ALTRE CONDIZIONI IN CUI VIENE UTILIZZATA LA DIETA SENZA GLUTINE

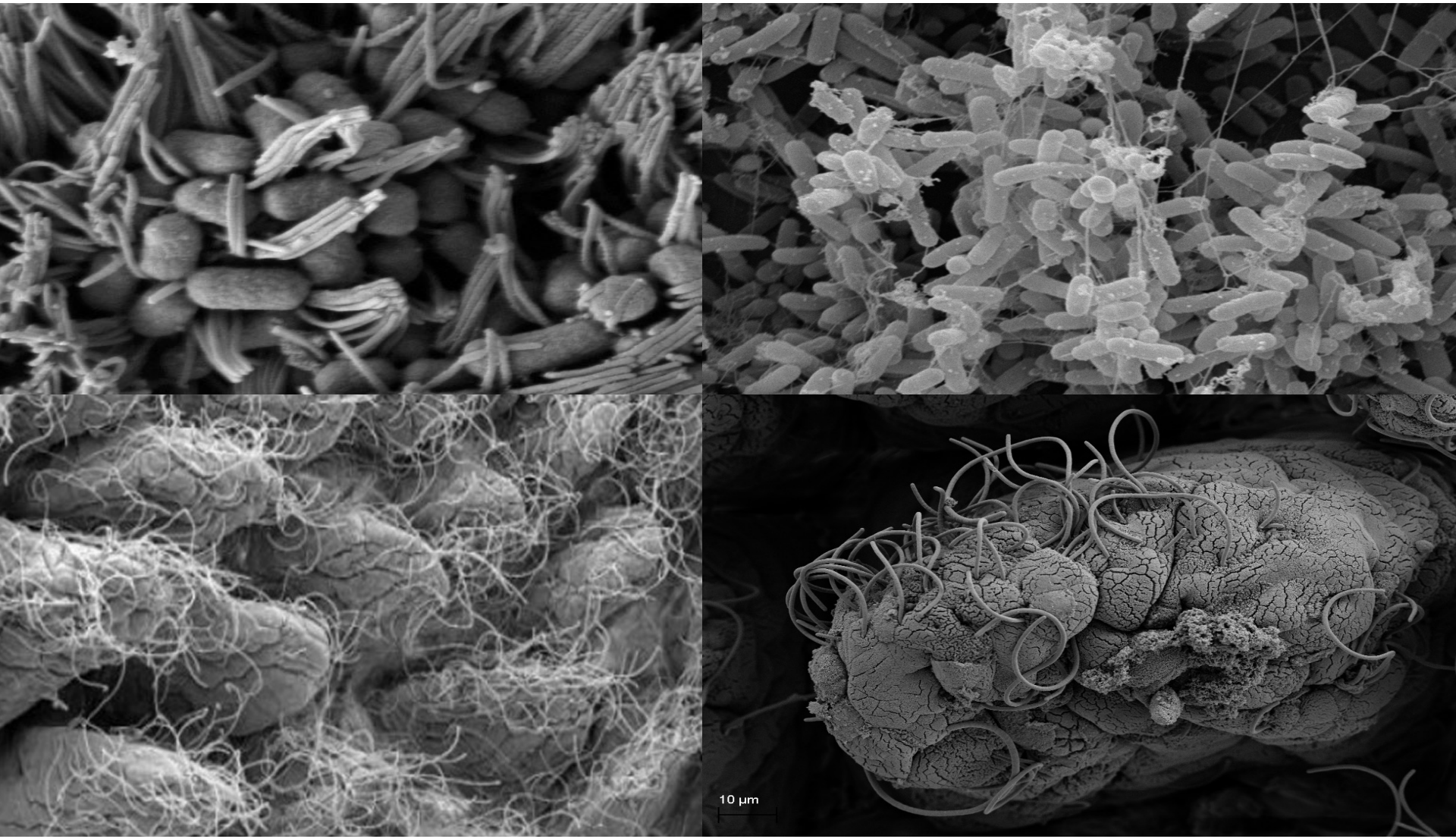
Antonio Gasbarrini
CEMAD Digestive Disease Center
Fondazione Policlinico Universitario Gemelli IRCCS
Univeristà Cattolica del Sacro Cuore, Roma

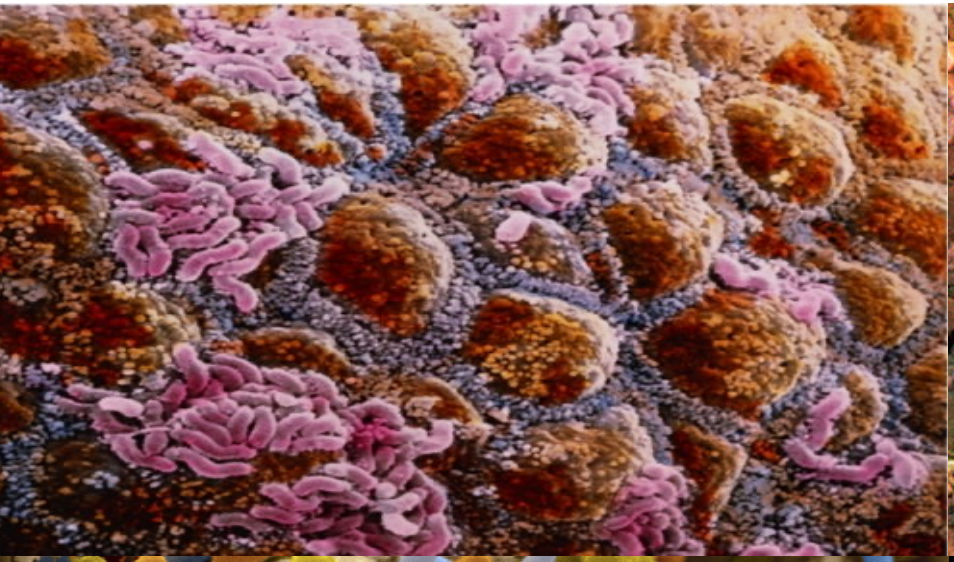
AGENDA

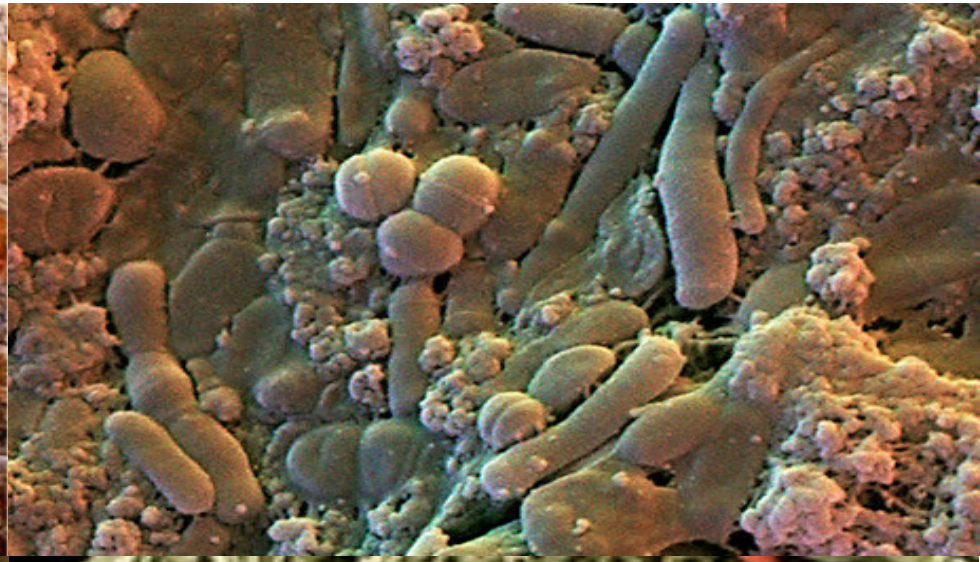
- GFD & microbiota
- GFD & IBS
- GFD & autoimmunità
- GFD & fibromialgia
- GFD & diabete

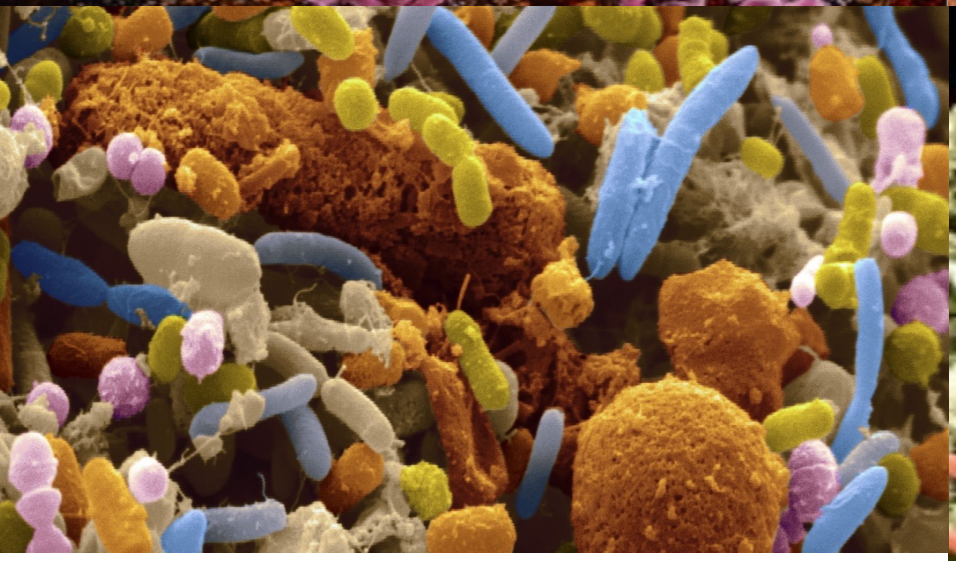
AGENDA

- GFD & microbiota
- GFD & IBS
- GFD & autoimmunità
- GFD & fibromialgia
- GFD & diabete


10 µm









ANATOMO-MICROBIOLOGICAL BARRIER



THE -OMICS REVOLUTION

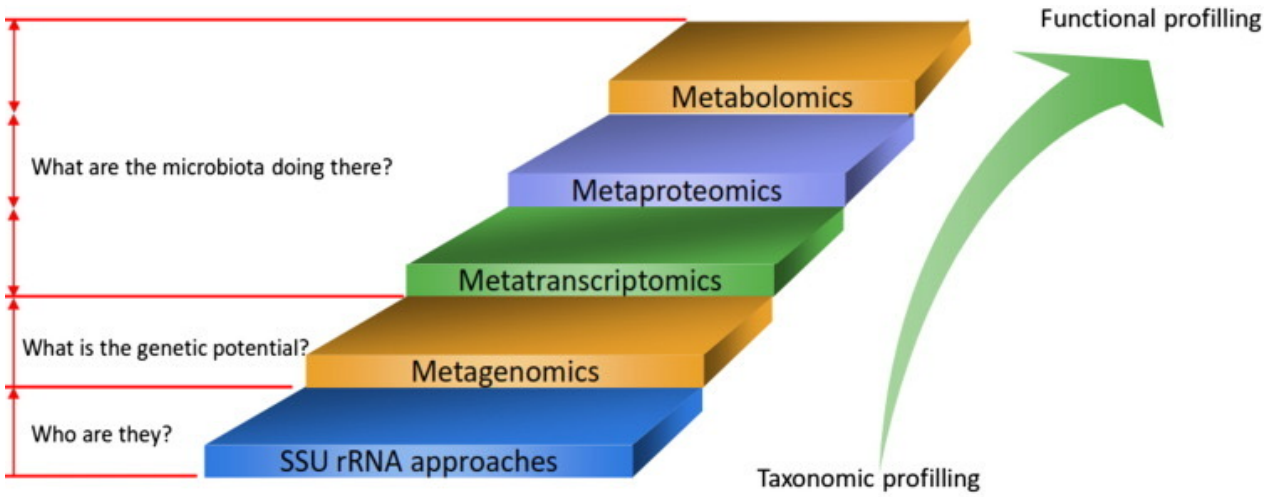
MICROBIOMICS: microbiota collective coding capacity

METAGENOMICS: experimentally determined dataset from shotgun sequencing the genomes of microorganisms in a particular sample.

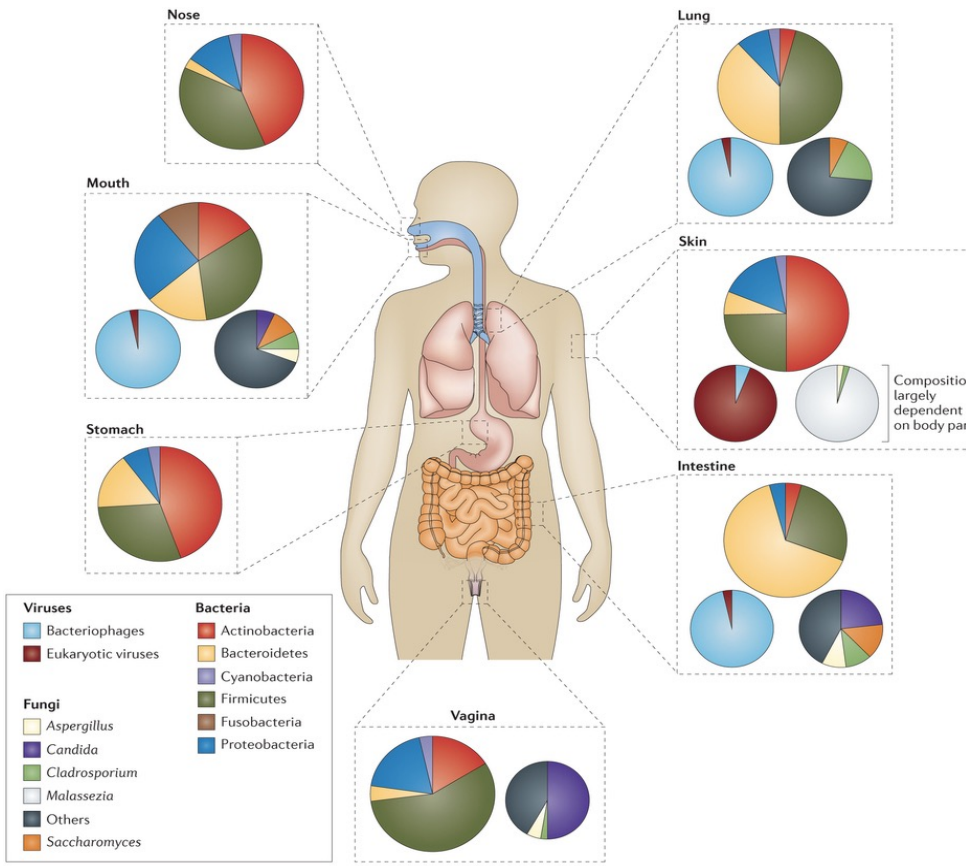
METATRANSCRIPTOMICS: shotgun sequencing of reverse-transcribed RNA transcripts

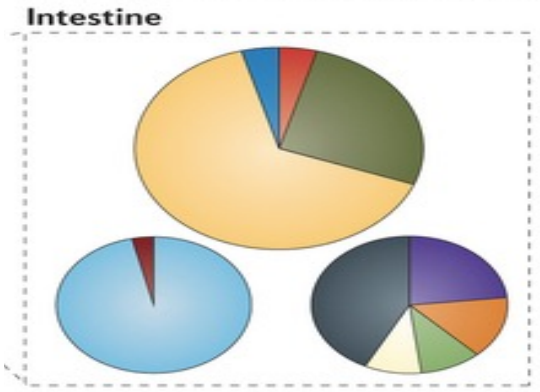
METAPROTEOMICS: the quantification of protein or peptide levels

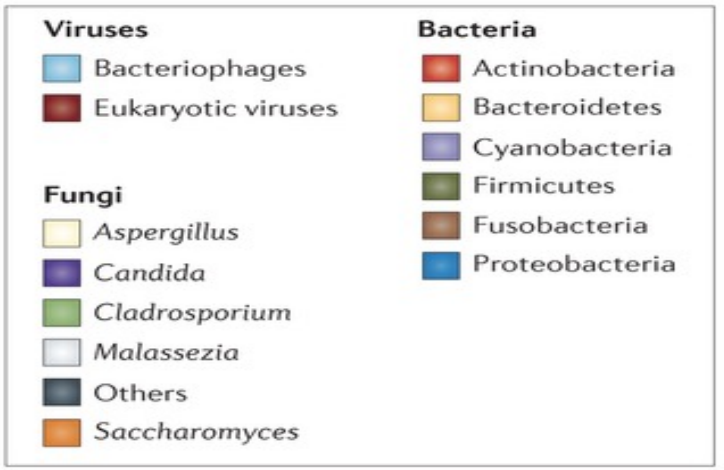
METABOLOMICS: investigation of small-molecule metabolites



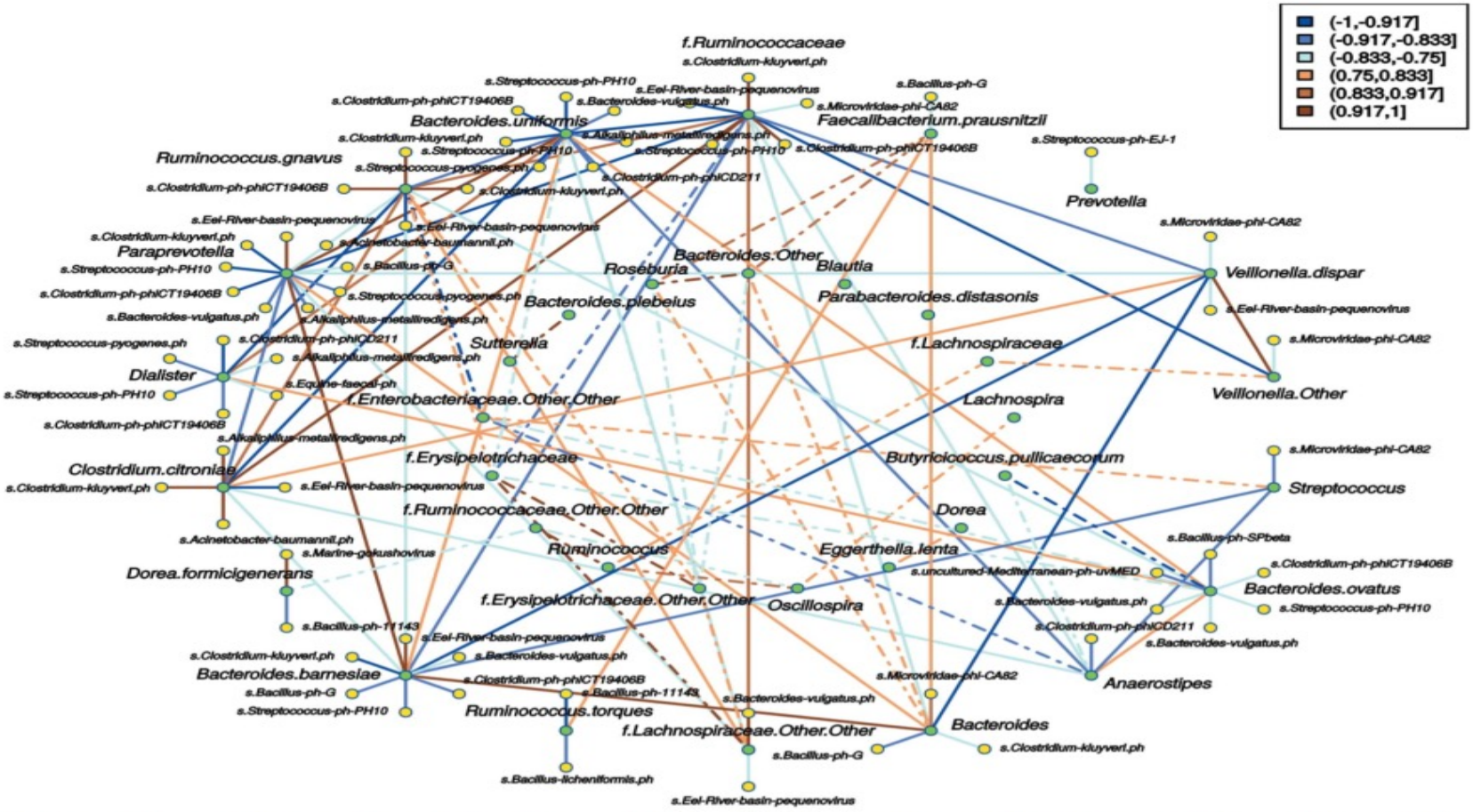
Human microbiota composition







Microbial correlation networkorking between relative abundance of *bacterial, yeast and bacteriophage*-matching reads



EUBIOSIS

EU= good; BIOS= life

An healthy relationship among commensal MICROBES (within an healthy gut anatomical barrier)

