b> mustard seed	<b>Nutmeg:</b> nutmeg, mace <b>Aster:</b> chamomile, chicory, goldenrod, tarragon <b>Nightshade:</b> cayenne, paprika, pimiento, chili peppers <b>Rose Stone:</b> almond extract <b>Madder:</b> coffee



# Food-specific IgG testing?

## Dietary advice based on food-specific IgG results

Geoffrey Hardman

*Centre for Health Economics, University of York, Heslington, York, UK, and*

Gillian Hart

*YorkTest Laboratories Ltd, York Science Park, York, UK*

- Purpose – To provide evidence that elimination diet based on food-specific IgG test results is an effective, reliable and valid aid to the management of chronic medical conditions.
- Food intolerance has been associated with a myriad of chronic symptoms including headaches, intestinal and skin symptoms, behavioural changes and respiratory disorders.
- 5,286 subjects who had taken the YORKTEST foodSCAN 113 test
- YORKTEST Laboratories Ltd carry out an enzyme-linked immunosorbant assay (ELISA) test for food-specific IgG antibodies, utilising a blood collection kit using a whole blood finger prick testing method a test for the presence of IgG antibodies to one-hundred and thirteen different foods.
- Based on these results the patient is advised to stop or reduce the intake of the foods identified, and patients are entitled and encouraged to take advice on obtaining a balanced diet from an independent Nutritionist as part of the service.



# IgG food intolerances

- 75.8 per cent of those that rigorously followed the recommended diet had a noticeable improvement in their condition. 68.2 per cent of those that benefited from following the recommendations felt benefit within three weeks of following the diet.
- The survey covered subjects with a wide range of medical conditions, and it was clear that those who reported more than one condition were more likely to report noticeable improvement. 81.5 per cent of those that dieted rigorously and reported three or more co-morbidities showed noticeable improvement in their overall condition.

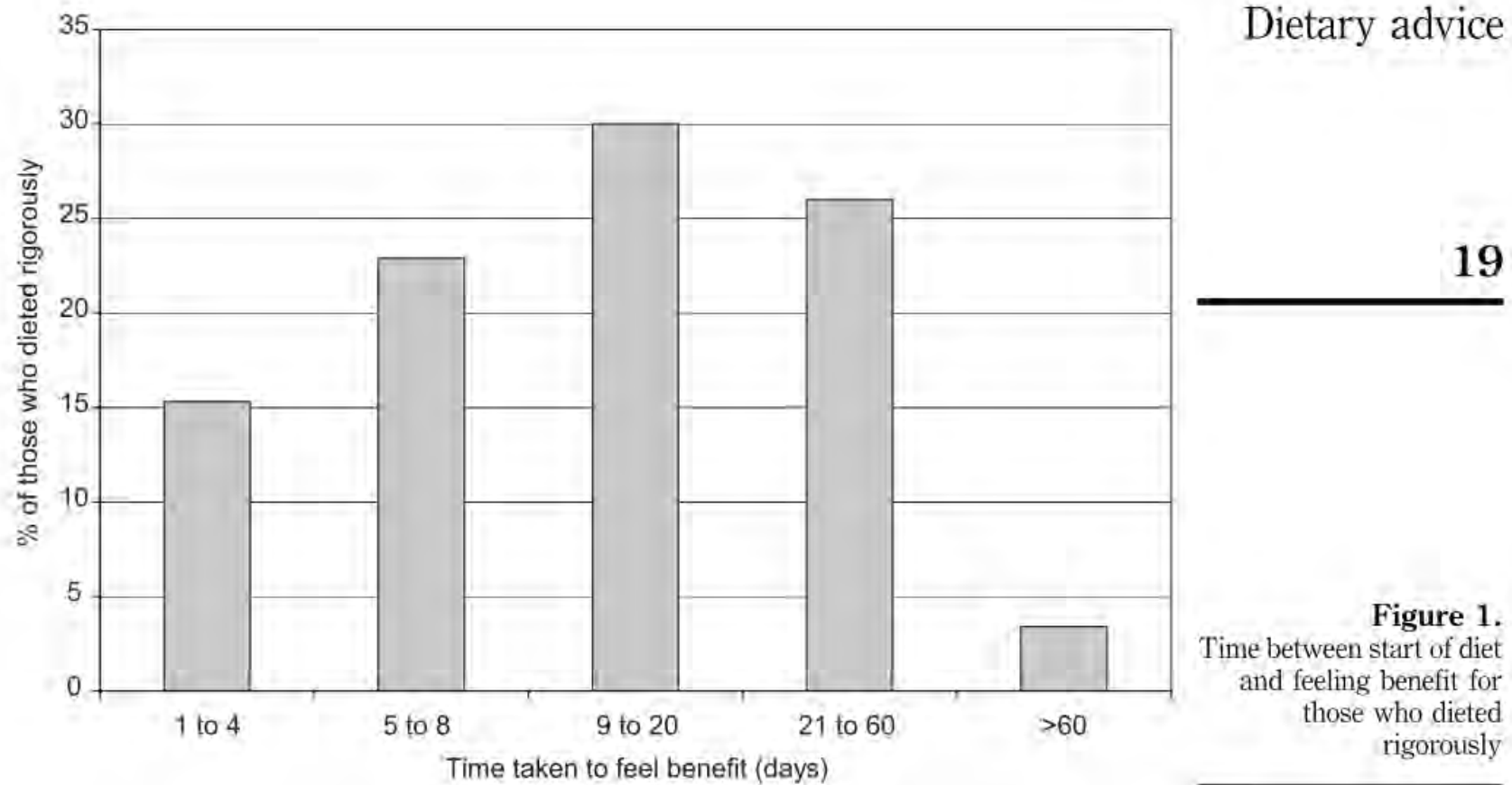
**Dietary advice based on  
food-specific IgG results**

Geoffrey Hardman  
Centre for Health Economics, University of York, Heslington, York, UK, and  
Gillian Hart  
YorkTest Laboratories Ltd, York Science Park, York, UK

- Patients were asked if they had reintroduced any of the offending foods after starting the diet. Subjects were asked specifically to say whether the result of reintroducing foods was a strong return of symptoms, a slight return of symptoms, or no change.
- Of the 3,026 subjects that responded to the second questionnaire, 2,275 (75.2 per cent) said they had reintroduced offending foods either on purpose or by accident. 2,219 of these patients also answered the question regarding the return of symptoms.
- 824 (37.1 per cent) reported a strong return of symptoms, 902 (40.6 per cent) reported a slight return of symptoms, and 493 (22.2 per cent) reported no change. That is 77.7 per cent reported the return of symptoms after the reintroduction of offending foods.



