

Slide 1

# AUTOIMMUNITY AND THE GUT



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Slide 2

## Autoimmunity – The Past

- The rationale - All about a malfunctioning immune system
- The immune system is overactive to the point of attacking the body
- Avoid anything that stimulates the immune system



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Slide 3

## Fast Forward A Few Years

- Immune system is not overactive – it's underactive
- Undernourished
- Reacting to allergies and toxins all the time has left it weak and confused



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## Slide 4

### In Both Scenarios

- Autoimmunity is a condition where the immune system is fighting the body
- In other words  
"Your body has turned against you"



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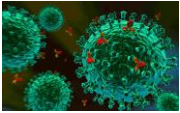
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## Slide 5

### The Truth Is...

- Your immune system has not turned against you
- It never liked you in the first place



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## Slide 6

### It Turns Out...

- There is a major player involved that determines if the immune system plays nice in the body
- Our good gut microbes
- Amongst their many responsibilities they deliver "immune tolerance" – to food, to body tissue – to everything that should not be attacked



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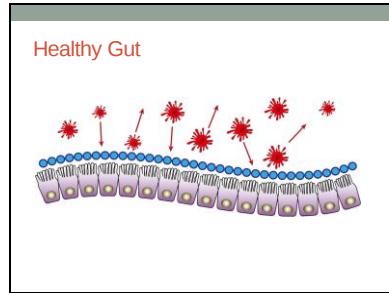
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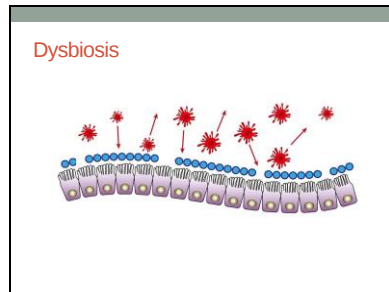
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Slide 9

**Causes of Dysbiosis**

- Antibiotics and other drugs
- Diet – Processed refined foods, lack of pre and probiotic foods
- Toxins - man-made and naturally occurring like LPS (lipopolysaccharide)
- Stress, negative attitudes
- Excessive physical exercise, surgeries, air flight, x-rays
- Chemotherapy, radiation

**Dysbiosis: Major factor leading to changes in intestinal permeability (leaky gut)**

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### Our Immune System

- **Innate:** Non-specific and defends against all pathogens no matter what they are
  - cytokines, C-reactive protein
  - first line of defense
- **Adaptive Immune System:** Must recognize everything it comes in contact with and then direct immune cells to attack anything it recognizes as a pathogen
  - it has memory
  - it has to learn



Macrophage T cell B cell Neutrophil

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### Gut Microbes

- Microbes interact with the adaptive immune system constantly
- In order for them to stay in our intestinal system – the immune system has to be able recognize them as foreign but not pathogenic
- The immune system constantly tests the microbes using cells located in the intestinal wall lining



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### Secretory IgA

- Intestinal cells secrete IgA (SIgA) which promote the removal of antigens and pathogens
- SIgA prevents them from locking onto intestinal wall receptor sites
- SIgA's relationship with the good bacteria allows the immune system to leave the good bacteria alone and target the pathogens
- Further research has found that good gut microbes play a role to stimulate the production of SIgA
- So they are not just sitting there – they are active players



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## Slide 13

### Gut Microbes

- There are many ways in which the gut microbes affect the immune response
- Germ-free mouse studies show that these mice have a lower number of immune cells than normal mice
- Introduction of bacteria in young mice allows for them to quickly gain immune cells
- Does not happen in adult mice
- The total exact nature of the relationship is not known



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## Slide 14

### Immune Tolerance

- Refers to the lack of reaction by the immune system to a substance or body tissue
- Baby in the womb has immune tolerance
- Gut microflora have immune tolerance
- Everything else must be given immune tolerance and this is controlled by the gut microflora
- Otherwise, we would be experiencing an immune reaction to everything we are exposed to