COMPOSITION

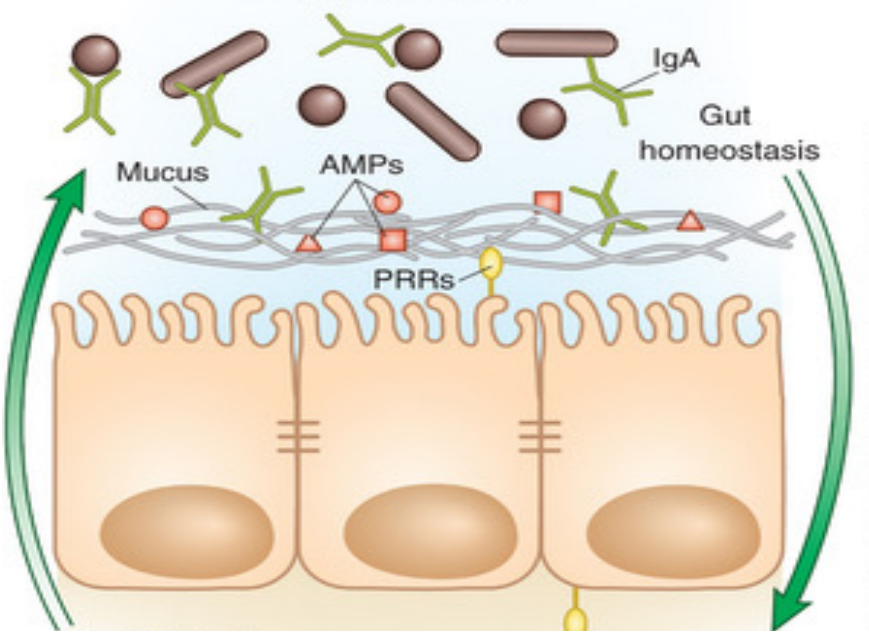
- **Diversity**
- **Richness**
- **Relative Abundance**

FUNCTION

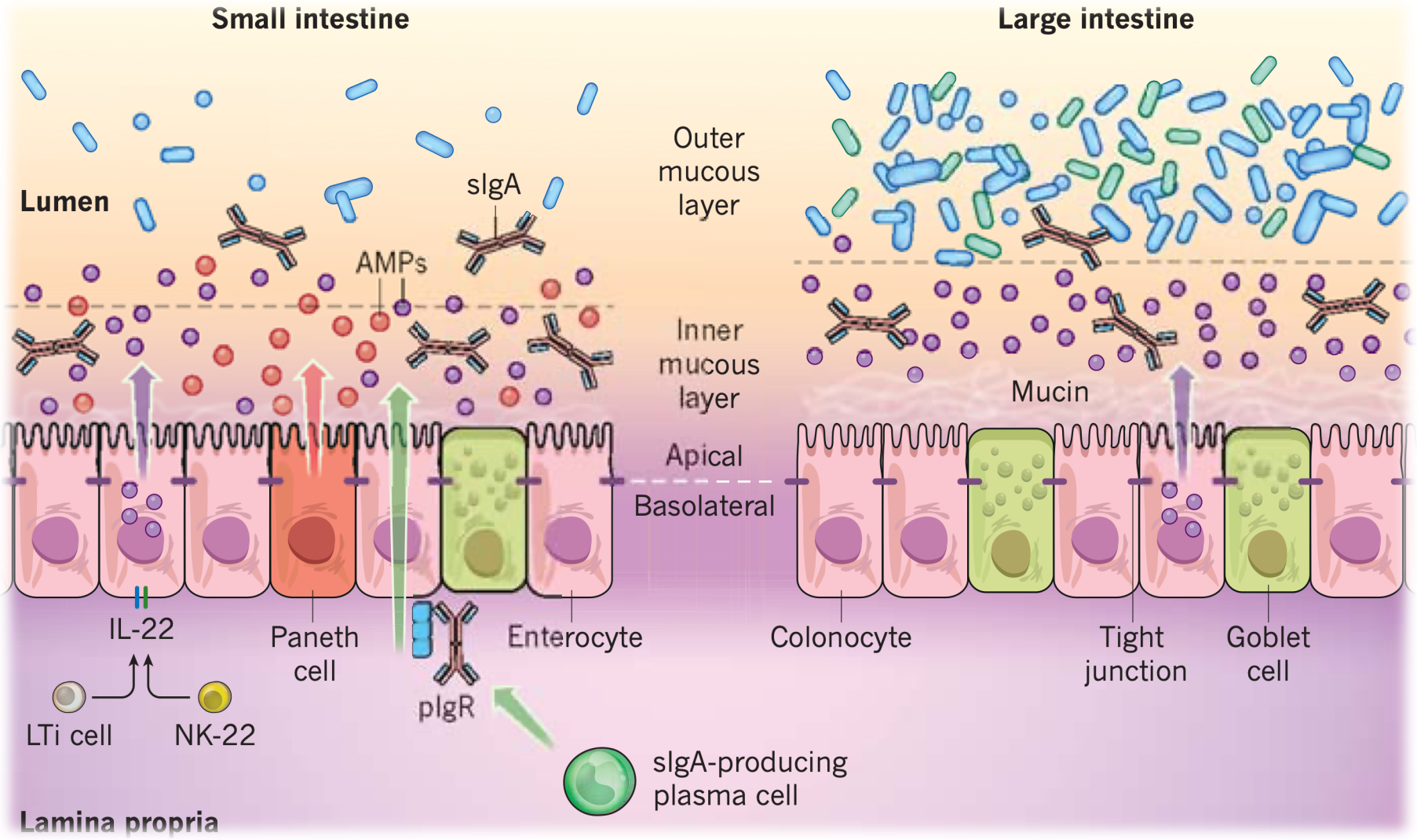
- **Microbiota's effect on host health**

FUNCTIONS OF GUT MICROBIOTA ON HOST HEALTH

- Immunocompetence/Tolerance
- Barrier effect
- Synthesis
- Metabolism
- Drug metabolism
- Behavior conditioning



Lifelong immune stimulation by enteric commensal and pathogenic bacteria



Maynard CL et al. Nature 2012

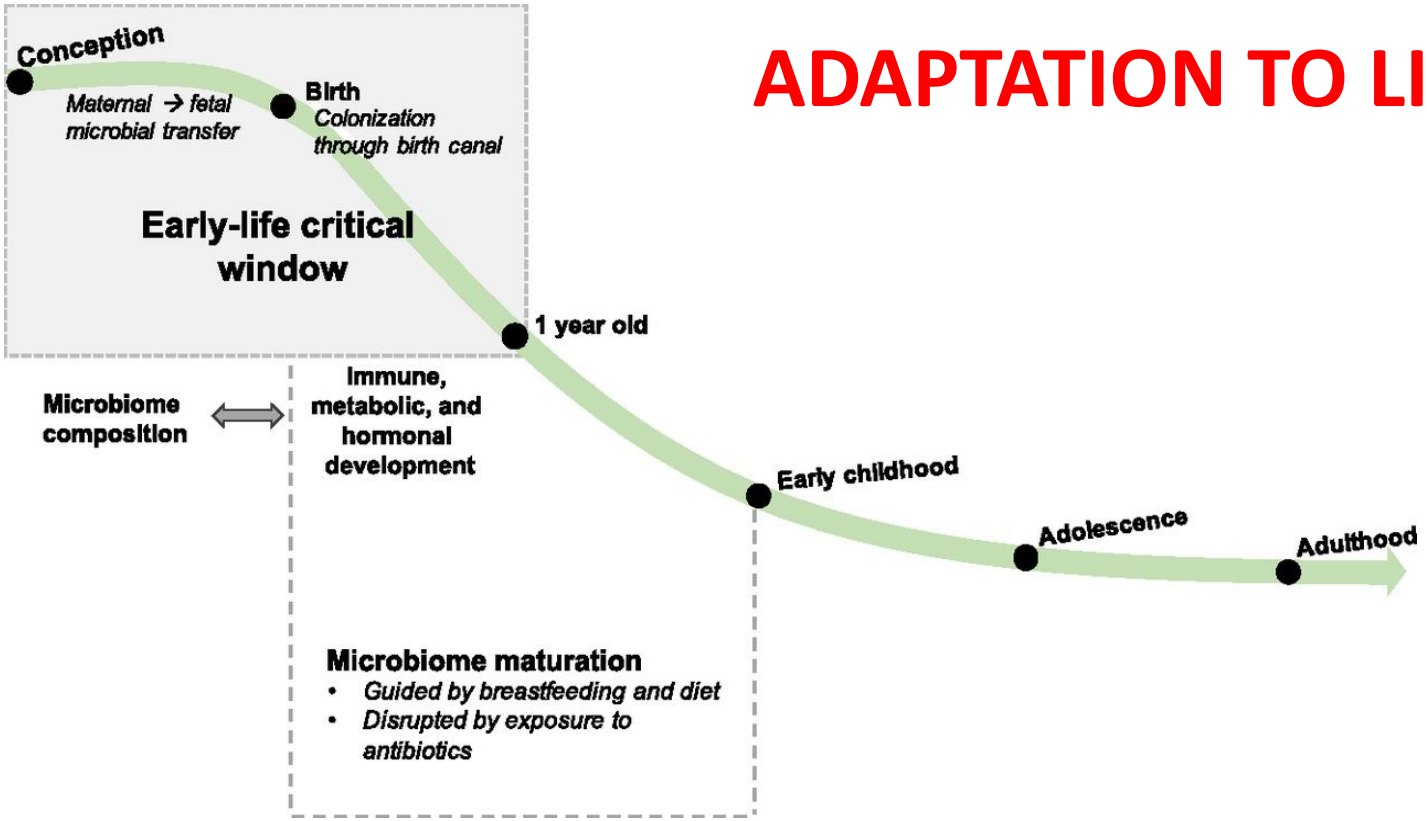
HOST-MICROBIAL INTERACTION

The microbial genome is the variable part of our genome that makes possible human adaptation to external perturbations *(ie diet, starvation, overfeeding, food preservatives, antibiotics, stress, violence..)*



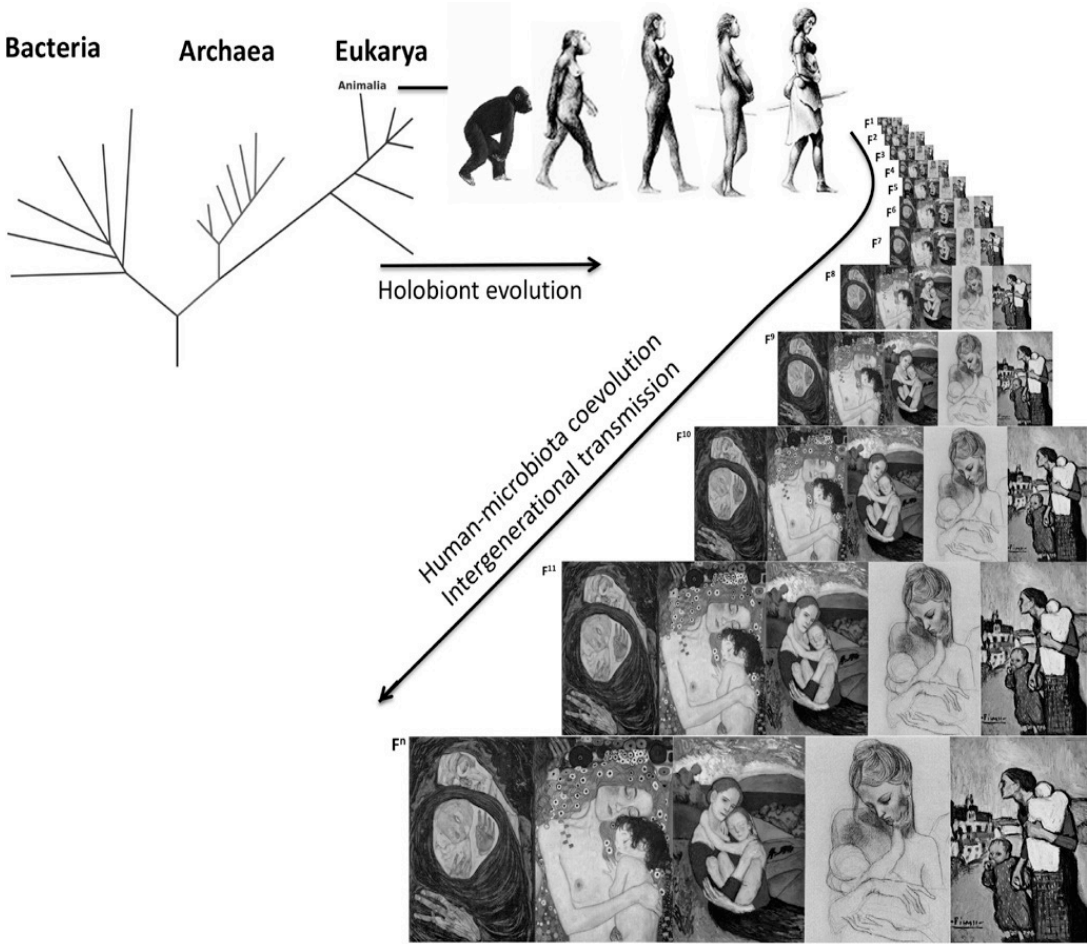
Past selective pressures during human evolution

ADAPTATION TO LIFE



*Any **stressor** in this phase = long term effects*

Milani C et al. Microbiol and Mol Biol Rev 2017



In stable condition The microbiota has been transferred throughout generations of humans with **MATRILINEAL VERTICAL LINE**

Vertical humans trasmission led to ***conservation of phylogenetic signal*** in human microbiota comunities

Dominguez-Bello MG,Gut, 2019

Gut microbiota and Celiac Disease:
Under the influence of HLA?

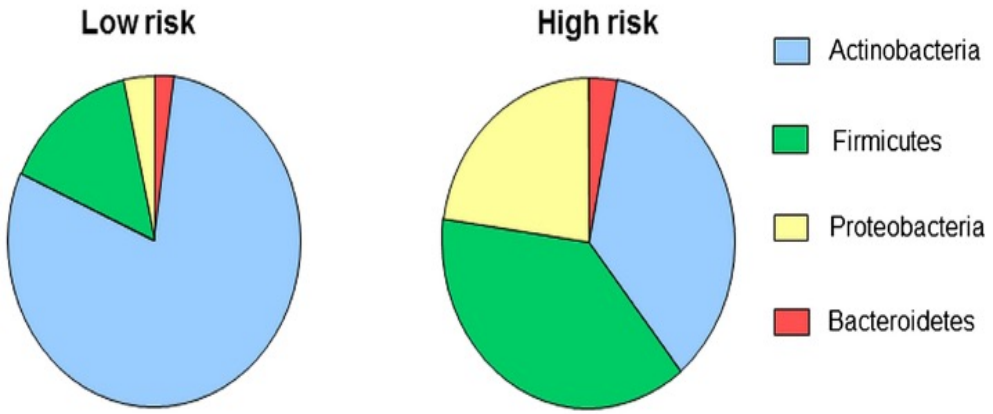
The HLA-DQ2 genotype selects for early intestinal microbiota composition in infants at high risk of developing coeliac disease

- ★ 22 breastfed and vaginally delivered infants with one first-degree relative with CD
- ★ HLA-DQ2 VS non-HLA-DQ2/8 carriers
- ★ 16S rRNA gene Pyrosequencing + qRT PCR

DQ2 vs Non DQ2/8 - Phylum level

Firmicutes
Proteobacteria

Actinobacteria



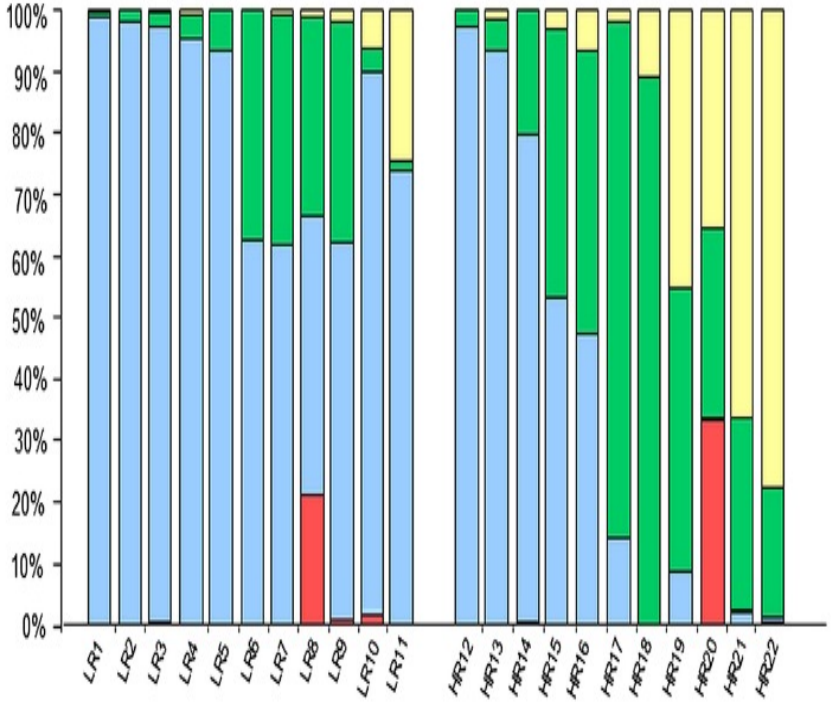
Olivares - Gut 2014

Gut microbiota and Celiac Disease:
Under the influence of HLA?

DQ2 vs Non DQ2/8 - Genus level

Corynebacterium; Gemella
Clostridium sensu stricto,
Unclassified Clostridiaceae
Unclassified Enterobacteriaceae
Raoultella

Bifidobacterium
Unclassified Bifidobacteriaceae



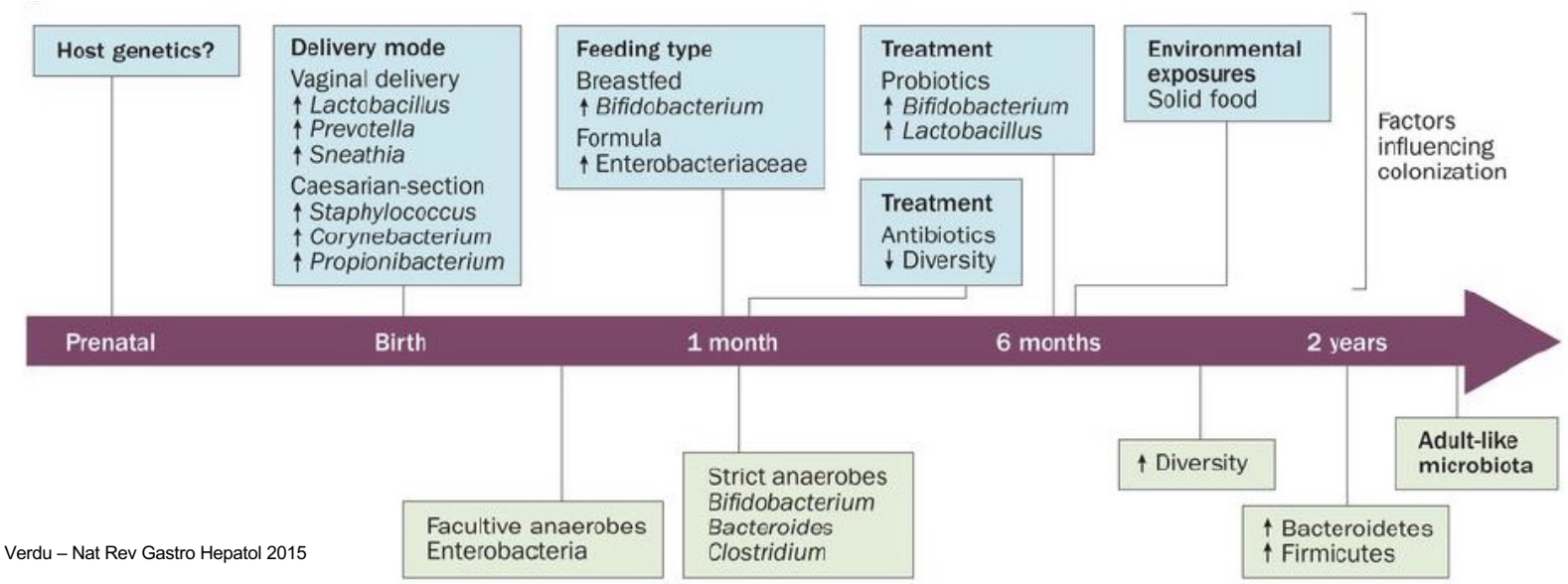
Olivares - Gut 2014

Native CORE microbiota

An early programming with life long-effects develops during weaning (first 24 months of life)