# Elimination diet duration of symptoms







# Adherence to elimination diet

**Table II.**  
Benefit by main medical condition for those who dieted rigorously

	Low or none	Level of benefit reported Moderate or considerable	High
Gastro-intestinal	108 (19.7%)	287 (52.5%)	152 (27.8%)
Respiratory	39 (28.3%)	70 (50.7%)	29 (21.0%)
Neurological	34 (22.1%)	72 (46.8%)	48 (31.2%)
Dermatological	48 (23.6%)	106 (52.2%)	49 (24.1%)
Musculo-skeletal	36 (36.0%)	43 (43.0%)	21 (21.0%)
Psychological	27 (18.9%)	58 (40.6%)	58 (40.6%)
Other	38 (20.7%)	97 (52.7%)	49 (26.6%)

**Note:** Pearson's chi-square  $\chi^2 = 32.3$ ;  $p = 0.001$

- 70.3 per cent of females and 68.2 per cent of males dieted rigorously



# *L. rhamnosus* GG & gliadin

Orlando et al. *BMC Microbiology* 2014, **14**:19  
<http://www.biomedcentral.com/1471-2180/14/19>



RESEARCH ARTICLE

Open Access

## Lactobacillus GG restoration of the gliadin induced epithelial barrier disruption: the role of cellular polyamines

Antonella Orlando<sup>1†</sup>, Michele Linsalata<sup>1</sup>, Maria Notarnicola<sup>2</sup>, Valeria Tutino<sup>2</sup> and Francesco Russo<sup>1\*\*</sup>

Aims of the study were to establish in epithelial cells whether;

- Gliadin affects paracellular permeability and polyamine profile.
- Co-administration of viable *Lactobacillus rhamnosus* GG preserves the intestinal epithelial barrier integrity and decreases of polyamines.

*Gliadin modifies the intestinal paracellular permeability and significantly increases the polyamine content in Caco-2 cells.*

*Concomitant administration of L.GG is able to counteract these effects.*

Interestingly, the presence of cellular polyamines is necessary for this probiotic to exert its capability in restoring paracellular permeability by affecting the expression of different TJ proteins



# *L. Rhamnosus* GG & gut barrier

*Lactobacillus rhamnosus* GG (American Type Culture no. 53103) has been shown to promote gut IgA response and thereby improve gut immunologic barrier in patients with Crohn's disease.

It inhibits attachment of pathogens to intestinal mucus.

- Recently, LGG has been shown to enhance the expression of mRNA for two predominant mucins MUC2 and MUC3. These glycoproteins are known to inhibit adherence of pathogenic bacteria such as enteropathogenic *Escherichia coli*.

*Lactobacillus* GG has also been shown to secrete inhibitory products that have antimicrobial properties against potential pathogens.

*Lactobacillus* GG has also been shown to stabilize the gut mucosal barrier.

It reverses the increased intestinal permeability induced by cow's milk in young rats and promotes intestinal barrier function in children with food allergy.

**These studies show that LGG may be effective in treatment of Crohn's disease by several potential mechanisms such as *altering the intestinal mucins, promoting local immune response, and stabilizing the gut mucosal barrier.***

Gupta, Puneet, et al. "Is *Lactobacillus* GG helpful in children with Crohn's disease? Results of a preliminary, open-label study." *Journal of pediatric gastroenterology and nutrition* 31.4 (2000): 453-457.



# ESP and *L.rhamnosus* GG?

## microbial biotechnology

Open Access

### Interplay between *Lactobacillus rhamnosus* GG and *Candida* and the involvement of exopolysaccharides

We found that *L. rhamnosus* GG was able to interfere with Candida growth, morphogenesis and adhesion. These three aspects of *Candida*'s physiology are all crucial to its opportunistic pathogenesis.

Compared the activity of *L. rhamnosus* GG with its exopolysaccharide (EPS)-deficient mutant, and purified EPS, to evaluate the involvement of this outer carbohydrate layer.

Their data demonstrated that purified EPS can both interfere with hyphal formation and adhesion to epithelial cells, which indicates that EPS is part of a combined molecular mechanism underlying the antihyphal (anti-fungal) and anti-adhesion mechanisms of *L. rhamnosus* GG.



# L. Rhamnosus GG & antifungal



RESEARCH ARTICLE

## Antifungal defense of probiotic *Lactobacillus rhamnosus* GG is mediated by blocking adhesion and nutrient depletion

Daniela Mailänder-Sánchez<sup>1oa</sup>, Christina Braunsdorf<sup>1ab</sup>, Christian Grumaz<sup>2</sup>, Christoph Müller<sup>3</sup>, Stefan Lorenz<sup>2</sup>, Philip Stevens<sup>4,5ac</sup>, Jeanette Wagener<sup>1ad</sup>, Betty Hebecker<sup>6,7ad</sup>, Bernhard Hube<sup>6,7,8</sup>, Franz Bracher<sup>3</sup>, Kai Sohn<sup>2</sup>, Martin Schaller<sup>1\*</sup>

LGG protects oral epithelial tissue from damage caused by *Candida albicans* (CA) in our in vitro model of oral candidiasis. Furthermore, we provide insights into the mechanisms behind this protection and dissect direct and indirect effects of LGG on CA pathogenicity.