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## Slide 15

### The Role of T-Cells

- The thymus makes T-cells and there are 3 types we are going to talk: reactive self-antigen T-cells, naive T-cells and regulatory T-cells
- Reactive self-antigen T- cells have the potential to be involved in autoimmunity
- Naive T cells (made by the thymus) are made into other types
- T-Regulatory cells exist as a distinct type of T-Cell



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## T-Regulatory Cells

- They modulate the immune system and maintain tolerance despite the presence of self-antigen T cells
  - Promote anti-inflammatory cytokines which suppresses self-antigen T cell activity
  - T-reg cells are produced in higher numbers to enable control and protect immune tolerance by suppressing self-reactive T cells
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## T-Regulatory Cells

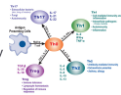
- Studies show that depletion of T-reg cells in normal mice immediately induces autoimmune disease and IBD
- Self-antigen T cells are implicated in type 1 diabetes, MS, and rheumatoid arthritis.
- Without the control exerted by T-reg cells we all have the potential to develop an autoimmune disease.**



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## Gut Connection

- T-reg cells are also produced in the intestines from naive T-cells promoted by metabolites (butyrate) made by the good bacteria
  - **This means that potentially autoimmune diseases and allergies can be resolved in the intestinal immune system**
  - Having sufficient good bacteria is the key to maintaining a normal response (to promote T-reg cells)
  - The maintenance of immune homeostasis by the gut is the key to preventing or resolving autoimmunity
- 
- The diagram illustrates the gut immune homeostasis. It shows a cross-section of the gut wall with 'Gut Bacteria' (green and blue shapes) and 'Dendritic Cells' (blue shapes). A central orange circle labeled 'Treg' is connected to a green circle labeled 'Th17'. The 'Treg' cell is also connected to 'Gut Bacteria' and 'Dendritic Cells'. The 'Th17' cell is connected to 'Gut Bacteria' and 'Dendritic Cells'. The 'Dendritic Cells' are also connected to the 'Treg' and 'Th17' cells. The diagram is labeled 'Gut Immune Homeostasis'.



## Slide 19

### Autoimmunity and 'Leaky Gut'

The Path To Autoimmunity:

1. Dysbiosis: Must be present
2. Genetic Susceptibility: There needs to be up-regulated receptors for a particular type of antigen Eg. In Celiac's, it is an overabundance of CXCR3 receptors on the intestinal wall surface
3. Environmental Triggers: Toxins, undigested food molecules; ie. gliadin for Celiac's
4. 'Leaky Gut': It's controlled by Zonulin and is secreted at higher levels in those with the previous three factors - This process is dynamic and reversible.

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## Slide 20

Journal homepage: [www.elsevier.com/locate/jhepr](http://www.elsevier.com/locate/jhepr)

review

### Modulation of intestinal barrier by intestinal microbiota: Pathological and therapeutic implications

ase M.M. Natividad, Elena F. Verdu\*

Researcher Group: Digestive Health Research Institute, Miquel Marqués University, Barcelona, Spain

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**Keywords:**  
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intestinal permeability  
dysbiosis  
and intestinal permeability

**Abstract:** Alterations in gut microbiota (dysbiosis) have been linked to the recent increased expression of obesity, allergy, autoimmunity, functional and inflammatory disorders such as irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD). In this article, we review the evidence supporting a role of gut microbiota in regulating intestinal barrier function.

**Keywords:** We discuss the hypothesis that the intestinal barrier can be modulated by the gut microbiota and its potential role in the pathogenesis of inflammatory bowel disease. A better understanding of the role of the intestinal microbiota in maintaining a functional intestinal barrier may help develop targeted strategies to prevent and treat IBD.