Koenig JE et al, PNAS 2010

Early determinants of microbiota composition

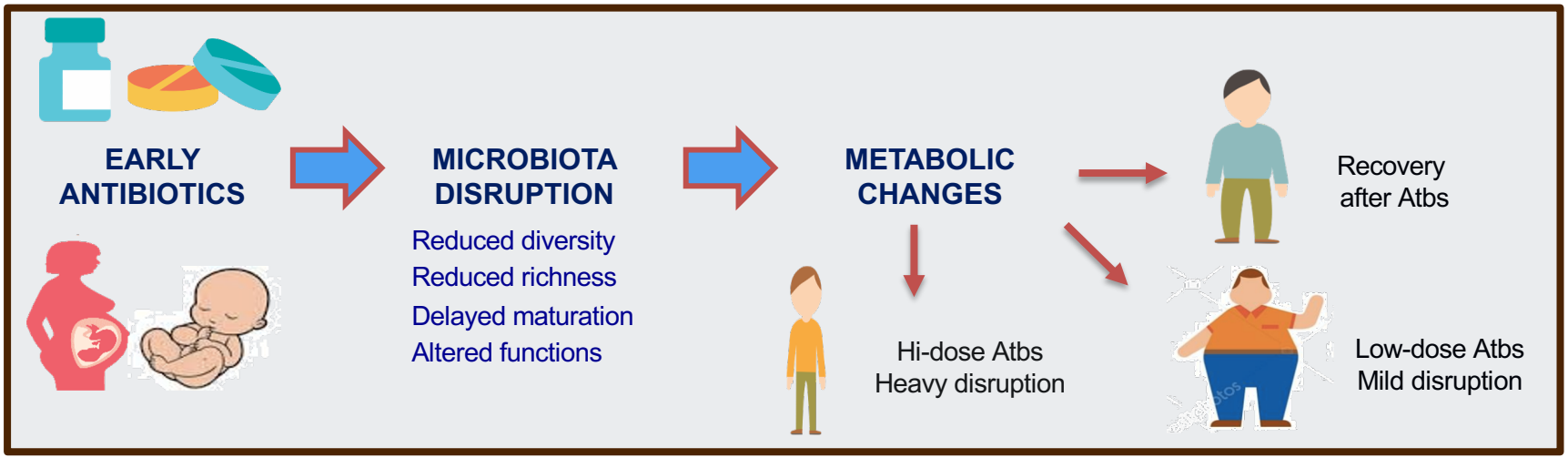


Verdu – Nat Rev Gastro Hepatol 2015

Early life is the key period for microbe-mediated programming of host metabolism

- There is a **critical window** (early life) where even transient alteration of healthy microbiota can drive to long-lasting effects

Cox et al – Cell 2014 Cox et al - Nat Rev Endocrin 2015



Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa

Carlotta De Filippo[a], Duccio Cavalieri[a], Monica Di Paola[b], Matteo Ramazzotti[c], Jean Baptiste Poullet[d], Sebastien Massart[d], Silvia Collini[b], Giuseppe Pieraccini[e], and Paolo Lionetti[b,1]

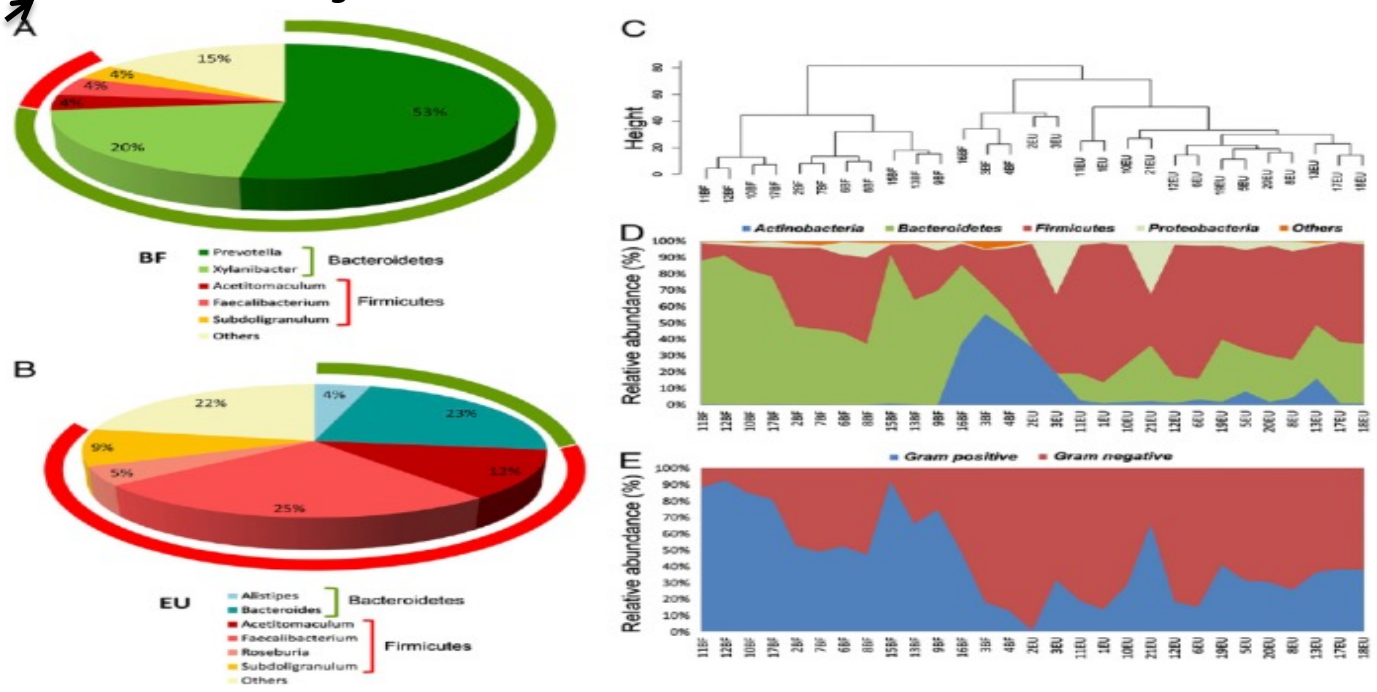
Resistant starch: millet and sorghum

Burkina Faso
Bacteroidetes >Firmicutes

Prevotella

Europe
Firmicutes >Bacteroidetes

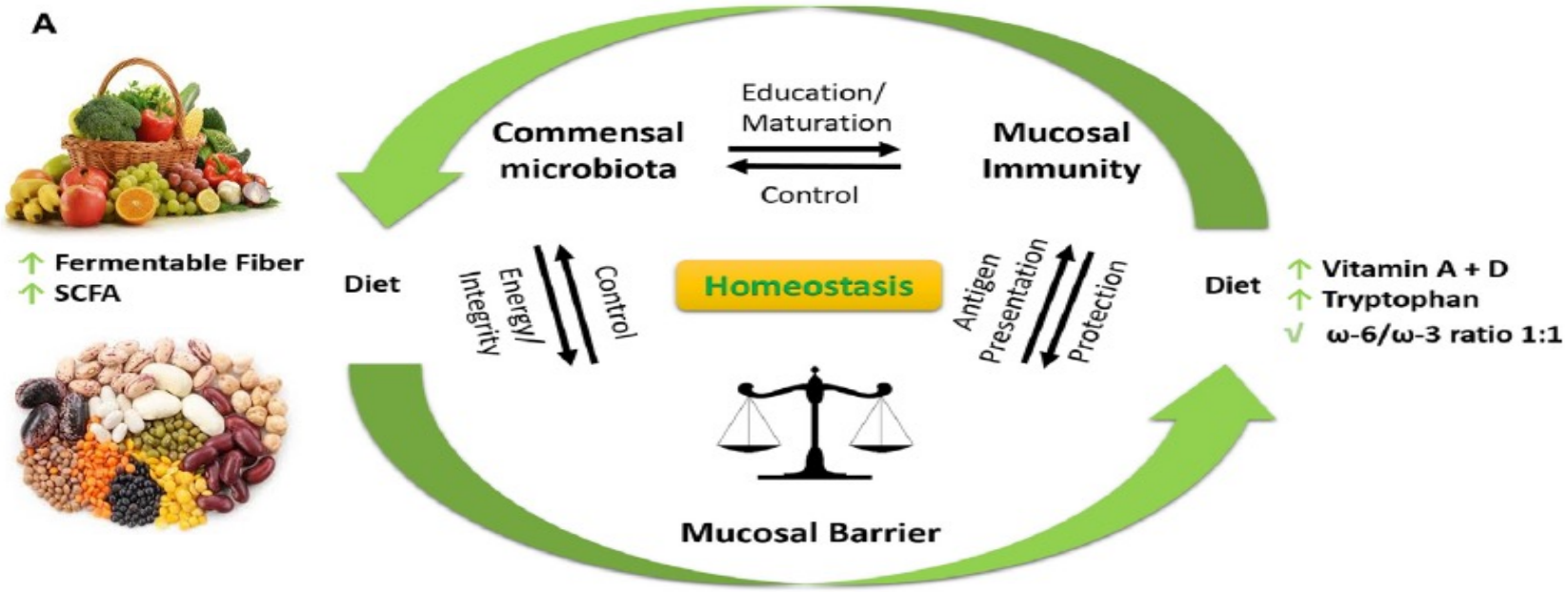
Bacteroides



De Filippo et al, PNAS 2010

Microbiota influencers
High-fiber diet

- ★ **High-fiber diet is associated with reduced risk for IBD, metabolic disease and asthma**



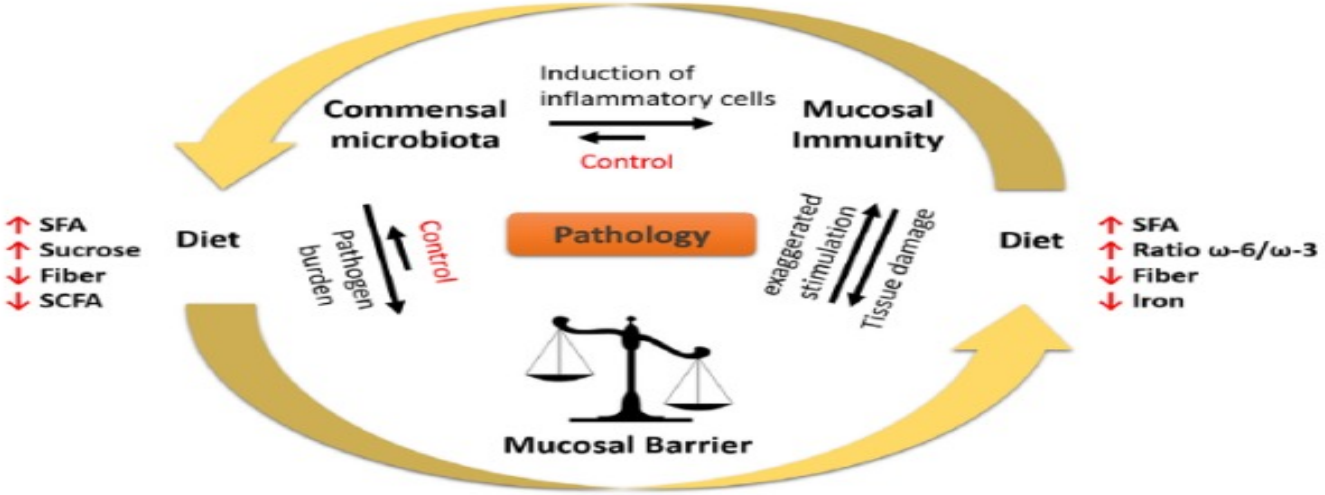
Statovci et al, Front Immunol. 2017

Microbiota influencers
Western diet

- ★ **Western diet is associated with increased risk for IBD, metabolic disease and asthma**







High-fat and sucrose-rich diet increases permeability of epithelial barrier

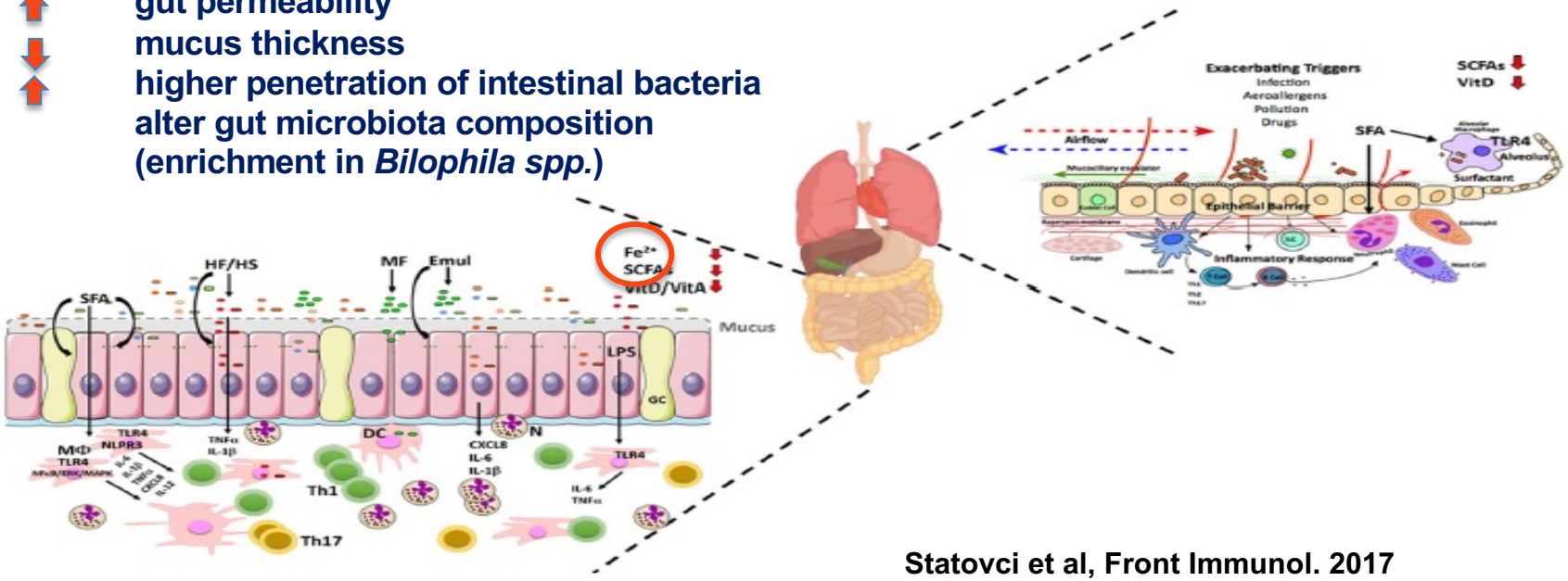
Statovci et al, Front Immunol. 2017

Microbiota influencers
Emulsifiers

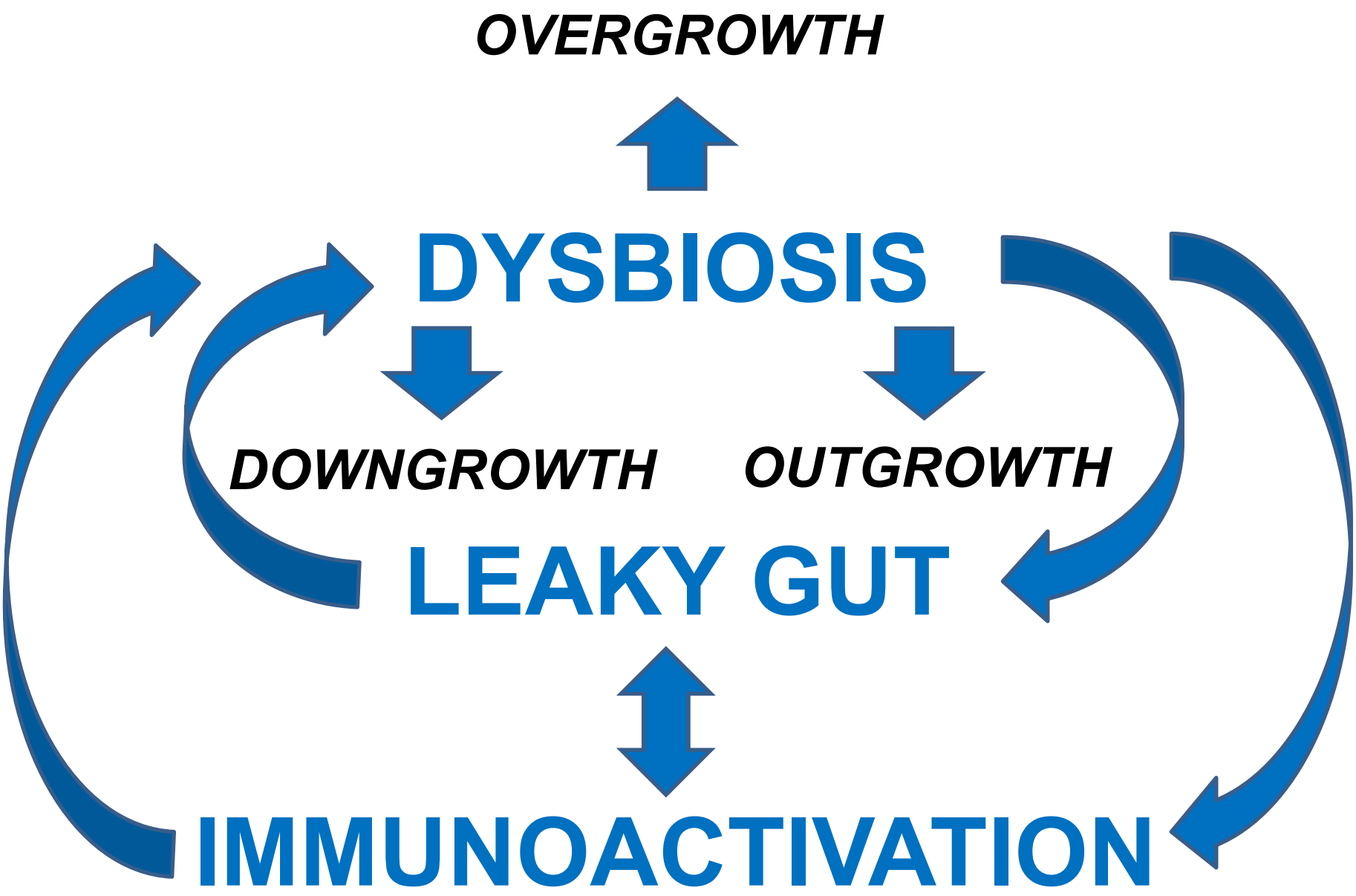
Emulsifiers such as polysorbate-80 and carboxymethylcellulose are used in processed foods

Emulsifiers could aggravate colitis:

- ↑ gut permeability
- ↓ mucus thickness
- ↑ higher penetration of intestinal bacteria
- alter gut microbiota composition (enrichment in *Bilophila spp.*)



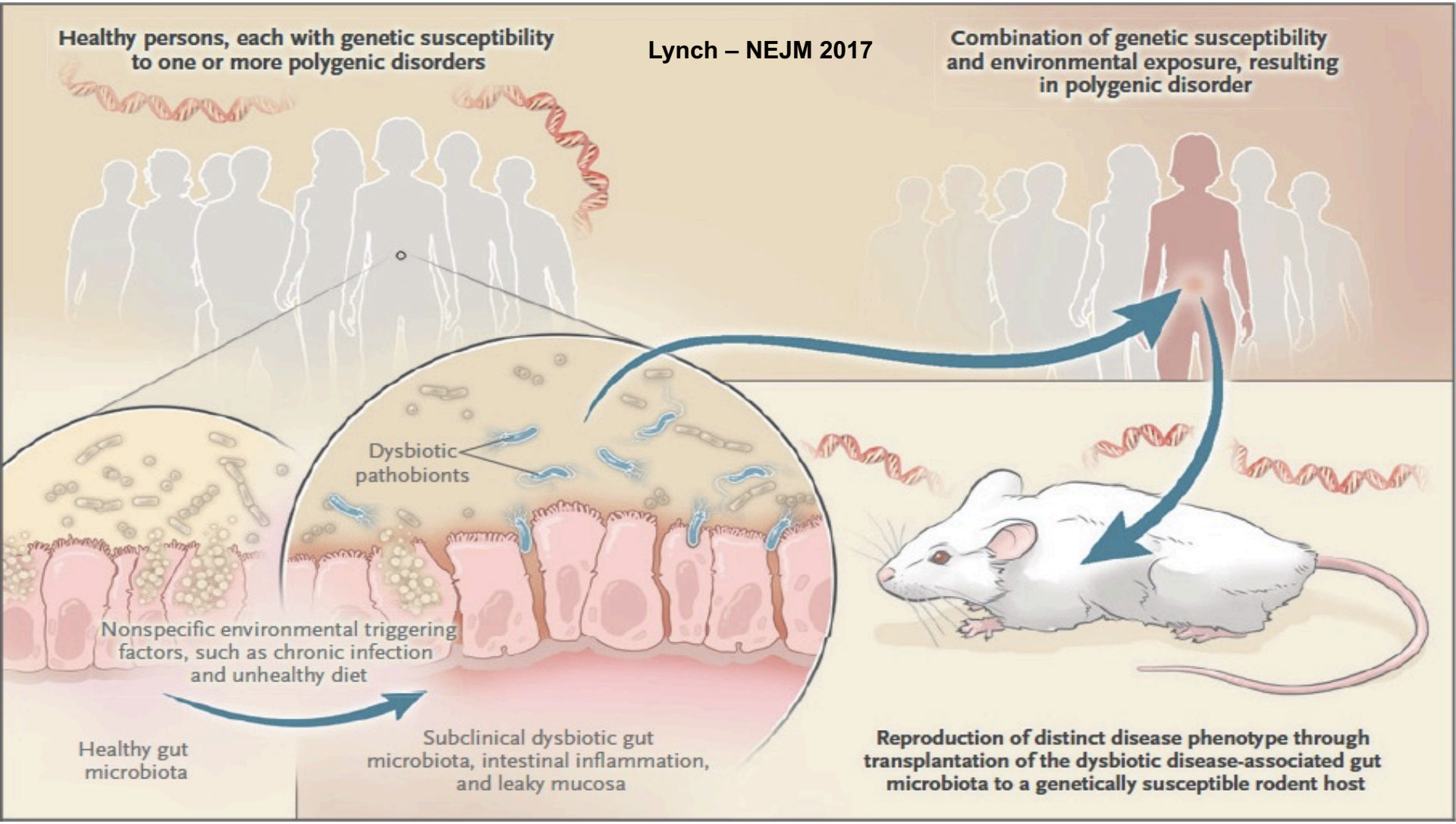
Statovci et al, Front Immunol. 2017


OVERGROWTH
DYSBIOSIS
DOWNGROWTH
OUTGROWTH
LEAKY GUT
IMMUNOACTIVATION

MICROBIOTA ASSOCIATED DISEASES

- *Gatrointestinal, lung, genito-urinary tract infections*
- *Irritable Bowel Syndrome*
- *Inflammatory Bowel Disorders*
- *Diverticulosis*
- *Celiac disease and Malabsorption*
- *Food Intolerance/Allergy*
- *Gastrointestinal Cancers*
- *Liver diseases*
- *Pancreatic diseases*
- *Obesity, Diabetes and Metabolic Syndrome*
- *Nephrological, Gynecological, Urological, Oncological, Rheumatological/autoimmune, Cardiovascular, Neurological (Parkinson, Alzheimer, MS..), Psichiatric disorders (schizofrenia, anxiety/depression, autism..)*