CA viability was not affected by LGG. Instead, transcriptional profiling using RNA-Seq indicated dramatic metabolic reprogramming of CA.

Additionally, LGG had a significant impact on major virulence attributes, including adhesion, invasion, and hyphal extension, whose reduction, consequently, prevented epithelial damage.

This was accompanied by glucose depletion and repression of ergosterol synthesis, caused by LGG, but also due to blocked adhesion sites.

Therefore, LGG protects oral epithelia against CA infection by preventing fungal adhesion, invasion and damage, driven, at least in parts, by metabolic reprogramming due to nutrient limitation caused by LGG.



# Lactobacillus rhamnosus GG and Butyrate



The ISME Journal (2016) 10, 742–750  
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## ORIGINAL ARTICLE


### ***Lactobacillus rhamnosus* GG-supplemented formula expands butyrate-producing bacterial strains in food allergic infants**

- Emerging evidence suggests that twenty-first century environmental interventions, including widespread antibiotic use, consumption of a high-fat/low fiber diet, elimination of previously common enteropathogens (including *Helicobacter pylori* and helminthic parasites), reduced exposure to infectious disease, Caesarean birth, and formula feeding, may have perturbed the mutually beneficial interactions established over millions of years of coevolution with the bacteria that comprise our commensal microbiota.
- Cow's milk allergy (CMA) is one of the most common food allergies of infancy and early childhood with an estimated prevalence of 2–3% worldwide**

- Acquisition of tolerance was evaluated by double blind placebo-controlled oral food challenge following 12 months of treatment. In total, 5 out of 12 (42%) EHCF+LGG-treated infants developed tolerance to cow's milk proteins, whereas all (7/7) of the EHCF-treated infants remained allergic.
- We hypothesized that EHCF+LGG promotes tolerance to cow's milk proteins in part by altering gut microbial community structure. The fecal concentration of butyrate was significantly greater in CMA infants treated with LGG-supplemented EHCF, when compared with those treated with EHCF alone.
- Butyrate is the preferred energy source for colonocytes and is often considered a sensor of intestinal health.



# Short Chain Fatty Acids

The Journal of Nutrition  
Nutrition and Disease 

## Fecal Butyrate Levels Vary Widely among Individuals but Are Usually Increased by a Diet High in Resistant Starch<sup>1,2</sup>


Alexandra L. McOris,<sup>1,4</sup> Rosalind B. Miller,<sup>1,7</sup> Anthony R. Bird,<sup>1,4</sup> Jennifer B. Keogh,<sup>1,4</sup> Manny Noakes,<sup>1,4</sup> David L. Topping,<sup>1,4</sup> and Michael A. Conlon<sup>1,4\*</sup>

- Butyrate and other SCFA produced by bacterial fermentation of resistant starch (RS) or non-starch polysaccharides (NSP) promote human colonic health.
- A randomized cross-over study was conducted that compared the effects of foods supplying 25 g of NSP or 25 g of NSP plus 22 g of RS/d over 4 weeks in 46 healthy adults (16 males, 30 females; age 31–66 y).
- SCFA, principally acetate, propionate, and butyrate, are produced in the human colon by the bacterial fermentation of complex carbohydrates not digested in the small intestine.
- These include modulation of colonic motility, promotion of visceral blood flow, and prevention of the overgrowth of potential pathogens in the lumen.
- The principal substrates for SCFA production are complex carbohydrates, non-starch polysaccharides (NSP) and resistant starch (RS).
- NSP equate to the traditional concept of dietary fibre (i.e. insoluble plant cell wall material) and RS is the fraction of starch escaping small intestinal digestion and entering the large bowel. There is evidence that RS fermentation favours butyrate production relative to NSP.
- Our aim was to determine the relative effectiveness of these diets in increasing faecal butyrate, particularly in those individuals with the lowest levels at entry.
- NSP diet and the other one-half consumed the RS diet daily for 4 wk. This was followed by 2 weeks where participants reverted to their habitual diet without supplements (wash-out period), and then a further 4 weeks consuming the alternate supplementary diet.



# Resistant starch and fecal butyrate

- The faecal concentrations of acetate, butyrate, and total SCFA (but not propionate) were significantly higher when participants consumed RS compared with entry and NSP diets.
- Showed that SCFA levels were increased by consumption of a diet high in RS in most individuals, including those with the lowest habitual butyrate levels. However, levels tended to fall in response to RS consumption in those individuals with the highest entry butyrate levels.
- Both the NSP and RS diets increased SCFA levels.
- When expressed as a proportion of the total SCFA, butyrate was higher during RS consumption, consistent with the concept that RS fermentation favours butyrate production.

The Journal of Nutrition  
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#### What are Some Common Examples of Insoluble Fiber?



- Whole wheat breads
- Wheat cereals
- Wheat bran
- Barley
- Beets
- Brussels Sprouts
- Turnips
- Apples (eat with skin)
- Rice
- Cauliflower
- Rye