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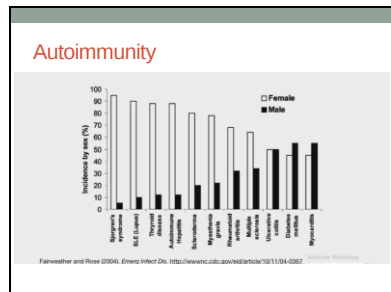
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## Slide 21




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## Autoimmunity

- Mouse study – found that female mice with Diabetes type 1 had lower testosterone than normal mice
- Transfer of adult male microbes to young female mice (with genetic risk) provided protection from developing Diabetes type I

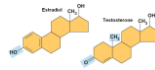
Markle et al, 2013 Science



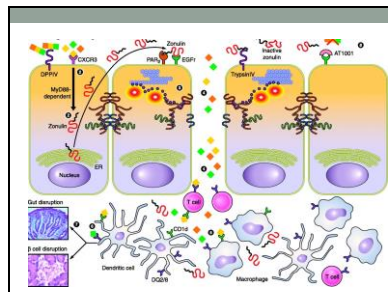
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## Hormones and the Gut

- Estrogen modulates permeability and the tight junctions
- Lack of testosterone delays intestinal healing
- Progesterone helps protect the lining
- Low thyroid hormones are linked to inflammation and immune dysregulation
- Whether there is a direct relationship between these hormones and the gut or the gut can encourage the production of these hormones is not known



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## Slide 25

### Autoimmunity

- Theory now is that the regulation of Zonulin could reverse the autoimmune conditions
- One drug is now in the testing phase which would block Zonulin from locking onto receptor sites – larazotide
- Bad bacteria, fungus (candida) and parasites can also increase Zonulin as can partial protein molecules of food
- Celiacs – gliadin (in the gluten) can effect Zonulin – Zonulin levels are 5 fold (not eating gluten) in Celiacs over those without CD (eating gluten) so something else is stimulating the Zonulin response
- Many CD patients go on to develop other autoimmune conditions



| Group          | Zonulin (pg/ml) |
|----------------|-----------------|
| Control        | ~0.2            |
| Celiac Disease | ~1.0            |

*p < 0.01*

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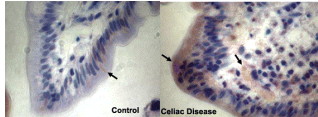
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## Slide 26

### Zonulin Comparison



Control Celiac Disease

Fasano 2011

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## Slide 27

### Autoimmunity

- For asymptomatic Crohn's sufferers, leaky gut (therefore zonulin increase) occurs up to 1 year before a relapse
- IBD – not a lot has been studies but small intestine leaky gut has been linked to the preceding the outbreak of the colitis patches
- Circulating endotoxin (LPS), leaky gut, impaired microbiome and systemic immune response in sporadic Amyotrophic Lateral Sclerosis (sALS)"



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## Slide 28

### Celiac Disease

- One study of celiac children found significantly lower levels of lactobacilli and bifidobacteria than healthy controls and higher bacteria counts for salmonella, staphylococcus, klebsiella and shigella
- One experiment of sourdough fermented with selected lactobacilli strains and fungal proteases, showed gluten and gliadin completely broken down
- B. Lactis can inhibit the damage of gliadin to the epithelial cells
- Other studies show probiotics can repair the intestinal damage of celiac disease and lower inflammation



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## Slide 29

### Diabetes Type 1

- Four children who develop Diabetes type 1 had 25% less types of bacteria than other children
- They also had more bacteria strains known to trigger inflammation
- GLP-1(1–37) is a peptide that can be produced in the intestinal cells that enhances insulin release
- One study of a engineered lactobacilli bacteria to produce GLP-1(1–37) was given to rats with type 1 diabetes
- Rats fed GLP-1-secreting bacteria showed significant increases in insulin levels and, additionally, were significantly more glucose tolerant than those fed the parent bacterial strain.
- DPP-IV inactivates GLP-1



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## Slide 30

### MS and The Gut

- One study of MS patients in comparison the healthy controls looked at the types of fecal bacteria – MS patients had dysbiosis and high populations of specific strains of bad bacteria
- In one study, mice with MS were given various combinations of L. paracasei DSM 13434, L. plantarum DSM 15312 and DSM 15313
- None of the strains works as well by themselves as they worked together
- But together they induced T-reg cell production in the mesenteric lymph nodes, and the CNS and IL-10 production was increased as well