ENTEROPATHOGENETIC SYNDROMES


Healthy persons, each with genetic susceptibility to one or more polygenic disorders
Lynch – NEJM 2017
Combination of genetic susceptibility and environmental exposure, resulting in polygenic disorder
Dysbiotic pathobionts
Nonspecific environmental triggering factors, such as chronic infection and unhealthy diet
Healthy gut microbiota
Subclinical dysbiotic gut microbiota, intestinal inflammation, and leaky mucosa
Reproduction of distinct disease phenotype through transplantation of the dysbiotic disease-associated gut microbiota to a genetically susceptible rodent host

Microbiota transmits Colitic phenotype

Garrett, Cell 2007;131(1):33-45

TRUC mice, deficient for Tbet and Rag





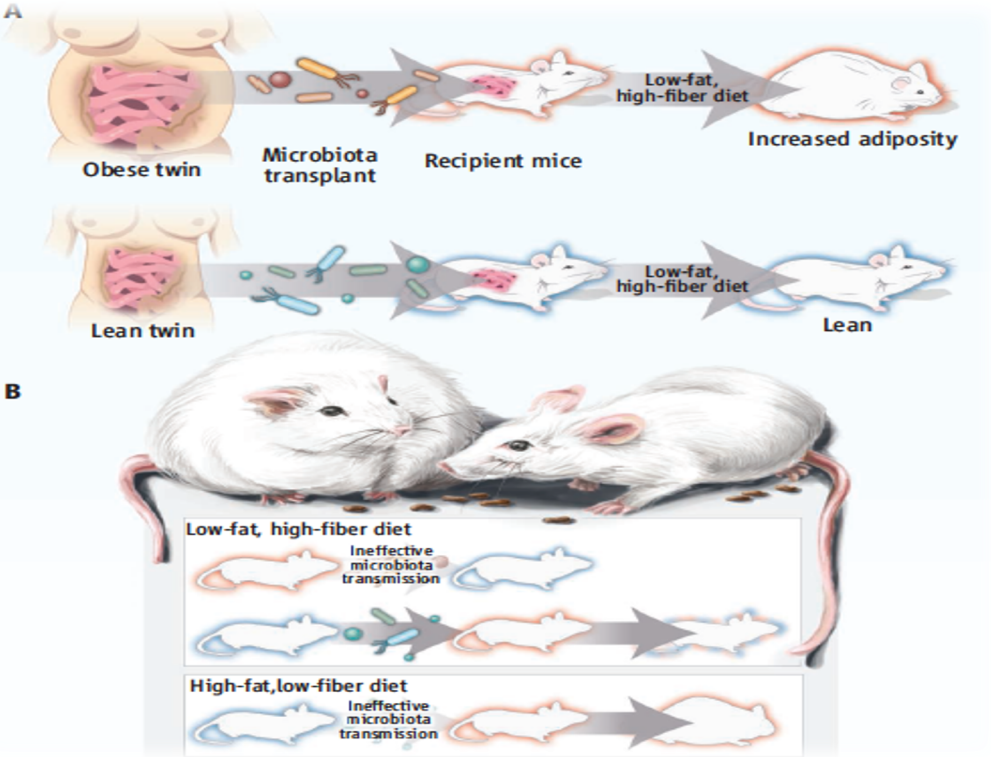


Colitic phenotype could be transmitted vertically to progeny of affected parents and horizontally to unrelated animals

Microbiota transmits an Obesity phenotype

Ridaura et al. Science 2013, 341 (6150)

Fecal microbiota from 4 human female twin pairs discordant for obesity



TRANSFERRED INTO THE INTESTINES OF GERM-FREE MICE

(Ob) twin + mice = ↑adiposity

(Ln) twin + mice = ↓ adiposity

TRANSMISSIBILITY OF INTESTINAL MICROBES AND ADIPOSITY PHENOTYPE ARE TIGHTLY LINKED

COHOUSING

(Ob) twin transplanted mice +

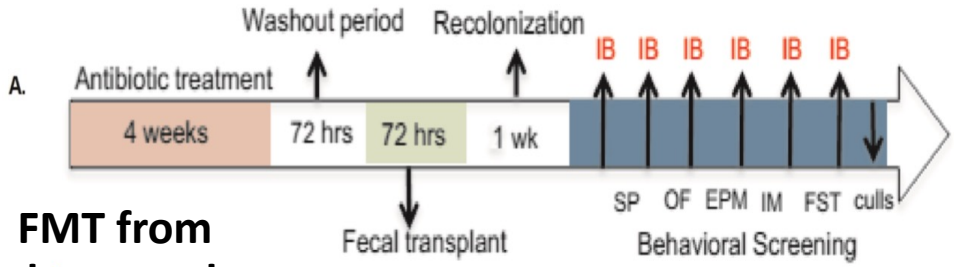
(Ln) twin transplanted mice =

(Ob) mice became LEAN

(Ln) mice remain LEAN

Microbiota transmits a Depressive phenotype

Kelly, J Psychiatric Research 2016, Kelly Nature 2019





Microbiota depleted antibiotic rat model

FMT from depressed patients to rats with a depleted gut microbiota (after antibiotics treatment)

DEPRESSIVE PHENOTYPE

Anhedonia

Anxiety-like behaviuors

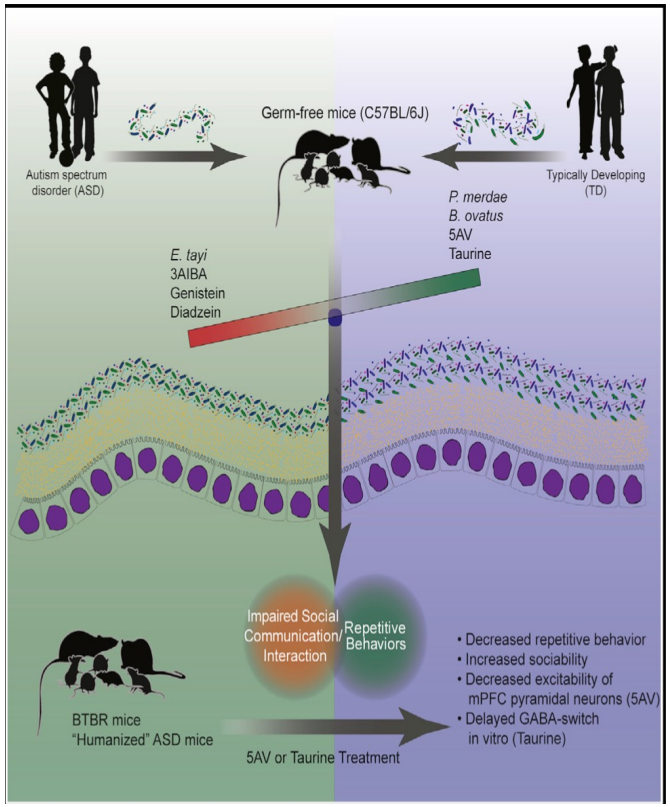
- Increased kynurenine/tryptophane ratio

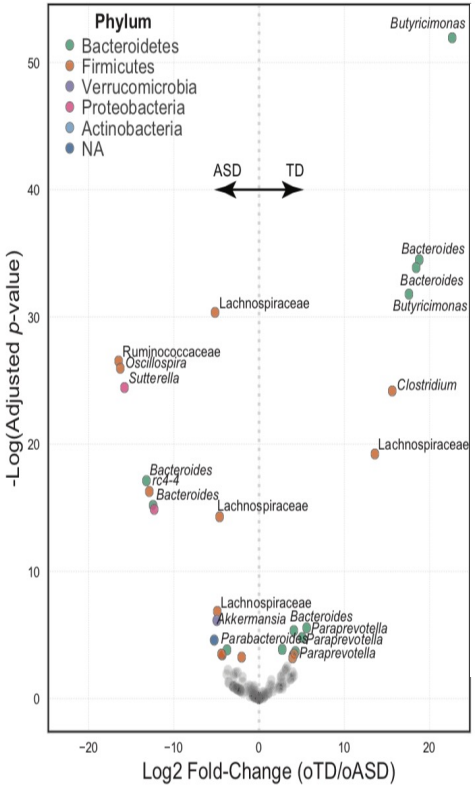
- Proinflammatory profile

IMMUNE MEDIATED MECHANISM for the development of the depressive phenotype in rats

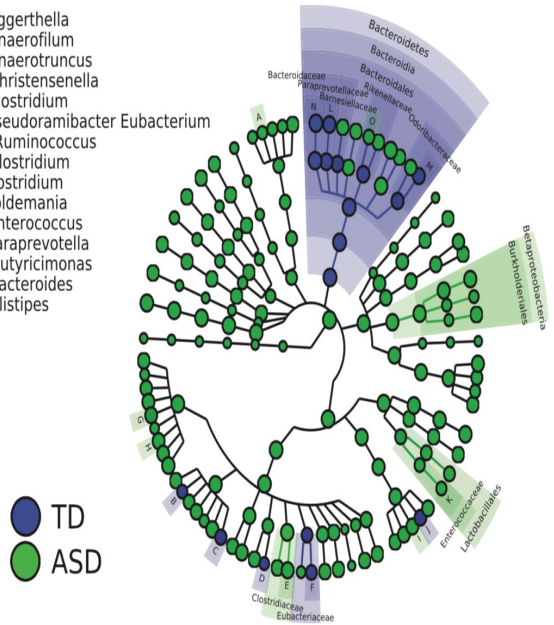
Microbiota transmits an Autistic Spectrum Disorders phenotype

Sharon, 2019, Cell





A:Eggerthella
B:Anaerofilum
C:Anaerotruncus
D:Christensenella
E:Clostridium
F:Pseudoramibacter Eubacterium
G: Ruminococcus
H:Clostridium
I:Clostridium
J:Holdemania
K:Enterococcus
L:Paraprevotella
M:Butyricimonas
N:Bacteroides
O:Alistipes

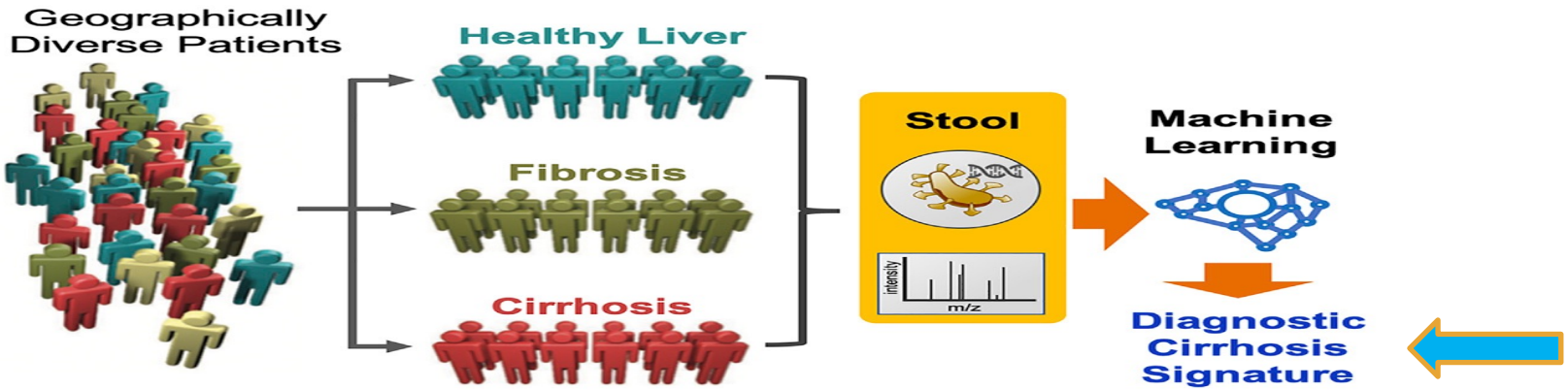


THE IMPACT OF MICROBIOTA ON DIGESTIVE AND EXTRADIGESTIVE DISORDERS

PROGRESSION

MICROBIOME SIGNATURE can predict progression from NAFLD to liver cirrhosis

Diagnostic signatures for fibrosis from stool metagenomic and metabolomic profiling that, when combined with serum AST levels, distinguishes cirrhosis in mixed fibrosis cohort.

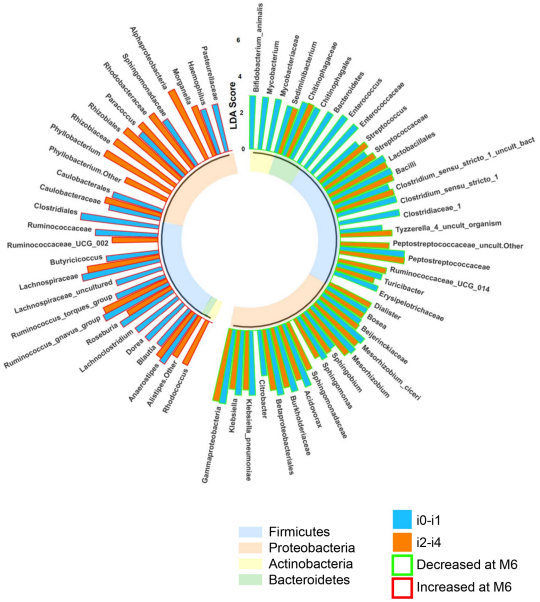


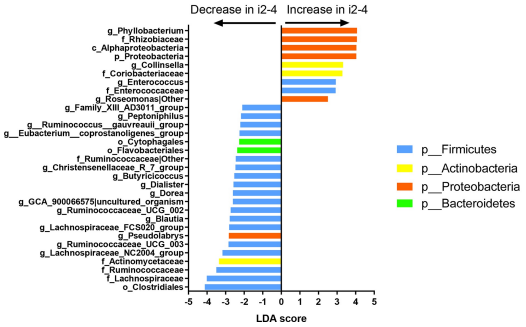
This combination signature was validated in racially and geographically independent cohorts

Oh et al – Cell Metab 2020

MICROBIOME SIGNATURE can predict post-surgical Crohn's recurrence

Endoscopic recurrence is associated with strong changes in ileal mucosa-associated microbiota

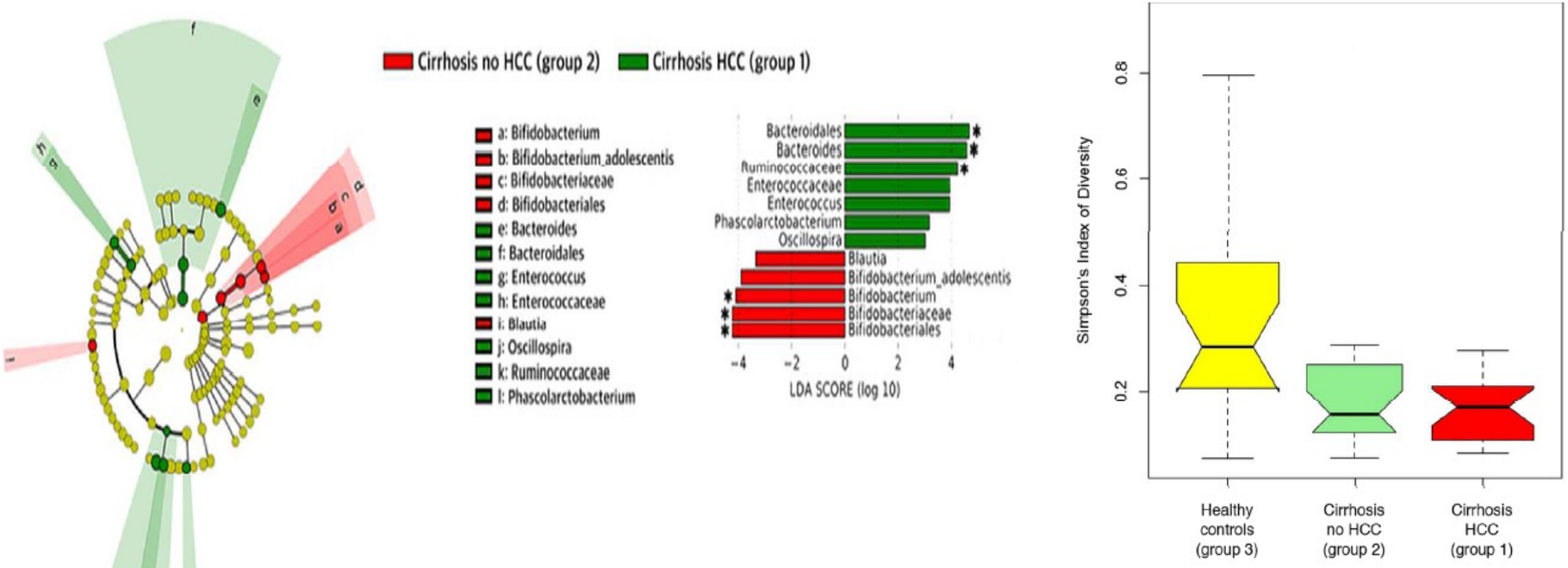




Gut microbiota at the time of surgery can predict endoscopic recurrence

Sokol et al – Gut 2020

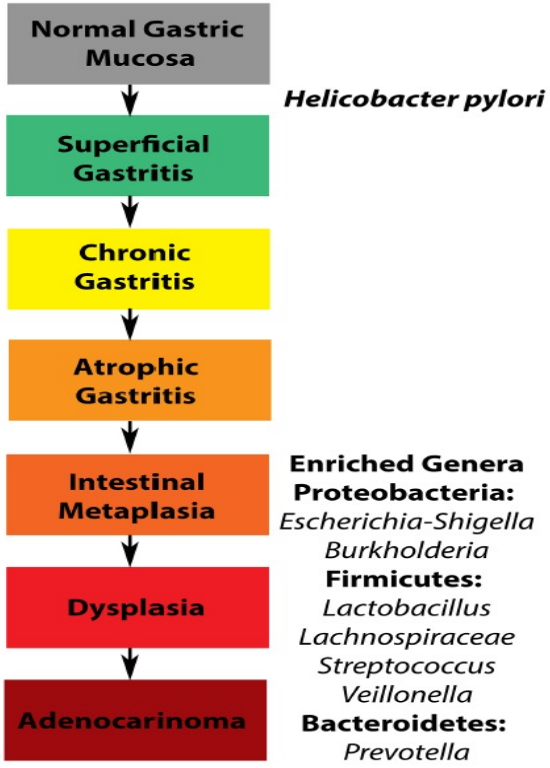
MICROBIOME SIGNATURE can predict progression from liver cirrhosis to HCC

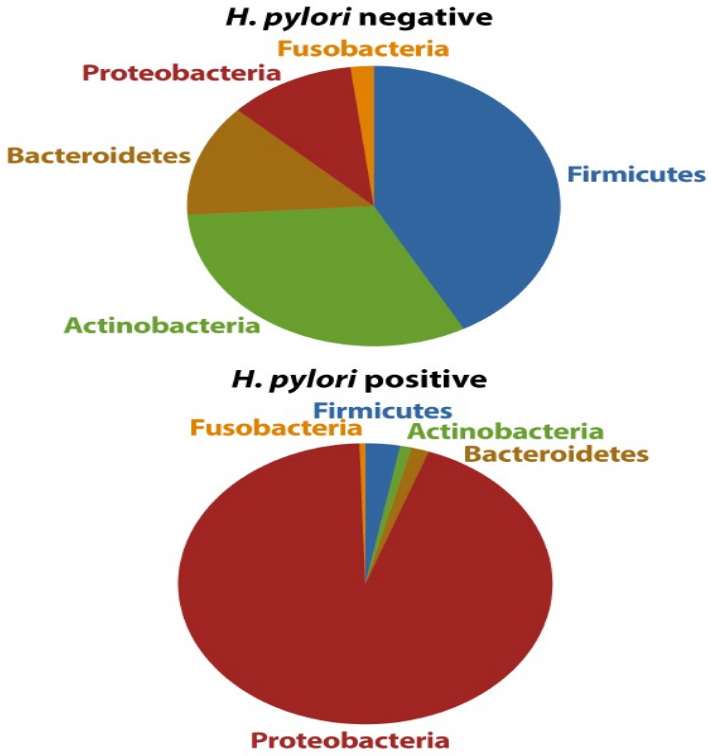


Ponziani, Hepatology 2018

MICROBIOME SIGNATURE can predict progression from H. pylori gastritis to Gastric Cancer