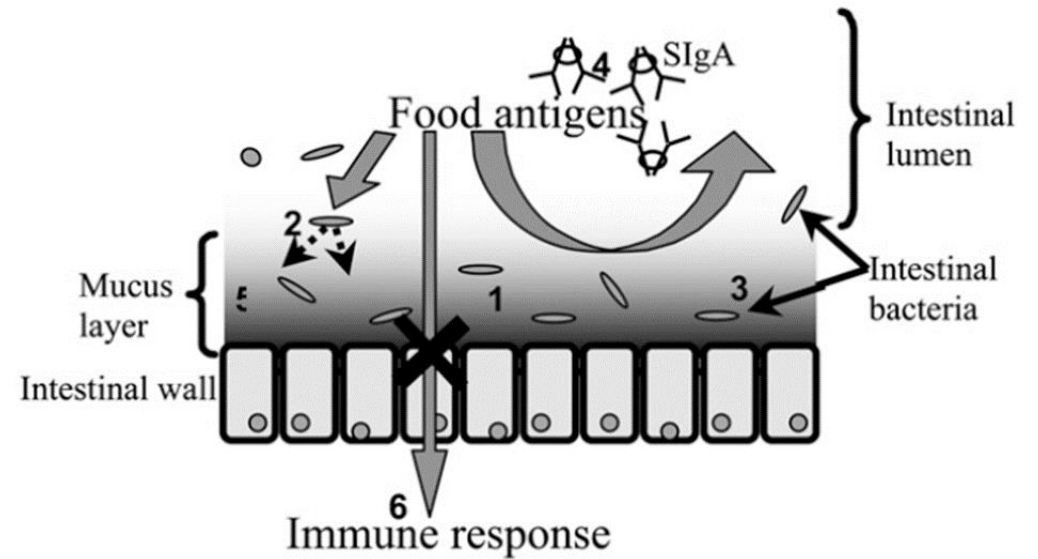




# Secretory IgA

sIgA can mediate protection at mucosal surfaces by binding to viruses and bacteria to prevent or inhibit their attachment to and/or invasion of epithelial cells, a process known as immune exclusion. This assists with preventing mucosal inflammation and the neutralisation of inflammatory mediators.

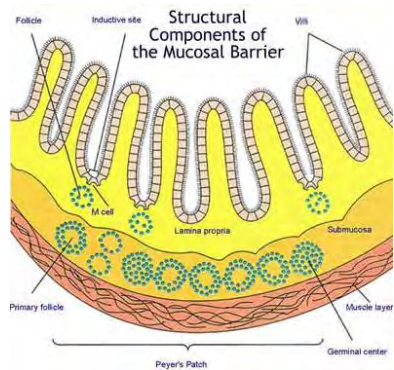
Several diseases have been linked to changes in the microbiota populations, or to reduction of the microbiota's diversity, including, atopic diseases, inflammatory bowel disease (IBD), diabetes, obesity, cancer and very recently, even neuropathologies. Some of these pathologies are associated with altered barrier function and increased permeability of the epithelium.



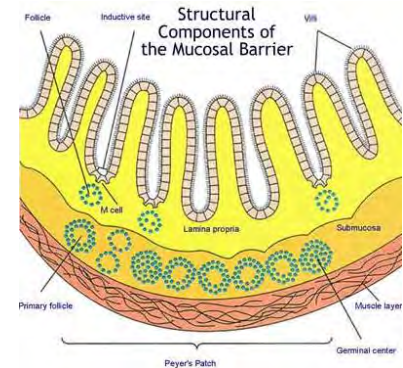


# Loss of mucosal tolerance

- Secretory IgA (SIgA) is the predominant class of antibody found in intestinal secretions with 3-5g produced by plasma cells daily in healthy individuals.
- SIgA plays an important role in the protection and homeostatic regulation of intestinal, respiratory, and urogenital mucosal epithelia.
- SIgA limits the access of numerous microorganisms and mucosal antigens to these thin and vulnerable mucosal barriers. Cross-talk between the probiotic bacteria and the intestinal mucosa is enhanced by SIgA



Corthésy, B. (2013). Multi-faceted functions of secretory IgA at mucosal surfaces. *Frontiers*

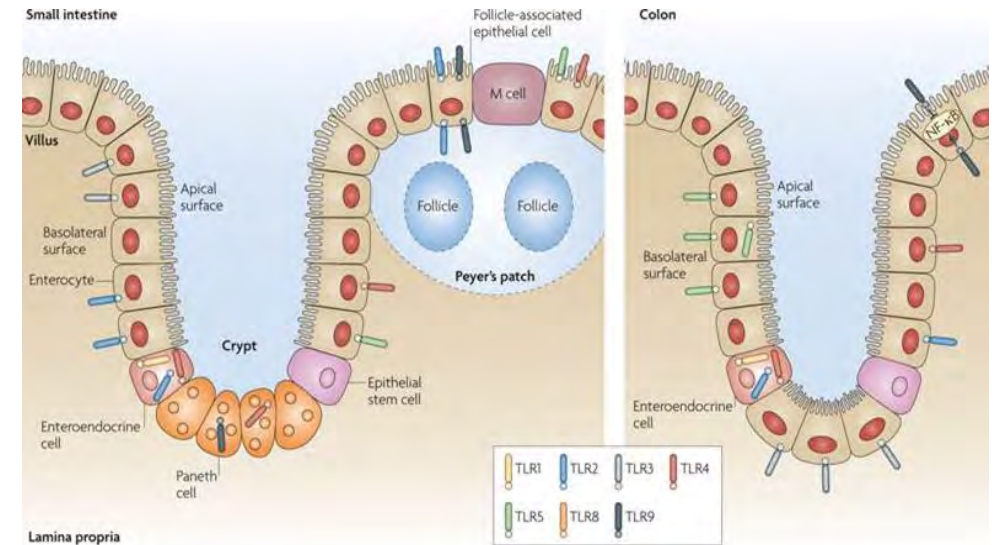




# Increase SIgA

Re-establish and increase SIgA, biofilm and restore lost mucosal tolerance and prime GIT for probiotic therapy

- Target pathogenic bacteria, virus, fungus, yeast
- Enhance & restores gastrointestinal enzymes to improve digestion discomfort, bloating, dysbiosis, & abdominal pain
- Repair damaged intestines and decrease inflammation
- Rapidly establish lost beneficial microflora





# *S. Boulardii* and Dysbiosis

- In contrast to other probiotics, *S. boulardii* was found to have a very broad clinical efficacy with significant positive effects in many different dysbiotic situations
- *S. boulardii* acts as a shuttle that could liberate, during the intestinal transit, at least 1500 molecules that have not all been totally characterized.
- This large number of molecules is why *S. boulardii* effects the intestinal mucosa and has a therapeutic effect on such a wide variety of gastrointestinal disorders including acute and chronic disorders.