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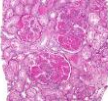
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## Slide 31

### Lupus

- A mouse model for Lupus found that the Lupus mice had lower levels of lactobacillus and higher levels of a type of clostridia and *lachnospiraceae* than controls and that the levels increased as the disease progressed
- The differences were only found in the female mice
- Same study and others found that probiotics with lactobacillus strains can help mitigate symptoms



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## Slide 32

### Rheumatoid Arthritis

- One study of fecal bacteria found that RA patients had higher levels of lactobacillus than controls
- Higher levels of *L. Salvarius* were found
- Also dysbiosis in the mouth was found
- Another double blind placebo study of Rheumatoid Arthritis sufferers found that *L. casei* supplementation lowered C-reactive protein and increase IL-10
- In another study, *L. Helveticus* also was found to reduce pro-inflammatory cytokines (TNF-Alpha), IgG responses and increased IL-10



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## Slide 33

### What We Can Make Of This

- Clearly, the dybiosis connection to autoimmunity is being established in the research
- However, what is also immerging is that the diversity – what types of strains are being linked to what type of autoimmune condition occurs
- This does not help once a person has the autoimmune disease but makes a great case for why we need better diet and lifestyle changes to prevent
- In the meantime, gut health work is essential and we get to use food
  - not just supplements



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## Slide 34

### Supplementing With Probiotics

- Meta-analysis of 57 human studies found probiotics safe for immune compromised adults (Van den Nieuwboer et al. 2015 *Beneficial Microbes*)
- Will help promote T-reg cells in the intestines (*Bacteroides fragilis*)
- Creates an environment of high concentration of anti-inflammatory chemicals TGF-Beta and IL-10 in the intestinal mucosa.
- The goal is to re-create immune tolerance which can provide a significant decrease in autoimmunity
- Strains that have anti-inflammatory benefit include *L. rhamnosus* GG, *L. breve*, *L. casei*, *L. plantarum*, *Streptococcus thermophilus* to name a few



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## Slide 35

### Developing A Protocol

- No whole food is the cause of anything (by itself)
- Before removing foods – do a food journal
- Be sure to not bias the client – do not tell them what you are looking for
- Consider whether a Candidiasis protocol is needed (an antimicrobial)
- IgG testing is one option (see CAHN-Pro website – [www.cahnpro.org](http://www.cahnpro.org) – trainings tab – click free webinar)
- Try to craft a food program that is as liveable as possible
- Digestive enzymes will be extremely helpful



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## Slide 36

### Diet and Autoimmunity

- Autoimmunity symptoms are generally worse for those who follow a Western-style diet
- Research is confirming that lower-calorie, moderate exercise and more whole foods especially prebiotic and probiotics foods can lower inflammatory markers
- Strategies to help clients understand that they can help their condition by making changes to their diet is going to be a the goal



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## Slide 37

### Prebiotic Foods

- Prebiotic foods including resistant starch foods – grains, legumes, nut, seeds potatoes and sweet potatoes etc.
- Bifidus bacterium ferments resistant starch to create short chain fatty acids such as butyrate which helps fix 'leaky gut' and promote T-reg cells
- Prebiotic foods such as tomatoes, broccoli, berries, apples, almonds, kale, spinach, asparagus help feed good bacteria (contain inulin, FOS)



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## Slide 38

- Dairy products contain GOS – another important prebiotic
- Some people may have issues with some of these foods – may be IgG issue or pancreatic enzyme issue
- Fermented foods contribute good bacteria to the gut and many also contain prebiotics – help lower inflammation



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## Slide 39

### Autoimmunity Strategy

- Plant sterols can play a role in supporting the immune system and calming the autoimmune reaction (help stimulate T-reg cells and lower inflammation)
- Glutamine and glutamine-rich foods (bone broths or vegetarian glutamine powder in veg broth) very helpful
- In severe cases, a leaky gut protocol may be necessary which can involve the removal of foods
- Autoimmune strategies will take years so finding a protocol that the client can live with is key



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