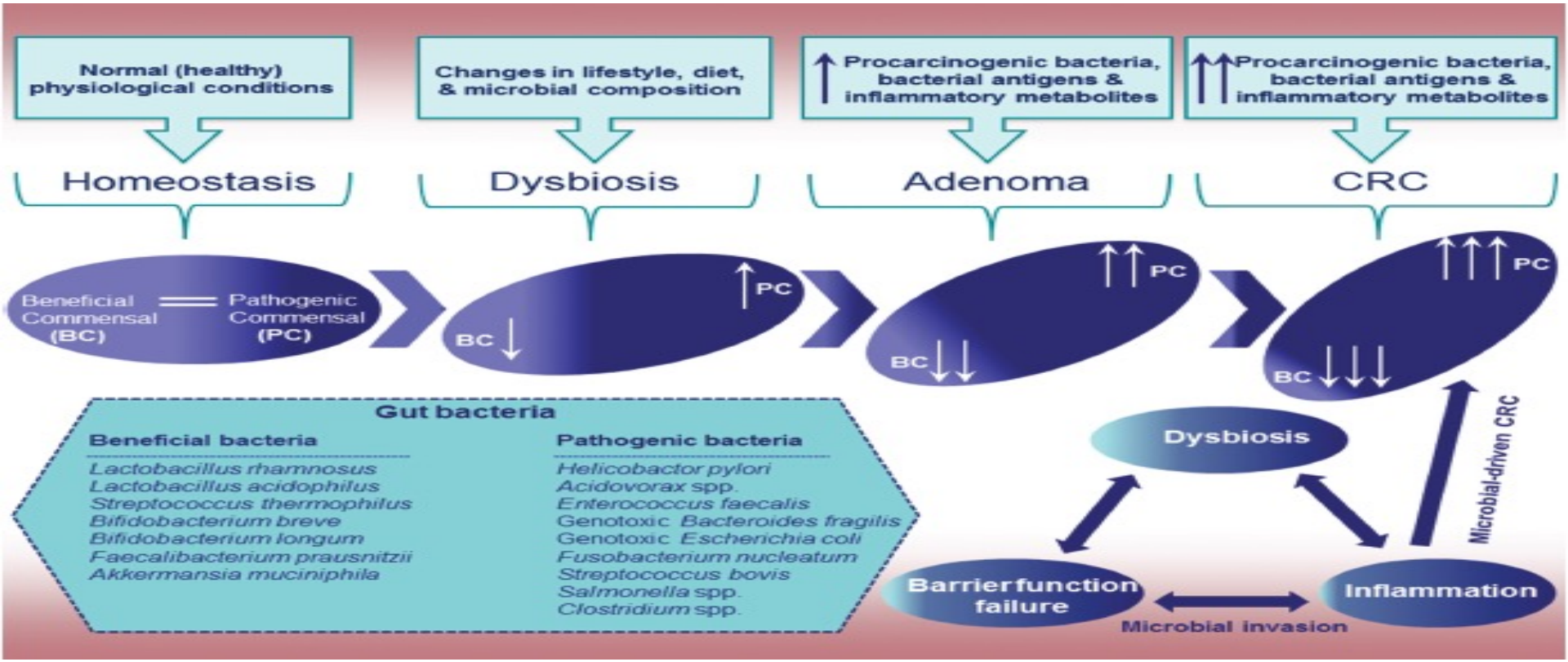
Alterations in the gastric microbiota following *Helicobacter pylori* infection





Noto, PLoS Pathog2017

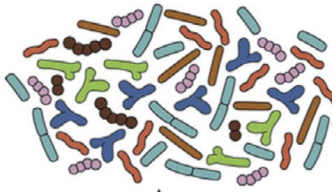
MICROBIOME SIGNATURE can predict progression from adenoma to COLORECTAL CANCER



Dulal - Cancer J 2014

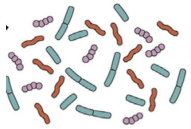
Strong rationale for a Microbiota modulation

Healthy microbiota



Diet & Lifestyle
Drugs
Systemic disorders
Stressful events

Dysbiosis (Loss of symbiosis)



Quantity



Quality

Diseases

GI infections



Metabolic disorders



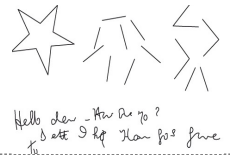
IBD



IBS



Hepatic Encefalopathy



Healthy individual

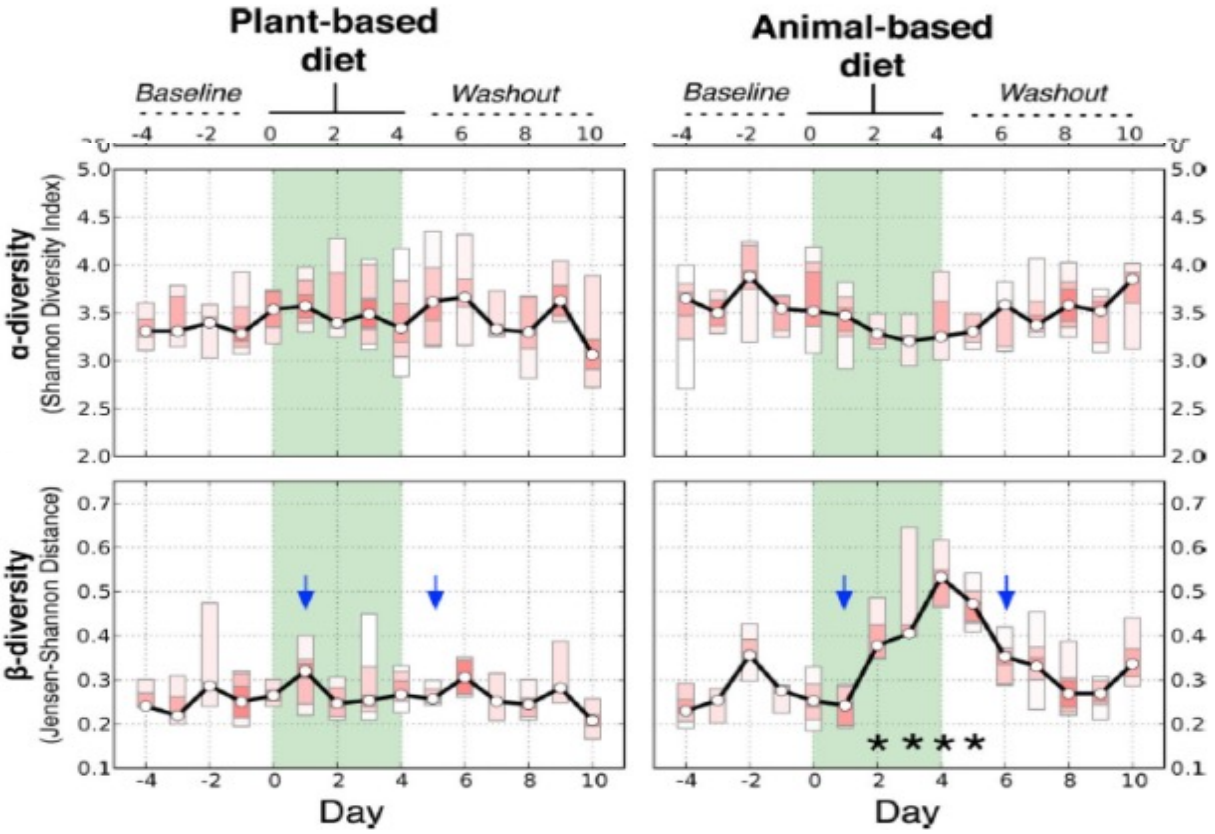


Diet
Prebiotics
Probiotics
Antibiotics
FMT

Diet & Gut microbiota

The short-term modification of diet alters microbial community structure and microbial gene expression

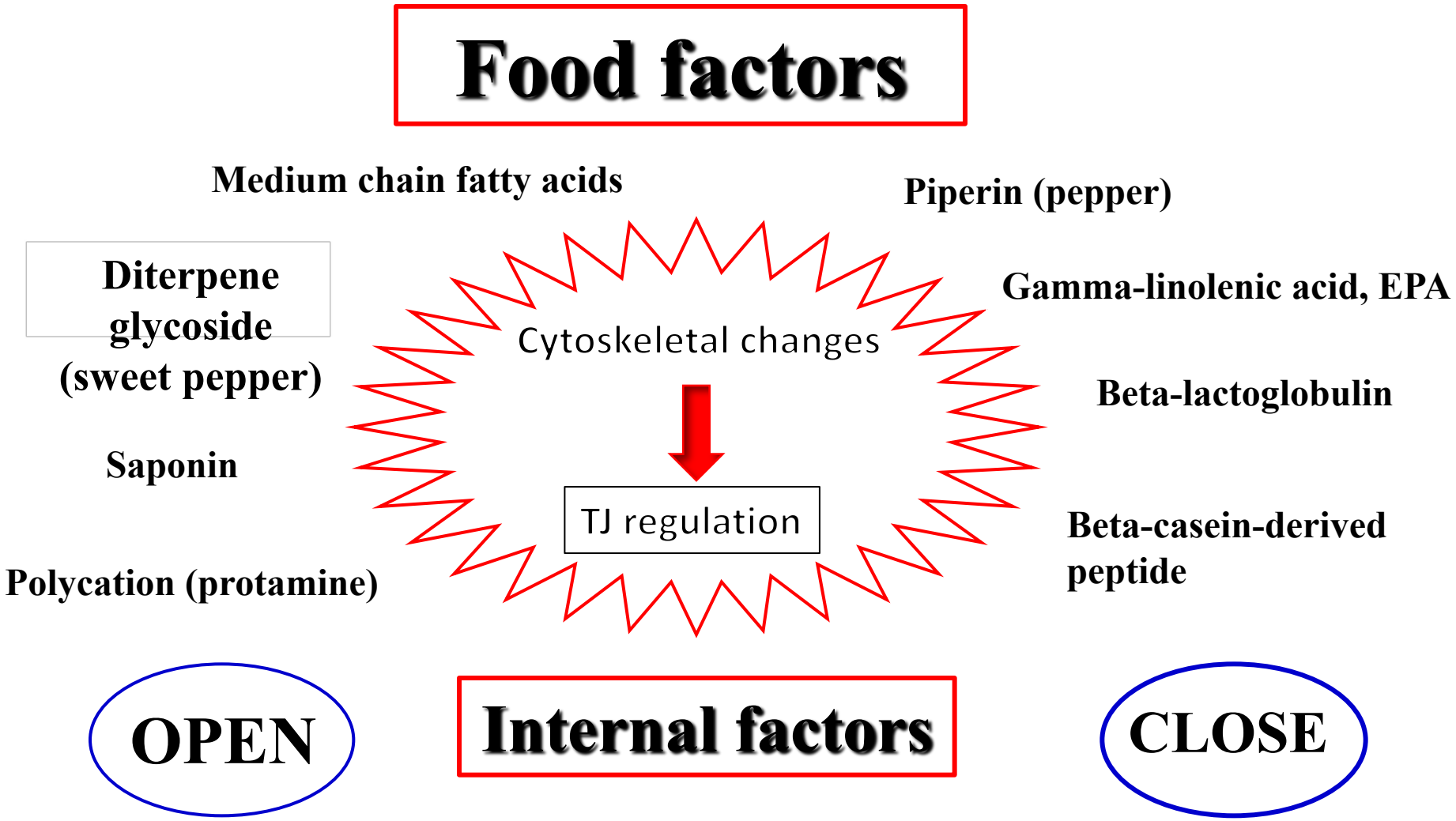
The animal-based diet increases the abundance of bile-tolerant microorganisms (Alistipes, Bilophila, and Bacteroides) and decreases the levels of Firmicutes that metabolize dietary plant polysaccharides (Roseburia, Eubacterium rectale, and Ruminococcus bromii)



The human gut microbiome can rapidly (as quickly as 24 hours!) switch between herbivorous and carnivorous functional profiles. It may reflect past selective pressures during human evolution.

David LA et al. Nature. 2014 January 23; 505(7484): 559–563

FOOD AFFECTS INTESTINAL PERMEABILITY



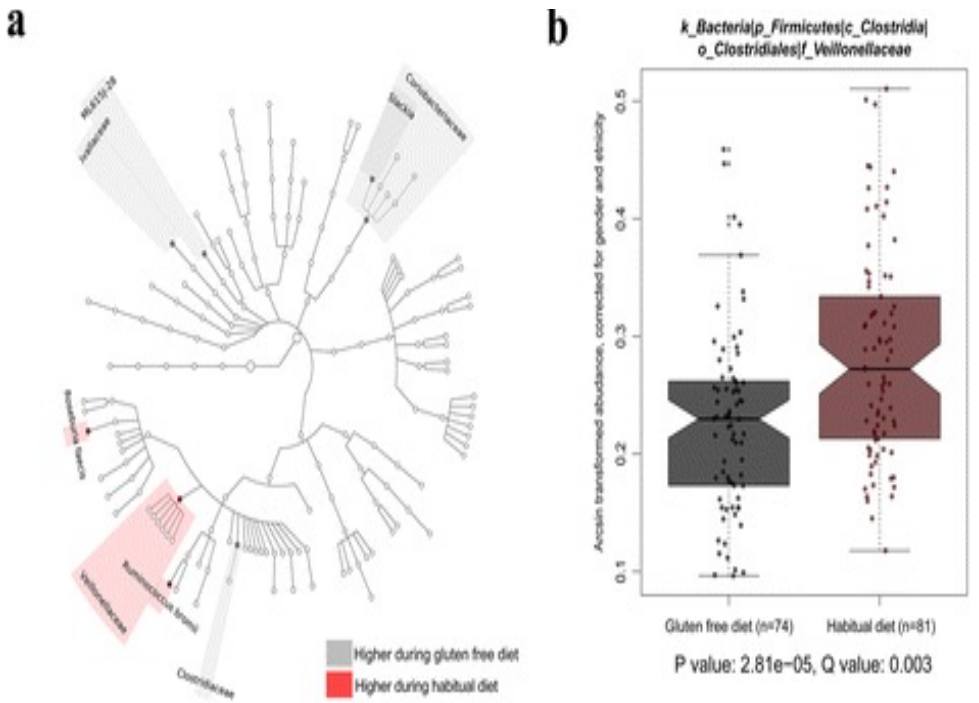
Shimizu M, Biosci Biotechnol Biochem 2010

GFD & microbiota alterations

RESEARCH Open Access

The influence of a short-term gluten-free diet on the human gut microbiome

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The family of Velloneillaceae (cl. Clostridia) was significantly reduced after introduction of GFD in 21 healthy volounteers studied following a GFD for 4 weeks

Cladogram showing the differentially abundant taxa. This plot shows the different levels of taxonomy. Gray indicates bacteria higher in the habitual diet and red indicates those higher in the gluten-free diet. The different circles represent the different taxonomic levels

Microbiota & GFD: healthy people

30 days of GFD in healthy people

↓ **Bifidobacterium**
C. lituseburense
F. prausnitzii

} **FISH**

↓ **Bifidobacterium**
Lactobacillus

↑ **Enterobacteriaceae**
E.coli

} **qPCR**

Microbial group	Adults under standard diet (*n* 10) Median	IQR	Adults under GFD diet (*n* 10) Median	IQR	*P*
Atopobium	6·09	3·46–9·60	3·35	1·8–4·87	0·122
Bifidobacterium	11·14	7·64–16·70	5·12	3·92–8·51	0·007*
Lactobacillus–Enterococcus	2·58	1·34–3·50	0·78	0·56–2·66	0·058
Bacteroides–Prevotella	5·99	3·21–9·49	2·05	1·54–6·61	0·102
Escherichia coli	6·08	3·46–10·56	8·42	4·21–12·21	0·501
Eubacterium rectale–Clostridium coccoides	6·56	4·19–20·15	4·52	1·81–9·77	0·122
Clostridium histolyticum	7·87	3·99–12·01	6·93	3·72–10·47	0·753
Clostridium lituseburense	5·39	3·44–8·02	3·43	1·41–4·21	0·031*
Faecalibacterium prausnitzii	13·77	8·37–17·98	5·08	4·41–7·20	0·009*

Microbial group	Adults under standard diet (*n* 10) Prevalence‡	Median	IQR	Adults under GFD diet (*n* 10) Prevalence‡	Median	IQR	*P*
Bifidobacterium	10	8·85	7·84–9·24	10	7·79	7·43–8·45	0·020*
Bacteroides	10	8·61	8·03–9·20	10	8·21	7·25–9·21	0·450
Clostridium coccoides	10	9·44	8·51–10·11	10	9·52	8·73–9·92	0·983
Clostridium leptum	10	9·54	9·18–10·31	10	10·11	9·81–10·52	0·141
Clostridium histolyticum	10	5·70	5·17–6·34	10	6·48	5·13–6·59	0·223
Lactobacillus	10	7·73	7·10–7·98	10	7·00	6·25–7·64	0·001*
Escherichia coli	10	6·29	5·67–6·77	10	7·40	6·83–7·96	0·003*
Enterobacteriaceae	10	6·64	5·86–7·99	10	8·16	7·41–8·42	0·005*

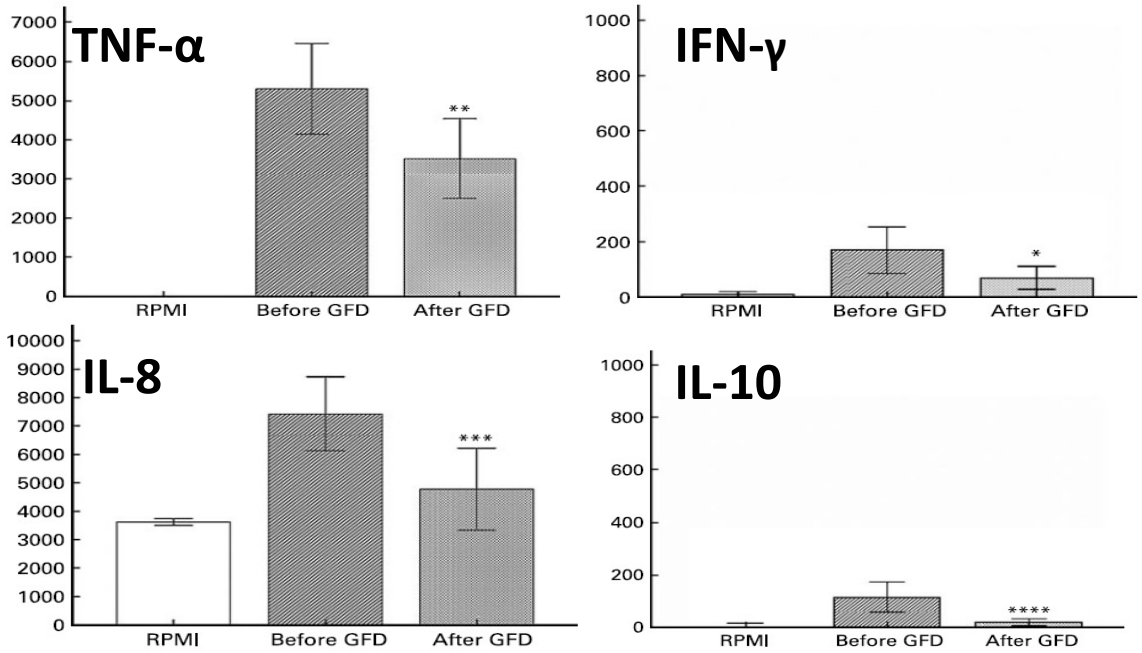
De Palma– Br J Nutr 2009

Microbiota & GFD: healthy people

30 days of GFD in healthy people

PBMC *stimulated with faecal samples

TNF-α
IFN-γ
IL-10
IL-8



*peripheral blood mononuclear cells

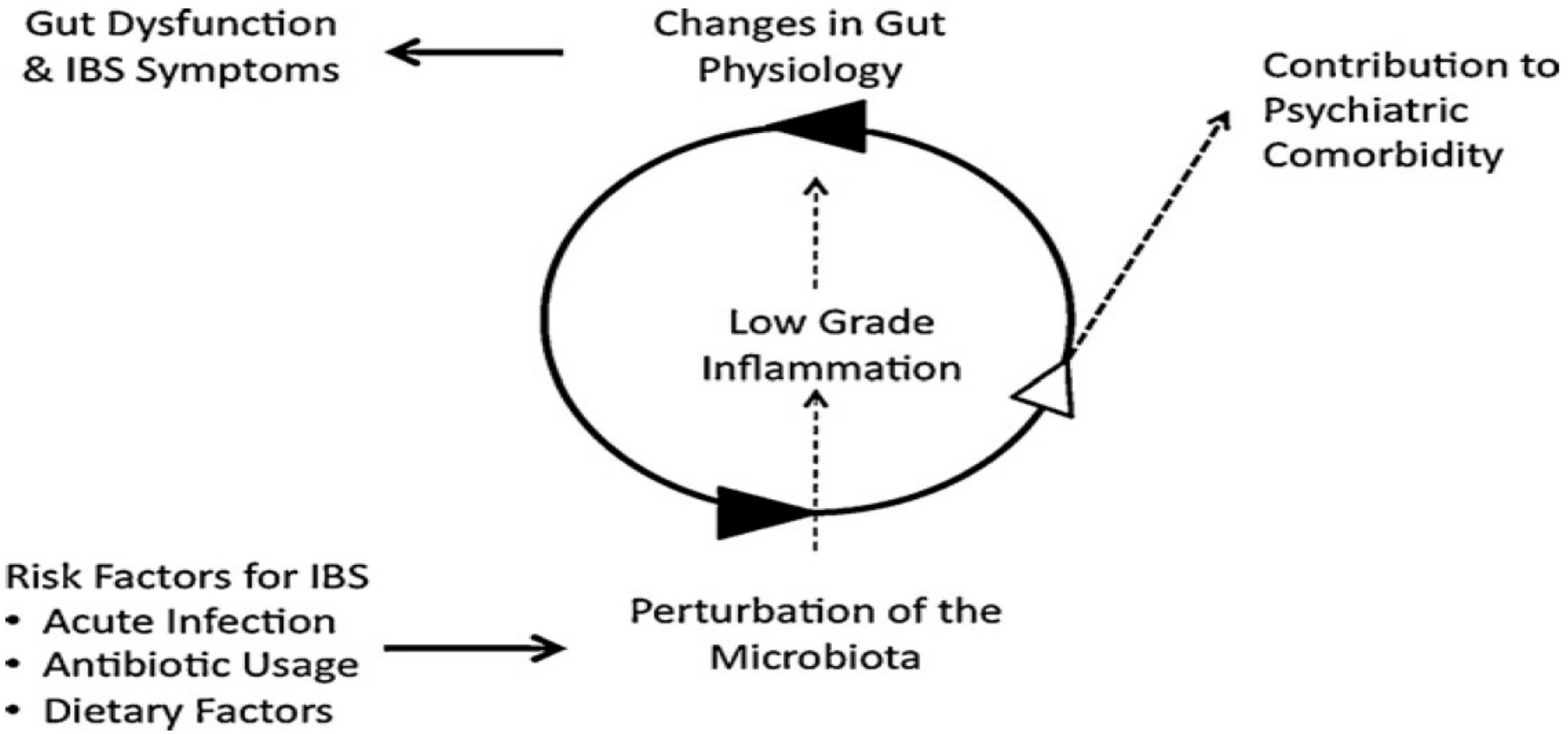
GFD leads to significant reductions in some gut bacteria and the ability of faecal samples to stimulate the host's immunity