McFarland LV. Use of probiotics to correct dysbiosis of normal microbiota following disease or disruptive events: a systematic review. *BMJ Open*. 2014;4(8):e005047.  
Buts, J. P. (2009). Twenty-five years of research on *Saccharomyces boulardii* trophic effects: updates and perspectives. *Digestive diseases and sciences*, 54(1), 15-18.



# *S. Boulardii* & Probiotics

- *S. boulardii* increases secretory IgA levels in the intestine
- Re-establishing SIgA **is vital as it's the means by which** microflora communicates with the immune system and establish lost GIT mucosal tolerance.
- In healthy individuals up to 74% of the microbiota is coated with SIgA. We found that association of a Lactobacillus or a Bifidobacterium with SIgA enhanced probiotic adhesion by a factor of greater than or equal to 3.4-fold.
- Cross-talk between the probiotic bacteria and the intestinal mucosa is enhanced by SIgA.

Corthésy, B. (2013). Multi-faceted functions of secretory IgA at mucosal surfaces. *Frontiers in Immunology*, 4.

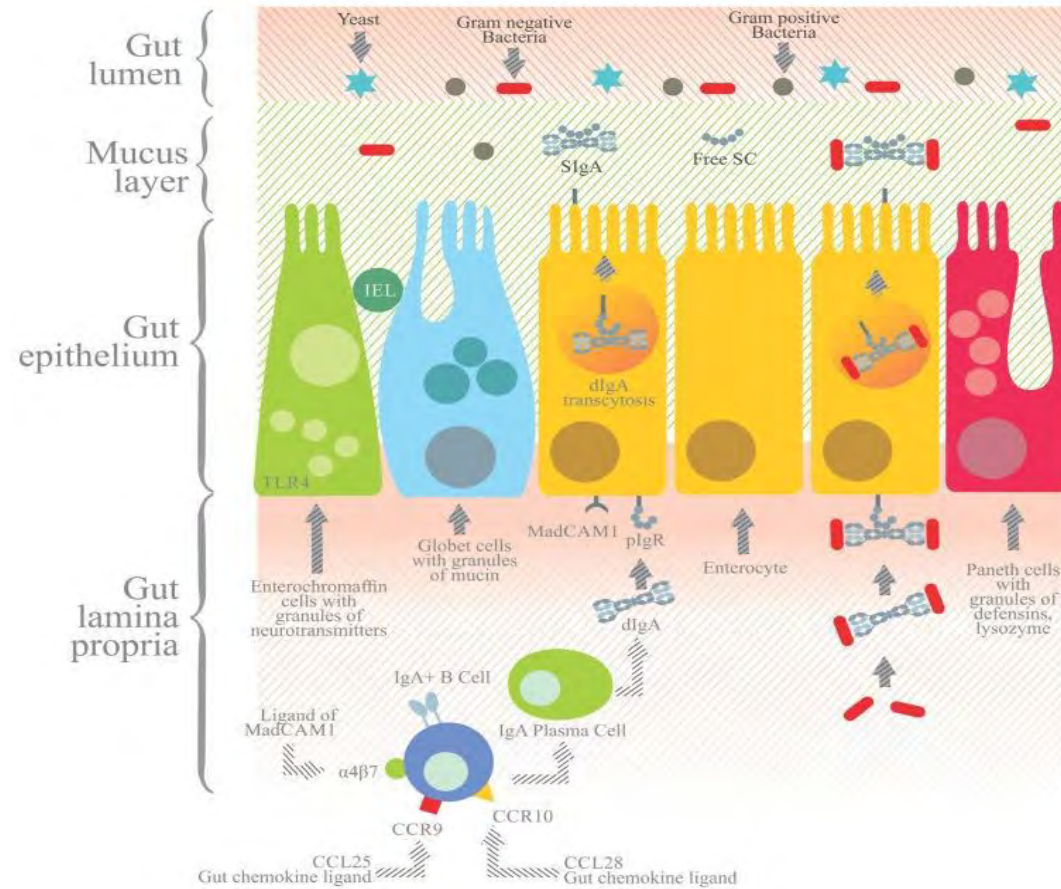
Mantis, N. J., Rol, N., & Corthésy, B. (2011). Secretory IgA's complex roles in immunity and mucosal homeostasis in the gut. *Mucosal Immunology*, 4(6), 603-611.



# Loss of mucosal tolerance

Increasing SIgA;

- Entraps dietary antigens such as wheat gluten and gliadin and microorganisms in the mucus,
- Down modulates the expression of pro-inflammatory bacterial epitopes on commensal bacteria,
- Promotes the maintenance of appropriate bacterial communities within specific intestinal segments



Xiong, N., & Hu, S. (2015). Regulation of intestinal IgA responses. *Cellular and Molecular Life Sciences*, 1-11.



# Repair damaged mucous membranes

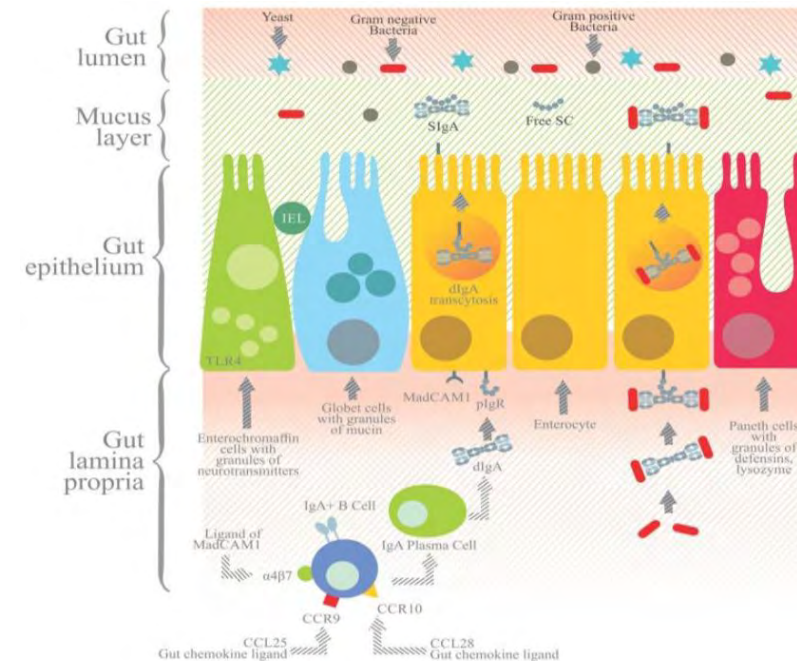
*S. boulardii* may also act by enhancing the integrity of the tight junction between enterocytes, thus preserving intestinal integrity and function.

*S. boulardii* may also interfere with NF- $\kappa$ B-mediated signal transduction pathways, which stimulate pro-inflammatory cytokine production.

Decreases expression of pro-inflammatory cytokines (IL-8, IL-6, IL-1 $\beta$ , TNF- $\alpha$  and IFN- $\gamma$ )

*S. boulardii* has also been shown to cause the trapping of T helper cells into mesenteric lymph nodes, thereby reducing inflammation.

Increases IL10 a major anti-inflammatory cytokine



Wu X, Vallance BA, Boyer L, Bergstrom KS, Walker J, Madsen K, O'Kusky JR, Buchan AM, Jacobson K. *Saccharomyces boulardii* ameliorates *Citrobacter rodentium*-induced colitis through actions on bacterial virulence factors. *Am J Physiol Gastrointest Liver Physiol*. 2008;294:G295–G306.

Mumy, K.L., Chen, X., Kelly, C.P. and McCormick, B.A. (2008) *Saccharomyces boulardii* interferes with *Shigella* pathogenesis by postinvasion signaling events. *Am J Physiol Gastrointest Liver Physiol* 294:G599–G609

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# Glutamine and gut

Glutamine is the preferred fuel for rapidly dividing cells, such as enterocytes in the small intestine and immune cells, such as lymphocytes, monocytes and macrophages.

For some patients, the synthesis and release of glutamine from skeletal muscle is insufficient to meet demands, and a deficiency in glutamine may lead to small intestine mucosal injury followed by increased wall permeability and bacterial translocation.

BIOMEDICAL REPORTS 6: 576-584, 2017

## **Therapeutic benefits of glutamine: An umbrella review of meta-analyses**

MARC P. McRAE

Department of Basic Science, National University of Health Sciences, Lombard, IL 60148, USA

Received February 8, 2017; Accepted March 9, 2017

DOI: 10.3892/br.2017.885





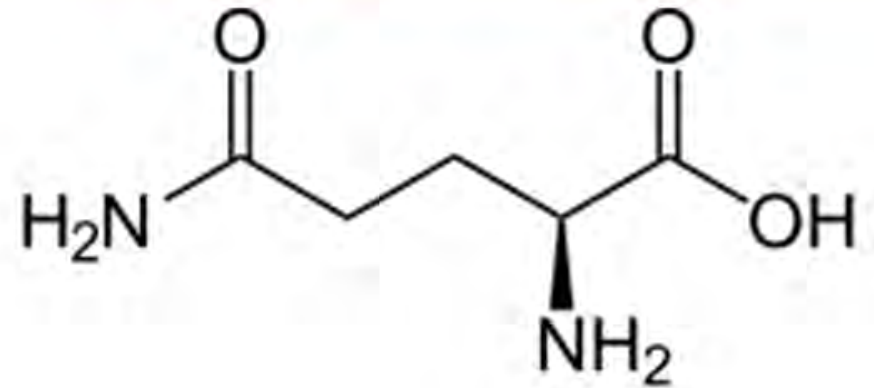
# Glutamine and gut 2017 meta-analysis

This research is supported by a meta-analysis that presented beneficial changes in the *markers of intestinal inflammation and mucosal permeability with abdominal surgery patients.*

Finally, glutamine supplementation enhances cellular heat shock protein production (HSP70 and HSP72) and glutathione expression, which both protect cells and enhance cell survival.

Heat shock proteins are involved in the repair and removal of damaged proteins, and glutathione reacts directly with reactive oxygen species in order to prevent oxidative damage.

## GLUTAMINE

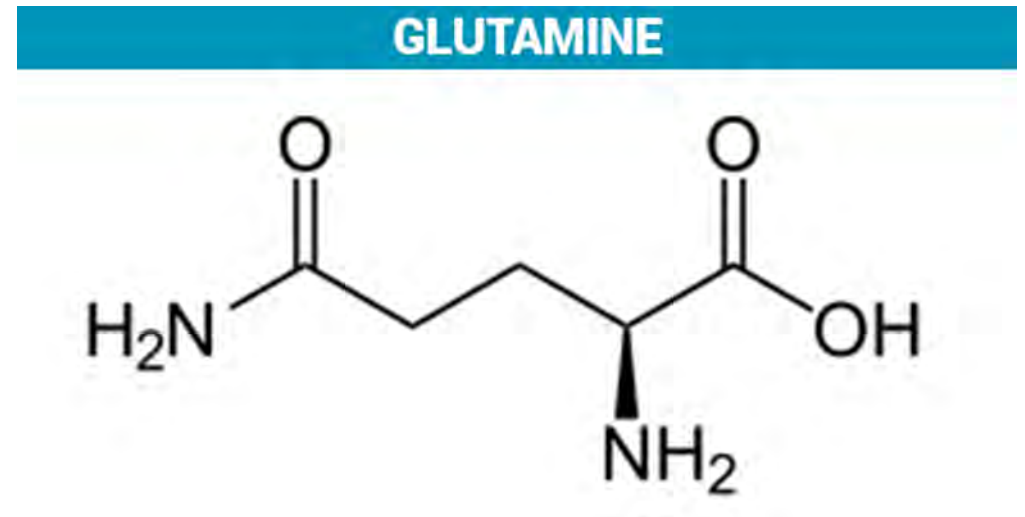


McRae, Marc P. "Therapeutic benefits of glutamine: An umbrella review of meta-analyses." *Biomedical Reports* 6.5 (2017): 576-584.