De Palma– Br J Nutr 2009

AGENDA

- GFD & microbiota
- GFD & IBS
- GFD & fibromialgia
- GFD & diabete
- GFD & autoimmunità

Gut microbiota & IBS

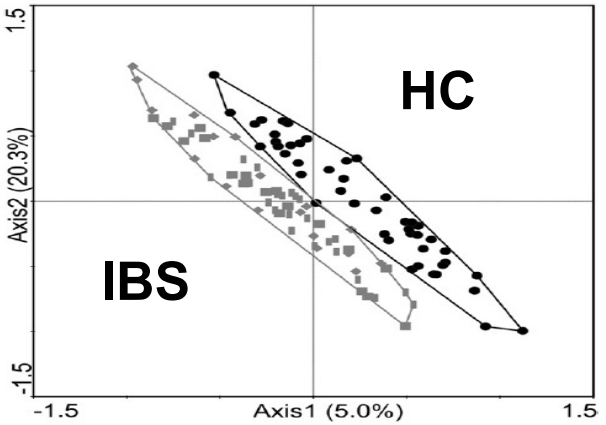


Collins - Dig Liver Dis 2009

Microbiota changes in IBS

Quantitative changes in IBS (Decreased bacterial richness)

- Microbiota of IBS and HS differs significantly between the two groups (P =0.0005)
- Species abundance is decreased in the IBS group



Qualitative bacterial changes in IBS

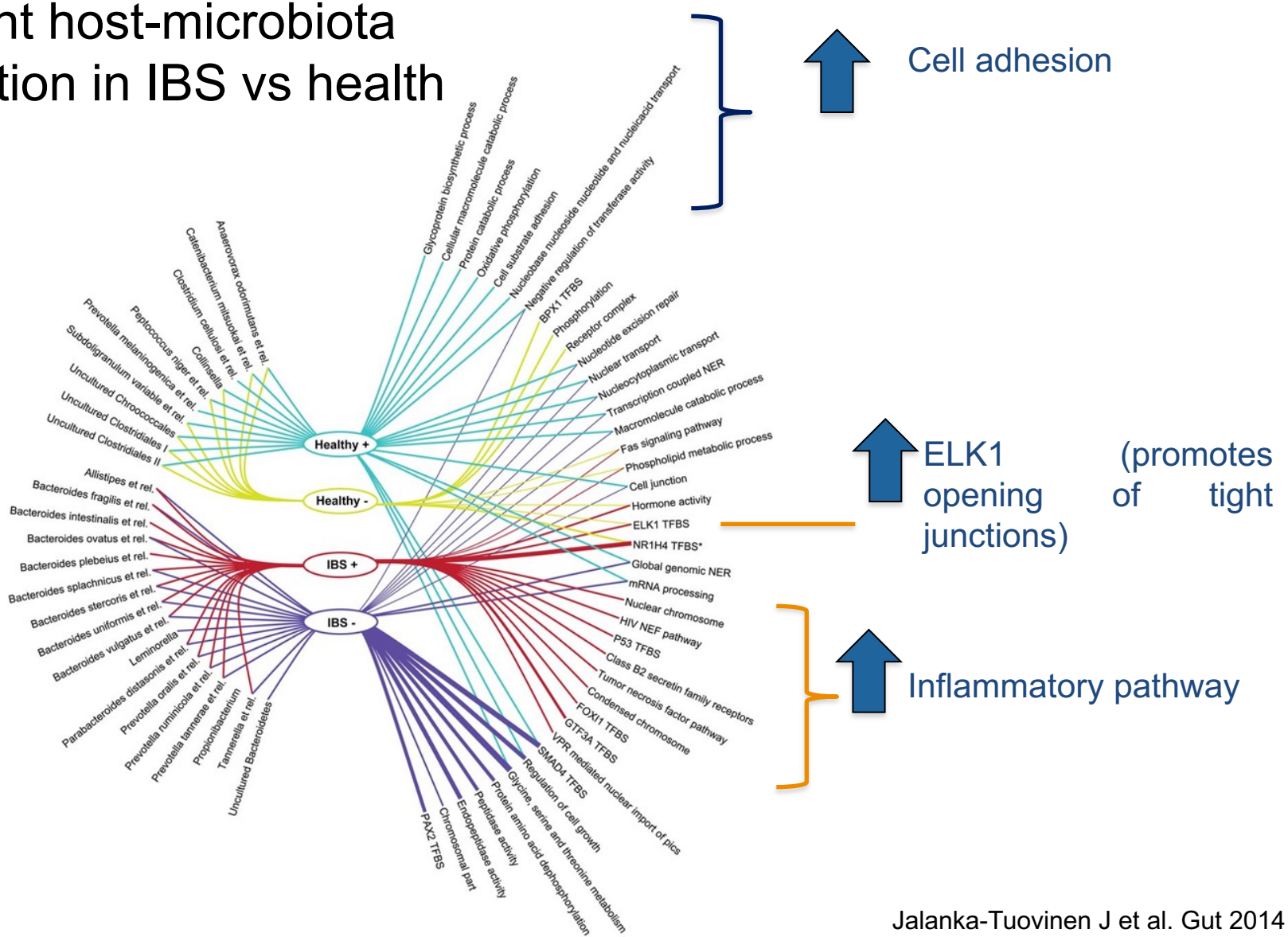
- 45 phylogenetic groups differed significantly between IBS and controls

Level 2	Mean hybridization signal intensity: Controls	IBS	IBS-A	IBS-C	IBS-D
Bifidobacterium	2498	1645[a]	2107	1335	1516
Allistipes	968	462[b]	310[b]	382[b]	634
Bacteroides fragilis et rel	666	455[b]	437[a]	338[b]	553
Bacteroides intestinalis et rel	1821	1090[b]	1248[a]	919[b]	1092[a]
Bacteroides ovatus et rel	817	602[a]	680	328[b]	741
Bacteroides plebeius et rel	2306	1141[b]	1002[b]	1127[b]	1257[a]
Bacteroides stercoris et rel	733	532[a]	656	729	297
Bacteroides uniformis et rel	4856	2753[b]	2041[b]	2940[b]	3159
Bacteroides vulgatus et rel	3691	1789[b]	2232[b]	1429[b]	1712[a]
Odoribacter	570	249[b]	225[b]	203[b]	300[a]
Parabacteroides	1136	515[b]	429[b]	457[b]	622[a]
Prevotella oralis et rel	696	417[b]	750	230[b]	300[a]
Prevotella ruminicola et rel	546	363[a]	352	276[a]	434
Prevotella tannerae et rel	1181	619[b]	657[b]	633[b]	580[b]
Tannerella	493	214[a]	185[b]	220[b]	231[b]
Uncultured bacteroidetes	1083	266[b]	122[b]	180[a]	438
Aneurinibacillus	2117	2848[b]	2424	3241[b]	2887
Streptococcus intermedius et rel	834	1221[a]	1502[a]	994	1171
Anaerotruncus	508	545	461	670[a]	517
Clostridium cellulosi et rel	1253	1525	1204	1881[a]	1512
Clostridium leptum et rel	1212	1499[a]	1123	1865[b]	1521
Clostridium orbiscindens et rel	984	1209[b]	1049	1398[b]	1195[a]
Faecalibacterium	4184	3327	2376[a]	3363	4025
Papillibacter	2018	2707[b]	2511[a]	3060[b]	2603
Ruminococcus bromii et rel	2959	4044	2766	5422[b]	4024
Ruminococcus callidus et rel	1548	1554	1084[a]	2016	1578
Sporobacter	721	886	613	1178[b]	883
Dialister	107	330[a]	271[a]	321	382
Peptococcus	750	1018[b]	962	1114[b]	992[a]
Anaerovorax	557	642[a]	625	687[a]	624
Clostridium difficile et rel	167	248[b]	212[a]	329[b]	217[a]
Blautia	3099	3784[b]	4420[b]	3590	3440
Bryantella	1482	1817[b]	1880[b]	1850[a]	1747
Butyrivibrio	1093	1165	1116	1053	1283[a]
Clostridium nexile et rel	5537	6951[b]	6902[b]	7375[b]	6682[a]
Clostridium sphenoides et rel	2388	2729	3023[a]	2578	2615
Clostridium symbiosum et rel	1658	2389[b]	2440[b]	2557[b]	2230[b]
Coprococcus eutactus et rel	2545	3009[b]	3086[a]	3163[b]	2841
Dorea	2374	3181[b]	3385[b]	3293[b]	2946[b]
Lachnospira	2878	3403[b]	3343	3469[a]	3400[a]
Outgrouping *Clostridium* cluster XIVa	1516	1731[a]	2027[b]	1506	1668
Roseburia	2541	3533[a]	3099	3493	3892[a]
Ruminococcus gnavus et rel	3101	4519[b]	5027[b]	4824[b]	3912[a]
Ruminococcus lactaris et rel	949	1202[b]	1118[a]	1165	1293[b]
Uncultured Clostridiales I	297	228[a]	176[a]	321	199

Rajilic-Stojanovic et al - Gastroenterology 2011

Microbiota changes in IBS

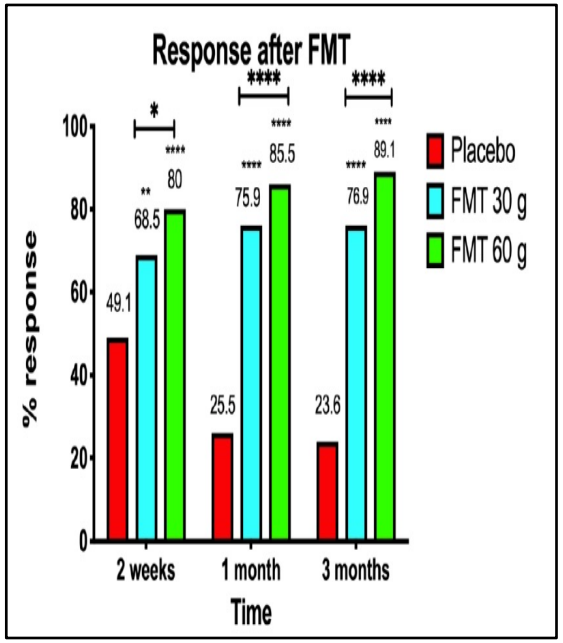
- Different host-microbiota interaction in IBS vs health



Jalanka-Tuovinen J et al. Gut 2014

Microbiota Transplantation success in IBS:
a matter of quantity and quality of microbes

- **RCT** of **164 patients with IBS** (all subtypes)
- Single donor FMT vs placebo (autolgous feces), **upper GI delivery**, **two dosages** (30 g and 60 g)
- **Single super-donor:** healthy, drug-free, lean, athletic, young male, born through vaginal delivery, breastfed, with a history of only three antibiotic courses in his life, eating a healthy diet, with a **favourable microbiota profile** (richer in Lactobacilli, Lachnospiraceae and Verrucomicrobia, and lower in Shigella and Escherichia spp)
- Primary endpoint: **reduction of IBS symptoms at 3 amonths**
- **Responses occurred in 23.6%, 75.9% (P<0.0001), and 89.1% (P<0.00001) of the patients who received placebo, 30-g FMT, and 60-g FMT**
- Significant improvements in fatigue and the quality of life, and changes of microbiome profiles, in the FMT group
- **>80 % of patients mantained response after 12 months (either 30 or 60 gr)**



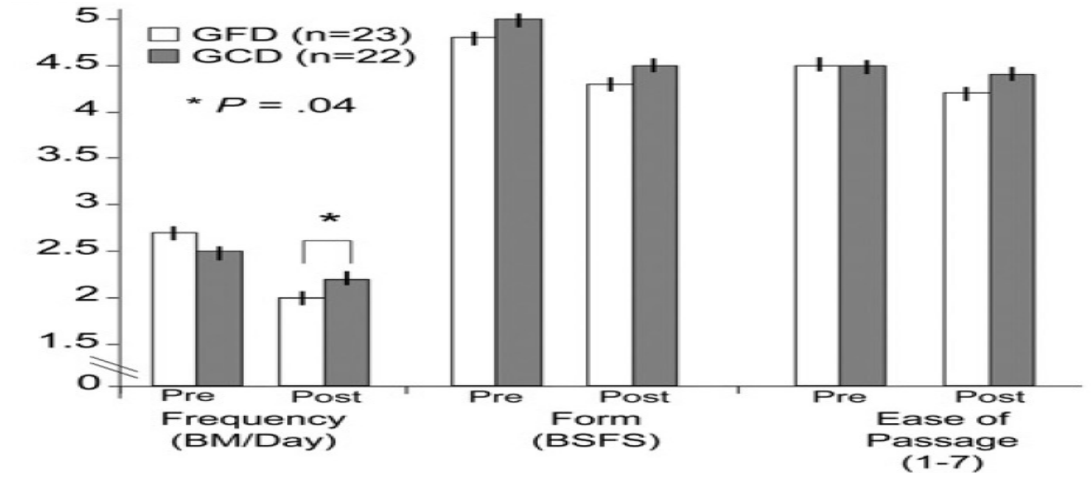
El Salhy et al- Gut 2020: Barbara & Ianiro, Gut 2020; El Salhy et al; Neurogas Motil 2021

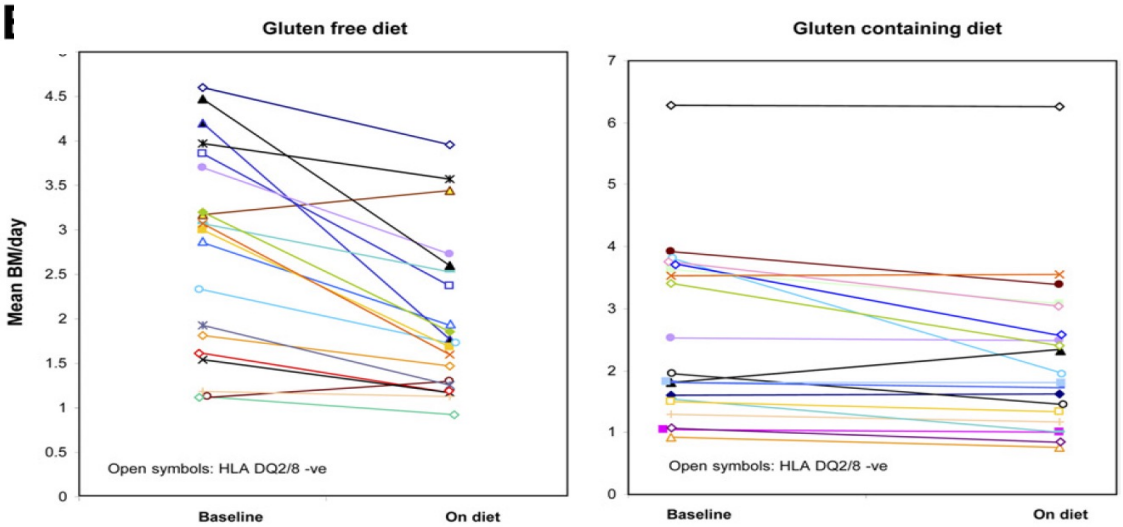
A Controlled Trial of Gluten-Free Diet in Patients With Irritable Bowel Syndrome

Bowel movements:

-GFD has a beneficial effect on frequency, form and easy passage

-The effect on stool frequency was greater in HLA-DQ2 or HLA-DQ8 positive patients





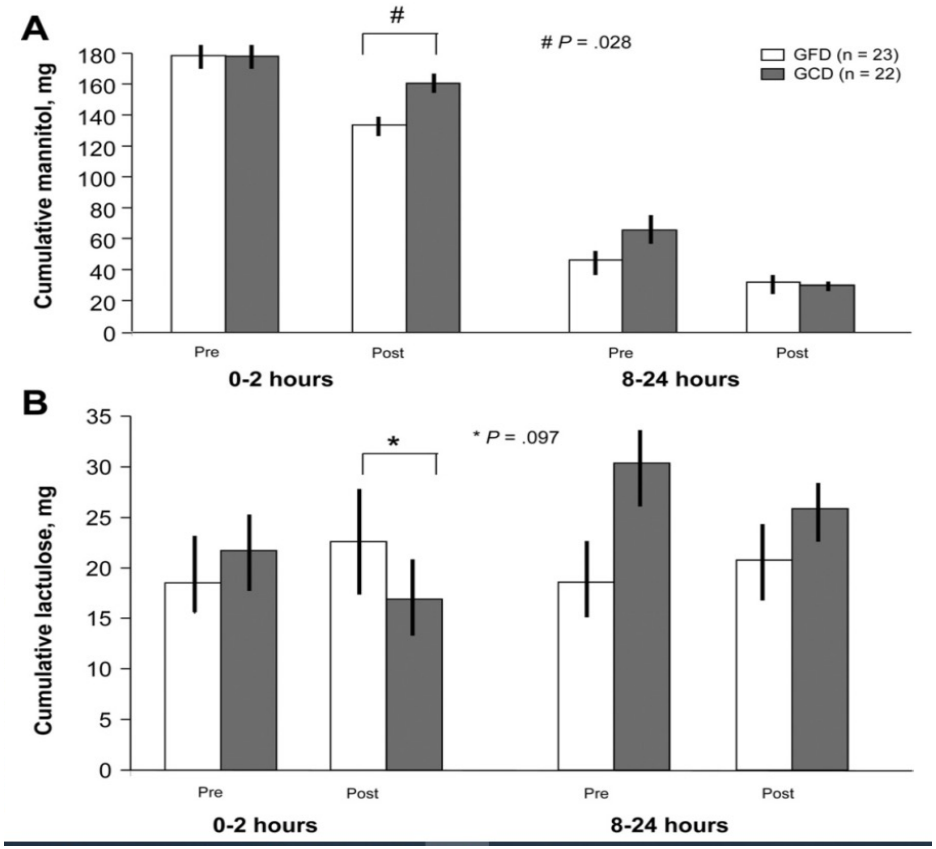
Vazquez-Roque MI, et al. Gastroenterology, 2013

A Controlled Trial of Gluten-Free Diet in Patients With Irritable Bowel Syndrome

Gastrointestinal and colonic transit:

-Small intestinal and colonic permeability by the cumulative mannitol and lactulose excretion.