# Glutamine

- Glutamine exerts protective effects on the gut mucosa by preserving epithelial tight junction integrity.
- Glutamine enhancing microcirculation in the colon wall.
- Glutamine improving barrier function of the colon lining, preventing nutrient and water loss and inhibiting the migration of endotoxins.





# n-3 PUFA deficiency induces dysbiosis

- n-3 PUFA deficiency induces dysbiosis, with increased numbers of potential pathobionts (Potentially pathological organisms), including bacteria from the Enterobacteriaceae family
- n-3 PUFA supplementation prevents the bloom of Enterobacteriaceae, as well as the translocation of bacteria into the submucosal region, and instead promotes the enrichment of Lactobacillus and Bifidobacterium species



Ghosh, S., Molcan, E., DeCoffe, D., Dai, C., & Gibson, D. L. (2013). Diets rich in n-6 PUFA induce intestinal microbial dysbiosis in aged mice. *British Journal of Nutrition*, 110(03), 515-523.



# New discovery

## Key findings:

- Elevated tissue Omega-3 fatty acids enhance intestinal production and secretion of intestinal alkaline phosphatase (IAP)
- IAP expression in the intestine is a critical determinant of the gut microbiota profile
- Lowering the n-6/n-3 PUFA ratio can improve the gut microbiota profile by increasing Bifidobacteria and reducing LPS producing bacteria

## SCIENTIFIC REPORTS

OPEN

**A host-microbiome interaction mediates the opposing effects of omega-6 and omega-3 fatty acids on metabolic endotoxemia**

Received: 08 February 2015  
Accepted: 05 May 2015  
Published: 11 June 2015

Kanakaraju Kaliannan, Bin Wang, Xiang-Yong Li, Kui-Jin Kim & Jing X. Kang



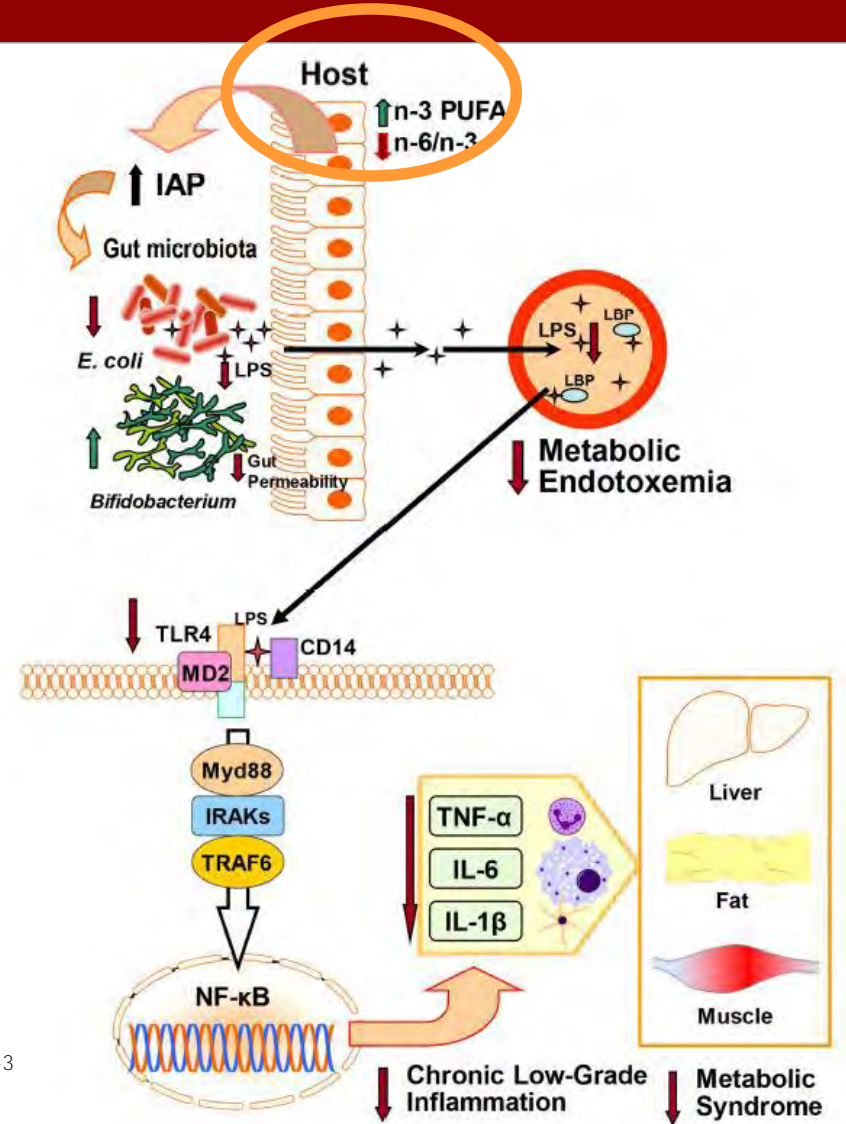
**HARVARD**  
**MEDICAL SCHOOL**

Kaliannan, K., Wang, B., Li, X. Y., Kim, K. J., & Kang, J. X. (2015). A host-microbiome interaction mediates the opposing effects of omega-6 and omega-3 fatty acids on metabolic endotoxemia. *Scientific reports*, 5.



# Omega 3 and metabolic endotoxemia

- The present study demonstrates for the first time, that n-6 and n-3 PUFA exert opposing effects on metabolic endotoxemia by modulating the endogenous expression of intestinal alkaline phosphatase(IAP)
- IAP modifies the gut microbiota, leading to differential outcomes in chronic low-grade inflammation and metabolic syndrome
- IAP induces changes in the gut bacteria composition resulting in;
  - decreased lipopolysaccharide production
  - decreased gut permeability
  - reduced metabolic endotoxemia and
  - reduced inflammation.



Kaliannan, K., Wang, B., Li, X. Y., Kim, K. J., & Kang, J. X. (2015). A host-microbiome interaction mediates the opposing effects of omega-6 and omega-3 fatty acids on metabolic endotoxemia. *Scientific reports*, 5.



# Vitamin D



## HHS Public Access

Author manuscript

*Dig Dis Sci.* Author manuscript; available in PMC 2016 July 01.

Published in final edited form as:

*Dig Dis Sci.* 2015 July ; 60(7): 1941–1947. doi:10.1007/s10620-015-3634-8.

### Transgenic Expression of Vitamin D Receptor in Gut Epithelial Cells Ameliorates Spontaneous Colitis Caused by Interleukin-10 Deficiency

Maya Aharoni Golan<sup>1,8</sup>, Weicheng Liu<sup>1,8</sup>, Yongyan Shi<sup>1,2</sup>, Li Chen<sup>1,4</sup>, Jiaolong Wang<sup>1,3</sup>, Tianjing Liu<sup>1,2</sup>, and Yan Chun Li<sup>1,\*</sup>

- Intestinal epithelial cells (IECs) are key components of the barrier that express a high level of vitamin D receptor, a nuclear hormone receptor that mediates the biological activity of the vitamin D hormone, 1,25-dihydroxyvitamin D.
- Epidemiological studies have established that vitamin D-deficiency is common in patients with IBD that is associated with increased risk of IBD whereas high vitamin D intake lowers the risk of IBD.
- The vitamin D receptor (VDR) is a nuclear hormone receptor mediating the activity of vitamin D hormone.
- VDR down-regulation is mainly caused by mucosal inflammation that is mediated by mircoRNA-346.
- VDR signaling in Intestinal Epithelial Cells prevents mucosal inflammation and inhibits colitis by protecting the integrity of the mucosal barrier, and this anti-colitic activity of the epithelial VDR appears to be independent of the VDR activity from the nonepithelial immune cells.
- Gut epithelial VDR signaling protects the mucosal barrier integrity by inhibiting IEC apoptosis



# Vitamin D

- The intestine, especially the colon, contains an enormous amount of commensal bacteria that can cause colonic inflammation if the intestinal homeostasis is disrupted.
- IL-10 is a key anti-inflammatory cytokine that plays an essential role in the maintenance of this hemostasis. It has been shown that IL-10 targets both the innate and adaptive immune cells in the colon, including macrophages, Treg cells and IL-17+ CD4+ T cells, to suppress immune response.
- IL-10-deficiency can cause Th1 cell-mediated intestinal inflammation that leads to the development of colitis in mice and humans .
- By raising epithelial VDR levels, through vitamin D therapy, the mucosal epithelial barrier can be strengthened.



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# Vitamin D & Intestinal permeability

Original Article

## Effects of vitamin D supplementation on intestinal permeability, cathelicidin and disease markers in Crohn's disease: Results from a randomised double-blind placebo-controlled study

Tara Raftery<sup>1</sup>, Adrian R Martineau<sup>2</sup>, Claire L Greiller<sup>2</sup>, Subrata Ghosh<sup>3</sup>,  
Deirdre McNamara<sup>4</sup>, Kathleen Bennett<sup>5</sup>, Jon Meddings<sup>3</sup> and Maria O'Sullivan<sup>1</sup>

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United European Gastroenterology Journal  
2015, Vol. 3(3) 294-302  
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DOI: 10.1177/2050640615572176  
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- Several published studies in experimental models of inflammatory bowel disease (IBD) demonstrate the effect of vit D on inflammation; however, few have investigated the effects on intestinal permeability (IP).
- Altered IP and impaired barrier function have been implicated in the pathogenesis of CD, moreover, an increase in IP may predict and precede a clinical relapse.

- Kong et al., report that activated vit D 1,25(OH)<sub>2</sub>D<sub>3</sub> increases the tight junction (TJ) proteins zonula occludens and E-cadherin, and enhances healing following an injury in the intestinal epithelium.
- To date, there are few randomised controlled intervention studies of vit D therapy in CD.
- Booth et al. 30 show that CD patients (n ¼ 15) treated with 10,000 IU/ day vit D have significantly improved **Crohn's Disease Activity Index (CDAI) scores**, compared to those treated with 1000 IU/day, after 26 weeks.
- A larger 12-month study in CD (n ¼ 96) reports a reduction in relapse rates among those treated with 1200 IU/day vit D, compared to placebo.





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- Randomised, double-blind, placebo controlled study, with patient data collected at baseline and at the 3-month follow-up. The active treatment consisted of 2000 IU of vitD3.
- Assigned 27 Crohn's disease patients in remission to 2000 IU/day vitD or placebo for 3 mos.

- our study demonstrated that 2000 IU/ day vitD was sufficient to raise 25(OH)D concentrations to 75 nmol/L in most study participants, after a 3-mo.
- Inter-group analysis in the treated group revealed an apparent maintenance of small bowel and gastroduodenal permeability and an increase in circulating LL-37.
- This is the first reporting of vitD, IP and LL-37 measures in a CD cohort, and while the data requires confirmation, it broadly supported emerging experimental evidence that suggests a role for vitD in maintaining intestinal barrier integrity.



# Vitamin D & Intestinal permeability

- Human cathelicidin (LL-37) and beta defensins are antimicrobial peptides (AMPs) of the innate immune system that are expressed by the gastrointestinal epithelium.
- AMPs work in synergy to protect against bacterial invasion and LL-37 promotes wound healing in intestinal epithelial cells and reduces intestinal inflammation in experimental colitis.

Original Article

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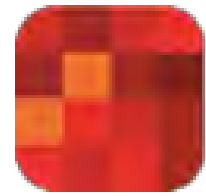
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