-There was an increased small intestinal permeability with gluten cointaing diet (GCD)

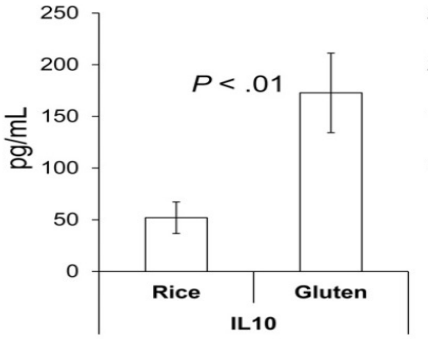


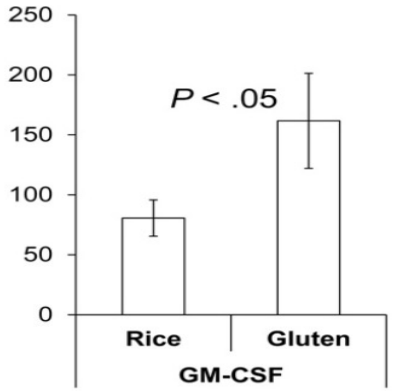
Vazquez-Roque MI, et al. Gastroenterology, 2013

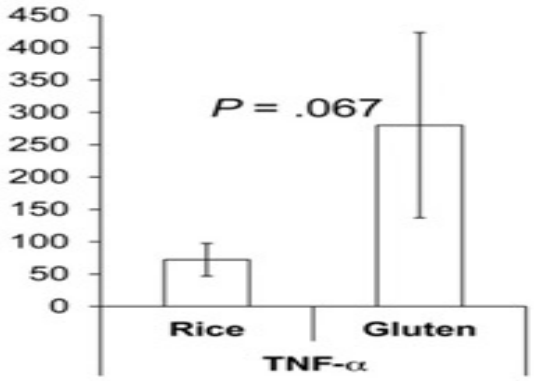
A Controlled Trial of Gluten-Free Diet in Patients With Irritable Bowel Syndrome

In vitro cytokine production by peripheral blood mononuclear cells in response to stimulation with either rice (control) or gluten.

- compared with rice, gluten caused an increased production of IL-10, GM-CSF and TNF-alpha







Vazquez-Roque MI, et al. Gastroenterology, 2013

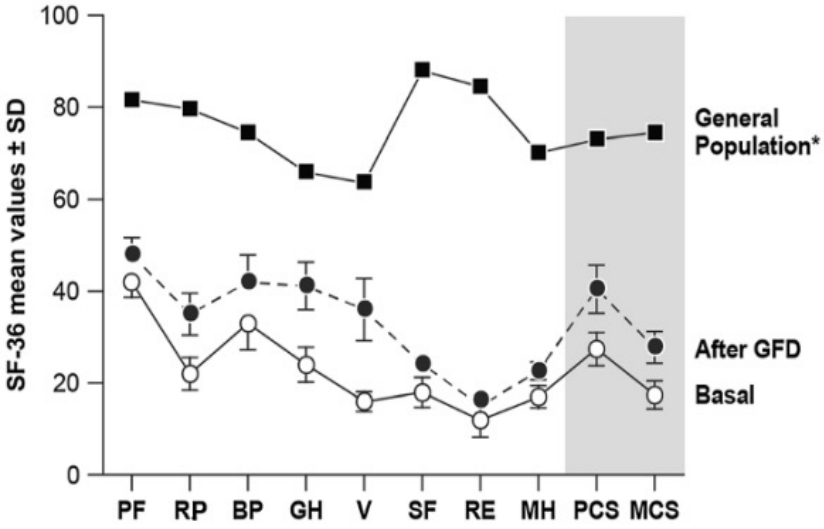
Rodrigo *et al. BMC Gastroenterology* 2013, **13**:157
http://www.biomedcentral.com/1471-230X/13/157

BMC Gastroenterology

RESEARCH ARTICLE Open Access

Clinical impact of a gluten-free diet on health-related quality of life in seven fibromyalgia syndrome patients with associated celiac disease

Luis Rodrigo[1*], Ignacio Blanco[2], Julio Bobes[3] and Frederick J de Serres[4]



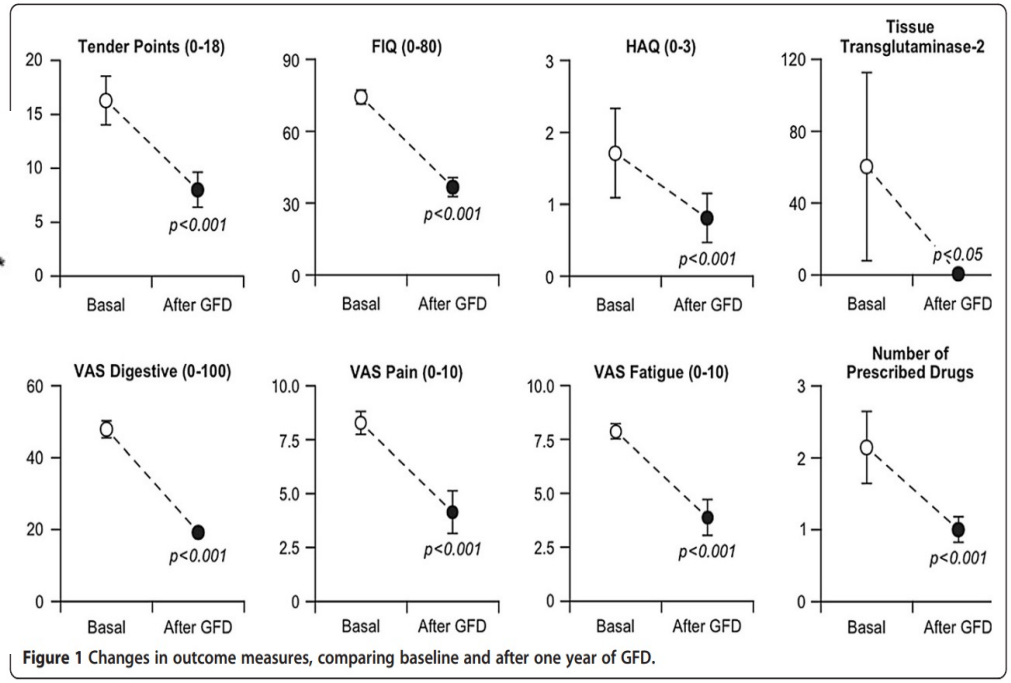
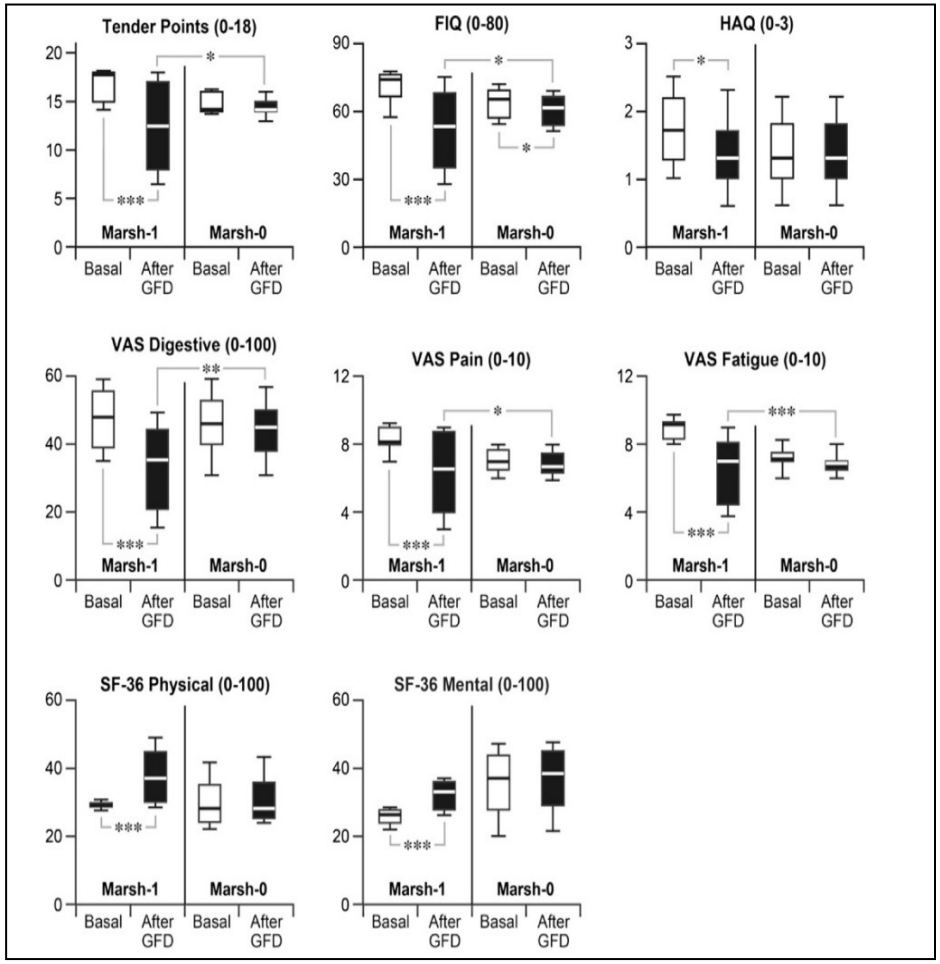


Figure 1 Changes in outcome measures, comparing baseline and after one year of GFD.

GFD is effective in IBS plus FIBROMYALGIA only in patients with an associated lymphocytic enteritis



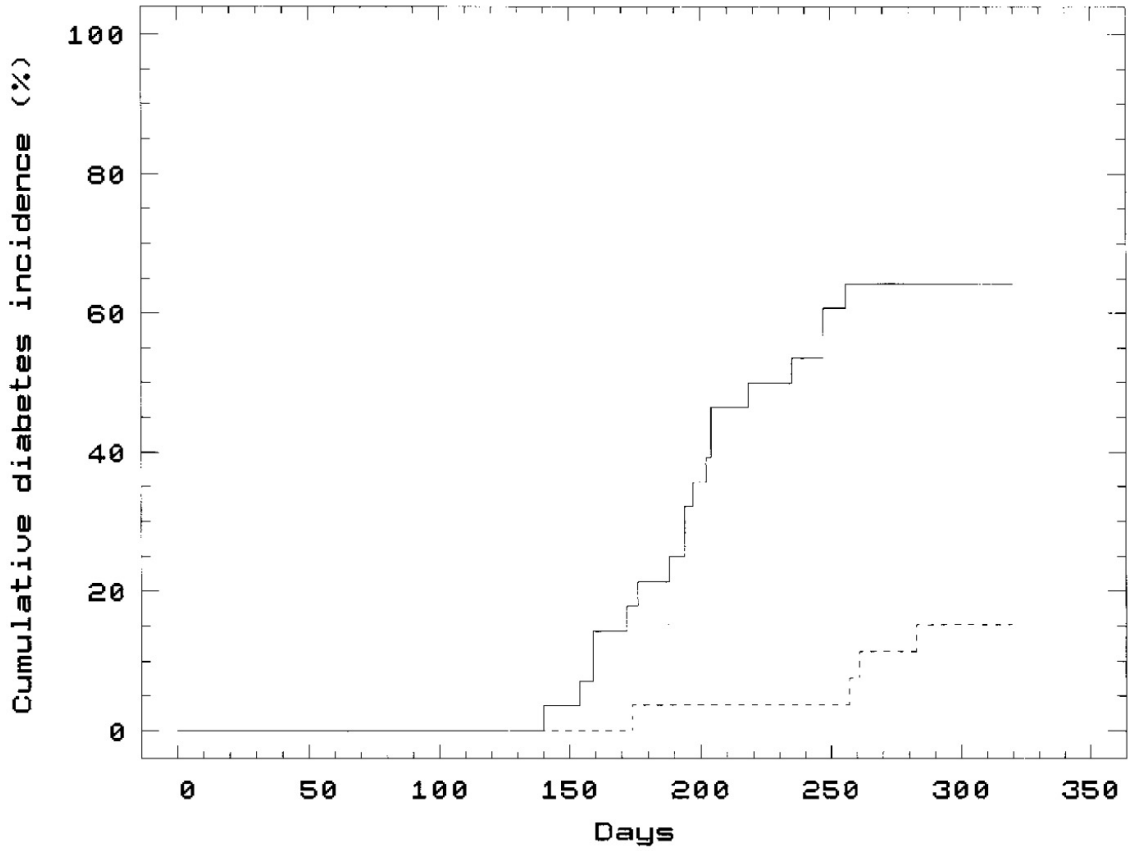
--At baseline, all patients had a poor quality of life (QoL) and high VAS scores.

--After one year on GFD, only in pts with an associated lymphocytic enteritis, all outcome measures were somewhat better, with a mean decrease of 27% in the TPs, FIQ, HAQ and VAS scales, accompanied by an increase of 27% in the SF-36 physical and mental component scores.

--However, in the IBS without an associated lymphocytic enteritis, the GFD had almost no effect

Rodrigo et al. Arthritis Research & Therapy 2014

GFD and T1D diabetes: evidences from animal models



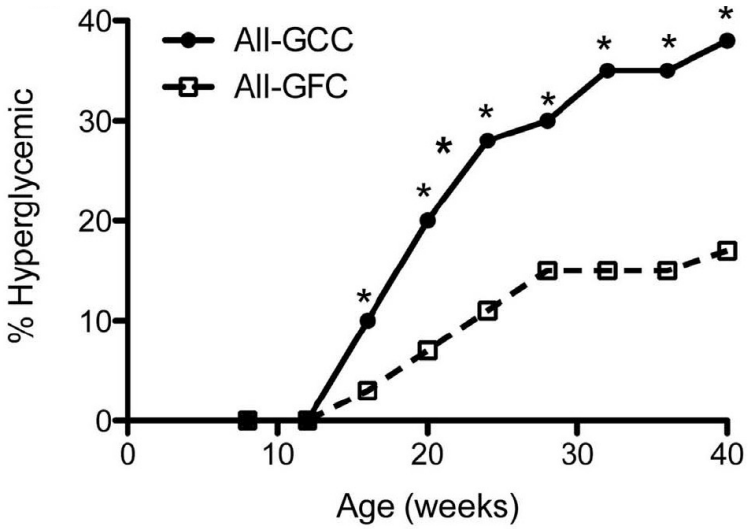
GFD reduces cumalative incidence of T1D diabetes in NOD mice

standard diet

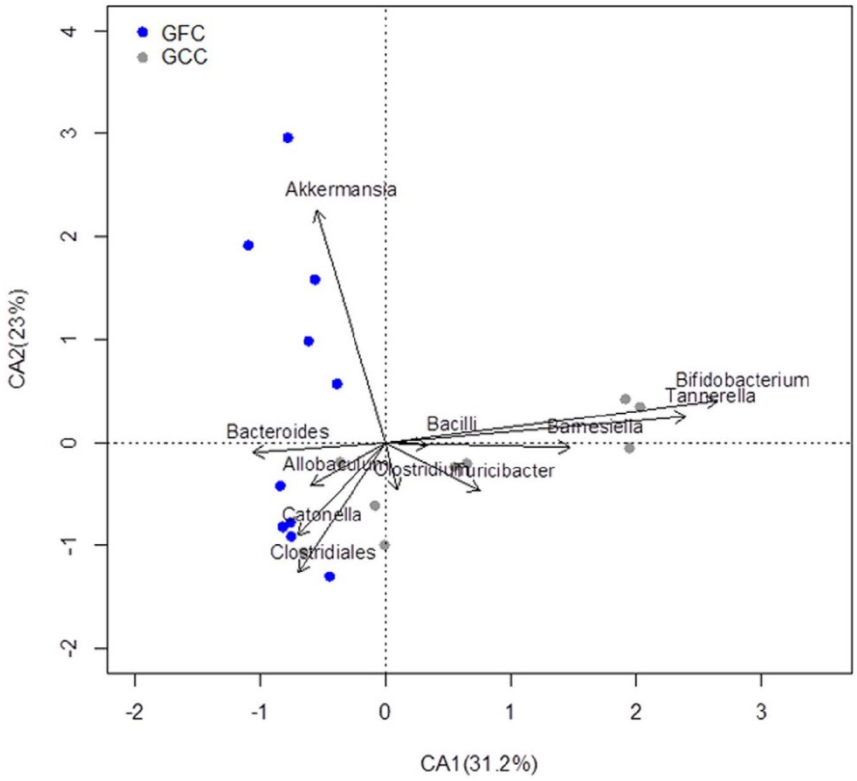
------- GFD

Funda DP, et al. Diabete Metab Res Rev, 1999

Low Incidence of Spontaneous T1D in NOD mice raised on GFD is associated with changes in the intestinal microbiome



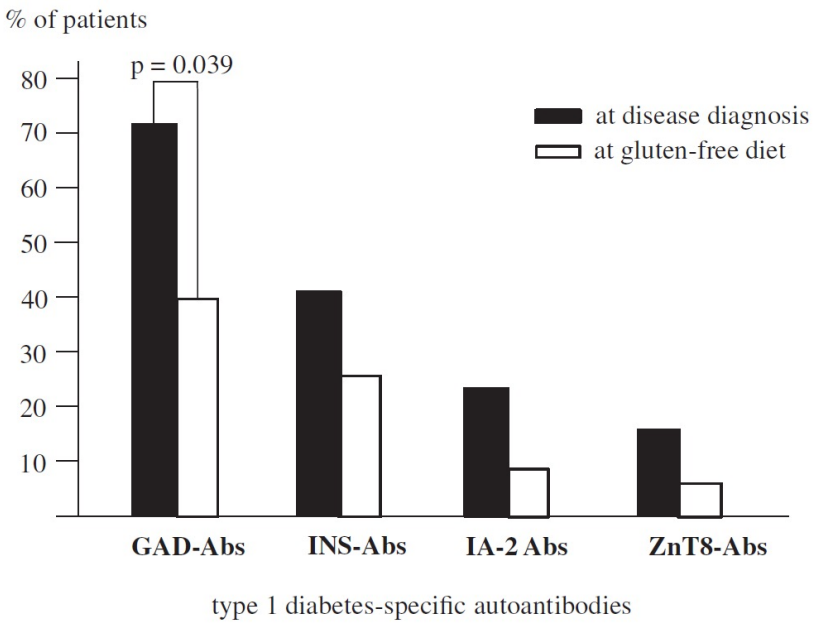
Reversal of the anti-diabetogenic effects of gluten-free chow by supplementation with gluten and overall effective of gluten-free chow on the incidence of hyperglycemia in NOD mice

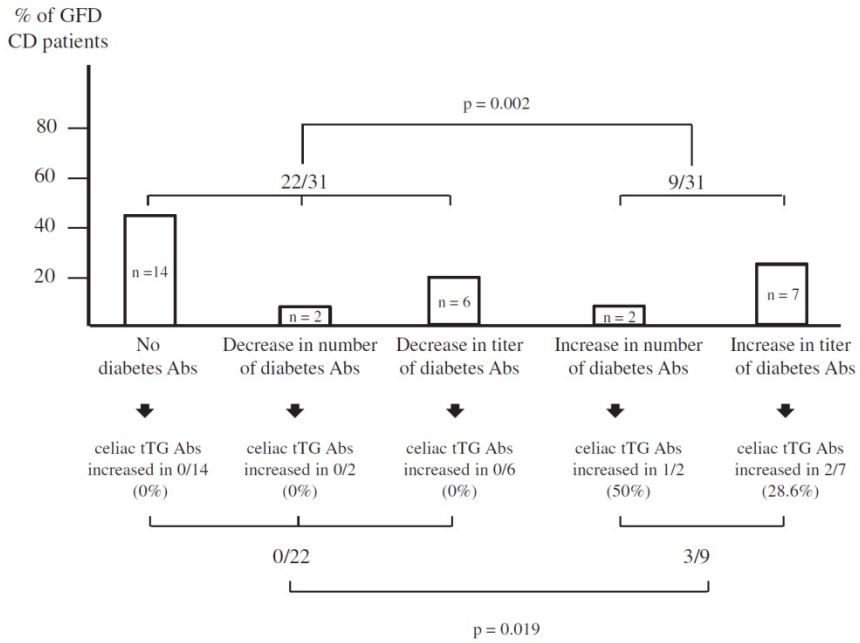


Effect of Dietary Gluten Upon Specific OTU (Genus) Abundance

Marietta E.V., Plos One, 2013

GFD impact on dynamics of pancreatic islet-specific autoimmunity detected at celiac disease diagnosis





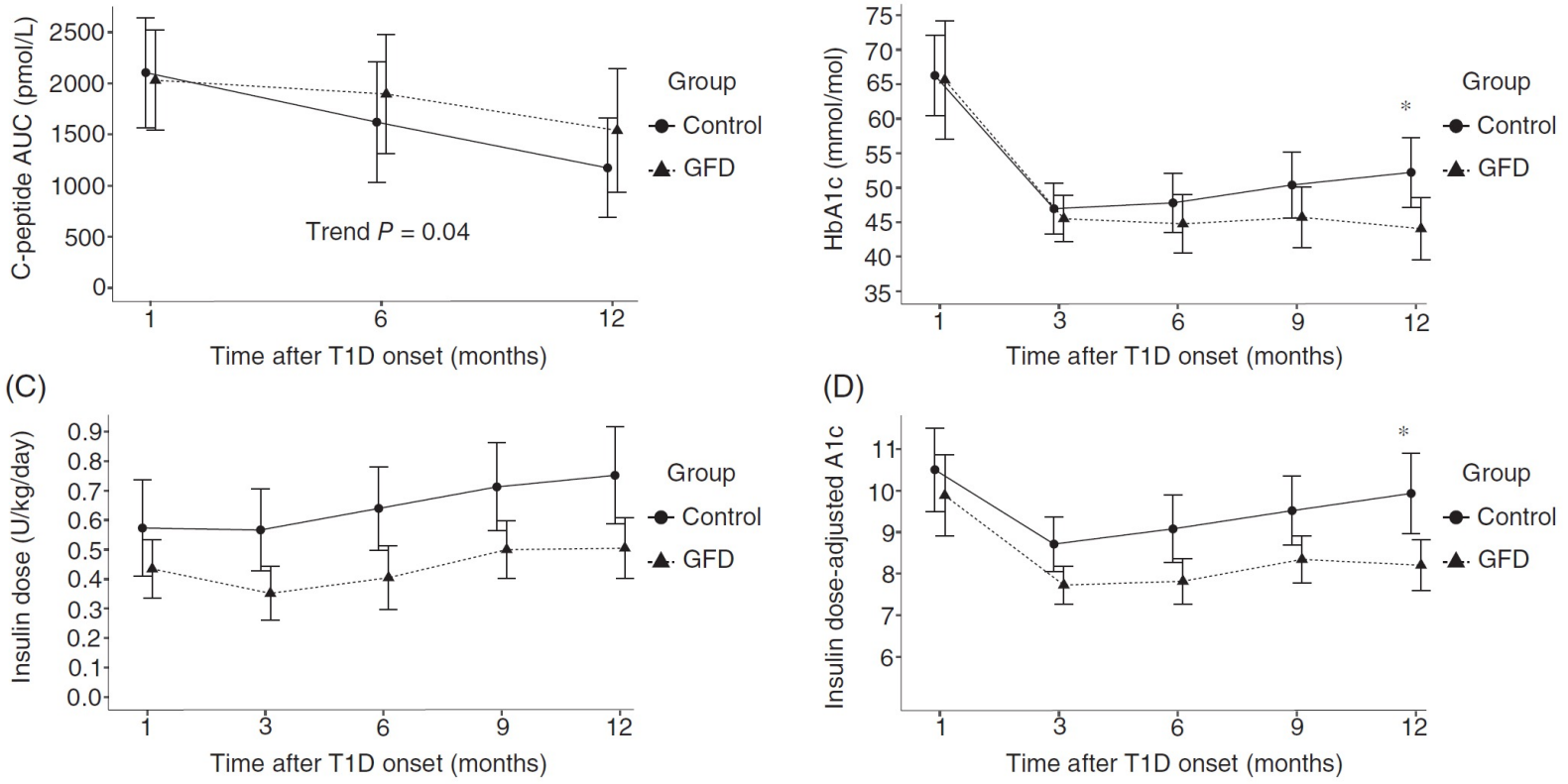
-GFD (> 12 months, median duration 39) was associated to a decrease or disappearence of the islet specific autoantibodies in 71% of CD patients

-80% of CD patients positive at diagnosis >2 islet-specifics ab were still positive after more than two year of GFD, 25% developping T1D

Tiberti C, et al. Pediatr. Diabetes. 2020

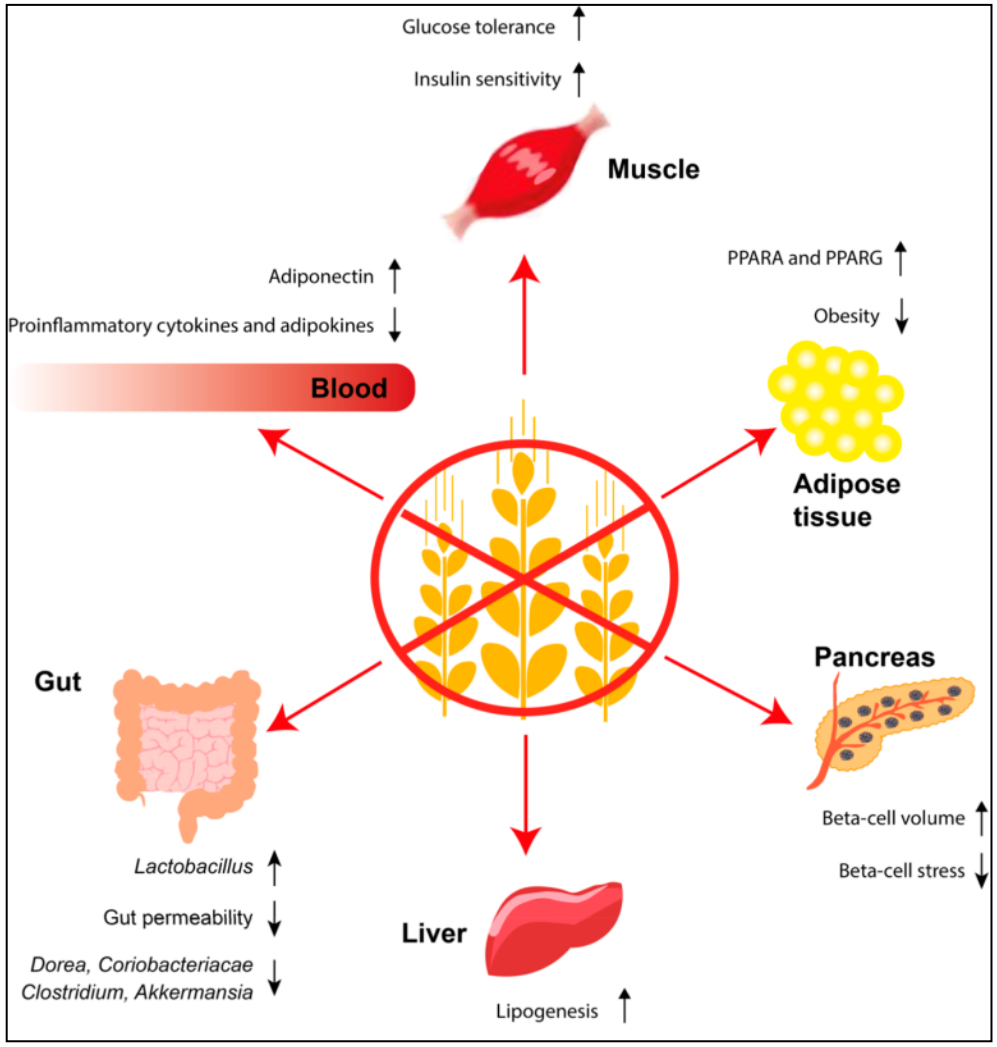
Gluten-free diet in children with recent-onset T1D

45 children (aged 10.2 ± 3.3 years) were recruited into a self-selected intervention trial: 26 started with a GFD within a median of 38 days post-onset, whereas 19 remained on a standard diet



Neuman V, et al. Diabetes Obes Metab. 2020

GFD and the development of T2D



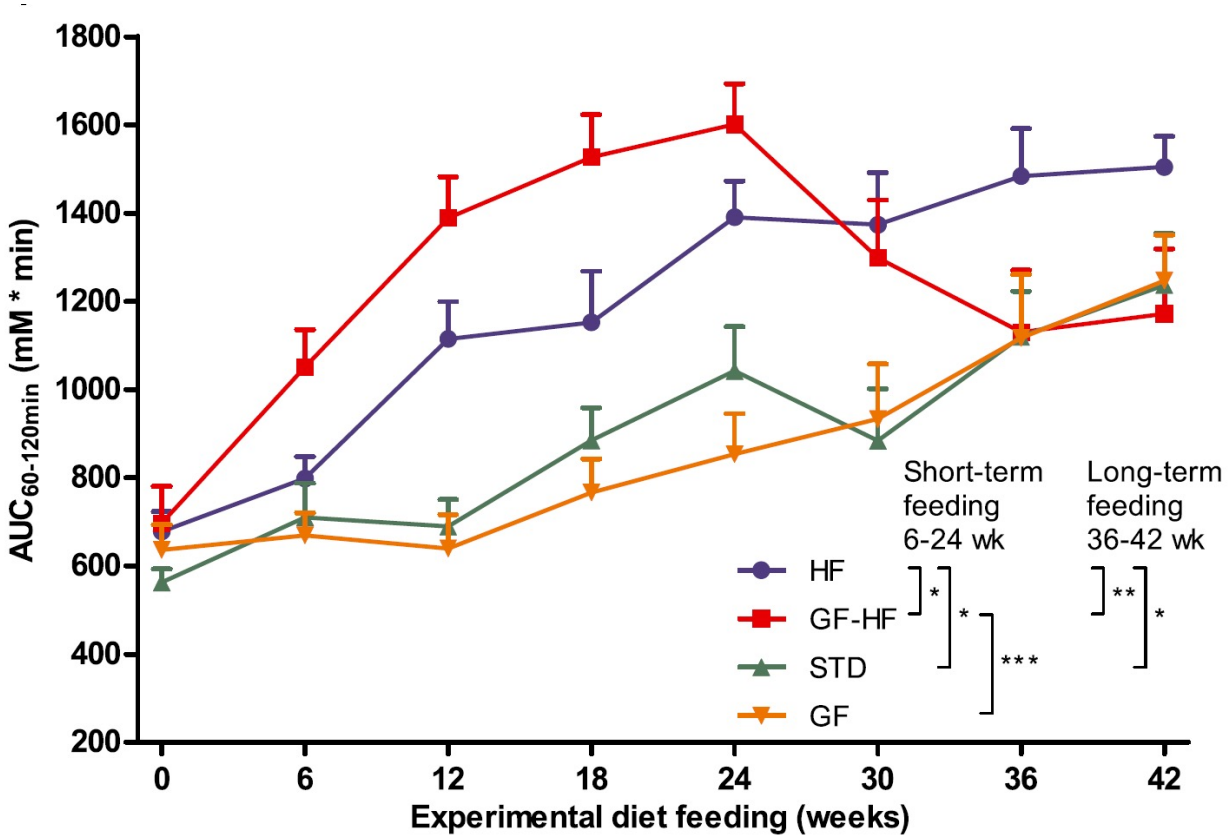
--GFD decreases intestinal permeability thereby preventing food particles such a gliadin from crossing the intestinal barrier and reaching the adipose tissue and pancreas.

--GFD increases the proportion of Lactobacillus and decreases the proportion of Akkermansia, Dorea, Clostridium, and Coriobacteriacae

Haupt-jorgensen. Nutrients. 2018

GLUTEN-FREE DIET AND TYPE 2 DIABETES

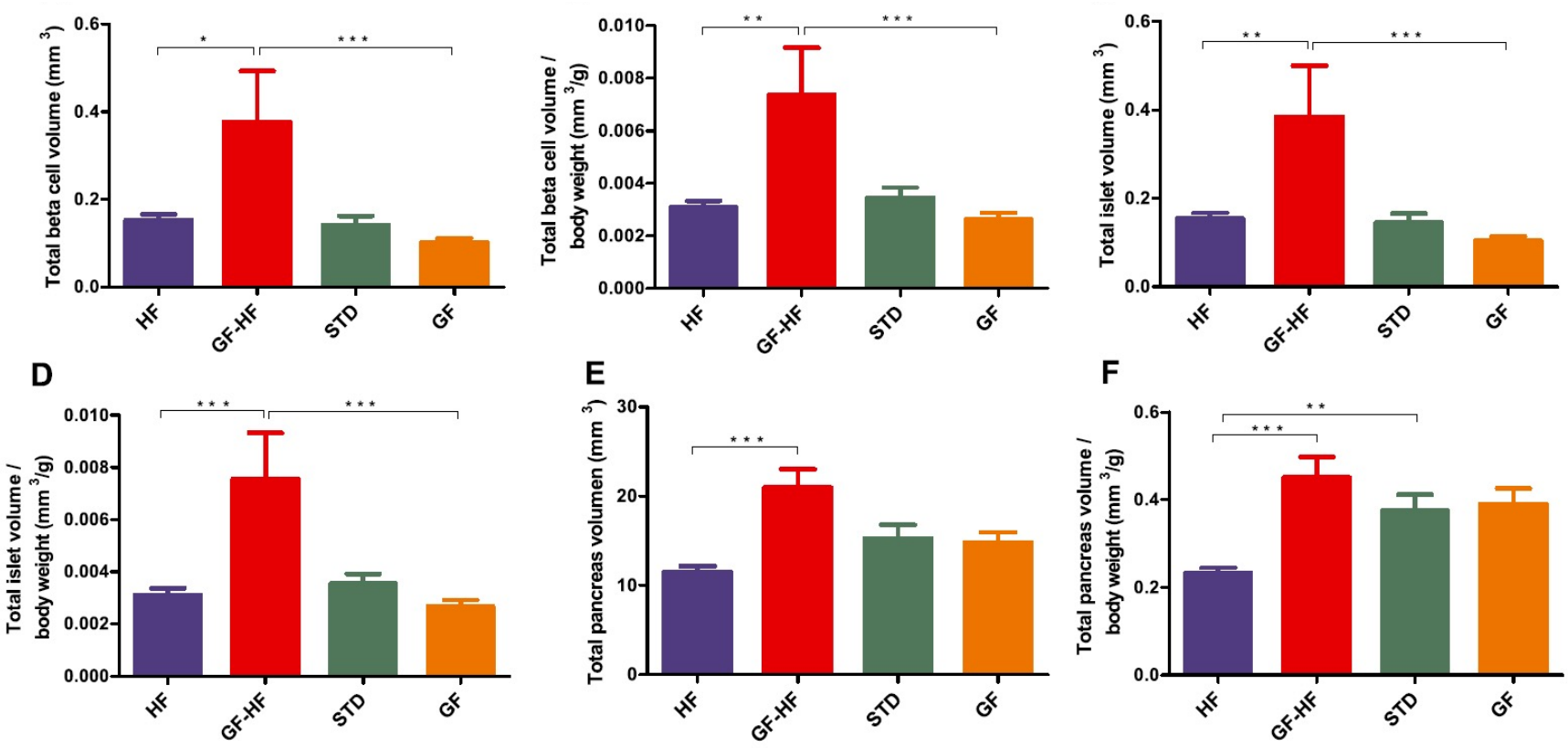
GF–HF versus HF diet affects glucose tolerance in B6 mice in a time-dependent manner



Haupt-Jorgensen, Diabetes Metab Res Rev 2016

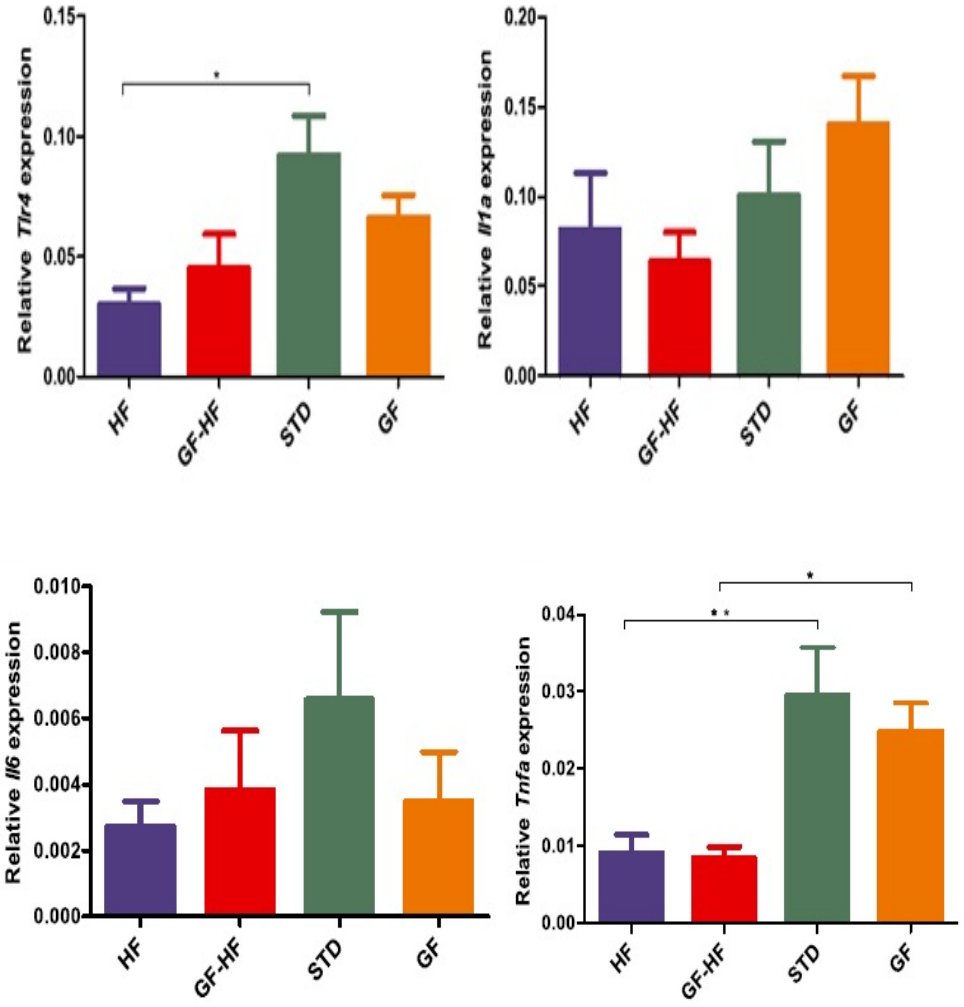
GLUTEN-FREE DIET AND TYPE 2 DIABETES

GF–HF versus HF diet for 42 weeks leads to higher volumes of beta cells, islets and pancreas, and reveals correlations between physical parameters in B6 mice



Haupt-jorgensen, Diabetes Metab Res Rev 2016

GLUTEN-FREE DIET AND TYPE 2 DIABETES



GF–HF versus HF diet for 42 weeks does not affect intestinal Tlr4, Il1, Il6 or Tnfa mRNA expression in B6 mice.

Relative mRNA expression of Tlr4, Il1a, Il6 and Tnfa in proximal jejunum from B6 mice after 42 weeks experimental diet feeding

Haupt-jorgensen, Diabetes Metab Res Rev 2016

Current Evidence on the efficacy of GFD in other autoimmune diseases

Remission of Pituitary Autoimmunity Induced by GFD in Patients With Celiac Disease

Gluten-Free Diet

Gluten- containing diet

GROUP 1 (LYH + CD)		GROUP 2 (LYH – CD)	
Pituitary function at baseline	**Pituitary function at the end of the study**	**Pituitary function at baseline**	**Pituitary function at the end of the study**
7 with normal function	All 7 with normal function[b]	8 with normal function	3 clinical ACTH deficiency[a] 2 subclinical GH deficiency 3 subclinical FSH/LH deficiency
13 subclinical GH deficiency	9 normal function 1 sublinical GH deficiency 2 subclinical GH+ + FSH/LH deficiency 1 subclinical GH + PRL deficiency	12 subclinical GH deficiency	11 subclinical GH deficiency 1 subclinical GH + PRL deficiency
7 subclinical ACTH deficiency (5 of them with high PRL)	5 normal function 2 subclinical ACTH deficiency	5 subclinical ACTH deficiency(4 of them with high PRL)	1 normal function 4 clinical ACTH deficiency + high PRL[a]
5 subclinical FSH/LH deficiency (2 of them with high PRL)	3 subclinical FSH/LH deficiencynormal function 2 clinical FSH/LH deficiency + high PRL[a]	16 subclinical FSH/LH deficiency(one of them with high PRL)	1 subclinical FSH/LH deficiency 1 subclinical FSH/LH + GH deficiency 13 clinical FSH/LH deficiency(one of them with high PRL)[a] 1 subclinical FSH/LH + ACTH deficiency
4 subclinical ACTH + GH deficiency (1 of them with high PRL)	4 subclinical ACTH + GH deficiency (1 of them with high PRL)	7 subclinical ACTH + GH deficiency(5 of them with high PRL)	2 subclinical ACTH + GH deficiency 5 clinical ACTH + GH deficiency + high PRL[a]
6 subclinical GH + FSH/ LH deficiency	6 subclinical GH + FSH/LH deficiency	1 subclinical GH + PRL deficiency	1 subclinical GH + PRL deficiency
1 subclinical ACTH + FSH/LH deficiency + high PRL	1 normal function	1 subclinical GH + TSH deficiency	1subclinical GH + TSH deficiency

In celiac patients GFD may be able to induce remission of subclinical Lynfocitic Hypophysitis (LYH) or prevent the progression to clinical stage of this disease

Bellastella et al. J Clin Endocrinol Metab, 2020

Current Evidence on the efficacy of GFD in other autoimmune diseases

AUTOIMMUNE THYROIDITIS: some studies support the idea that thyroid-related antibodies may respond to a GFD in patients with concomitant CD and ATD. In patients without CD, GFD appear to improve the intestinal absorbtion of levothiroxine

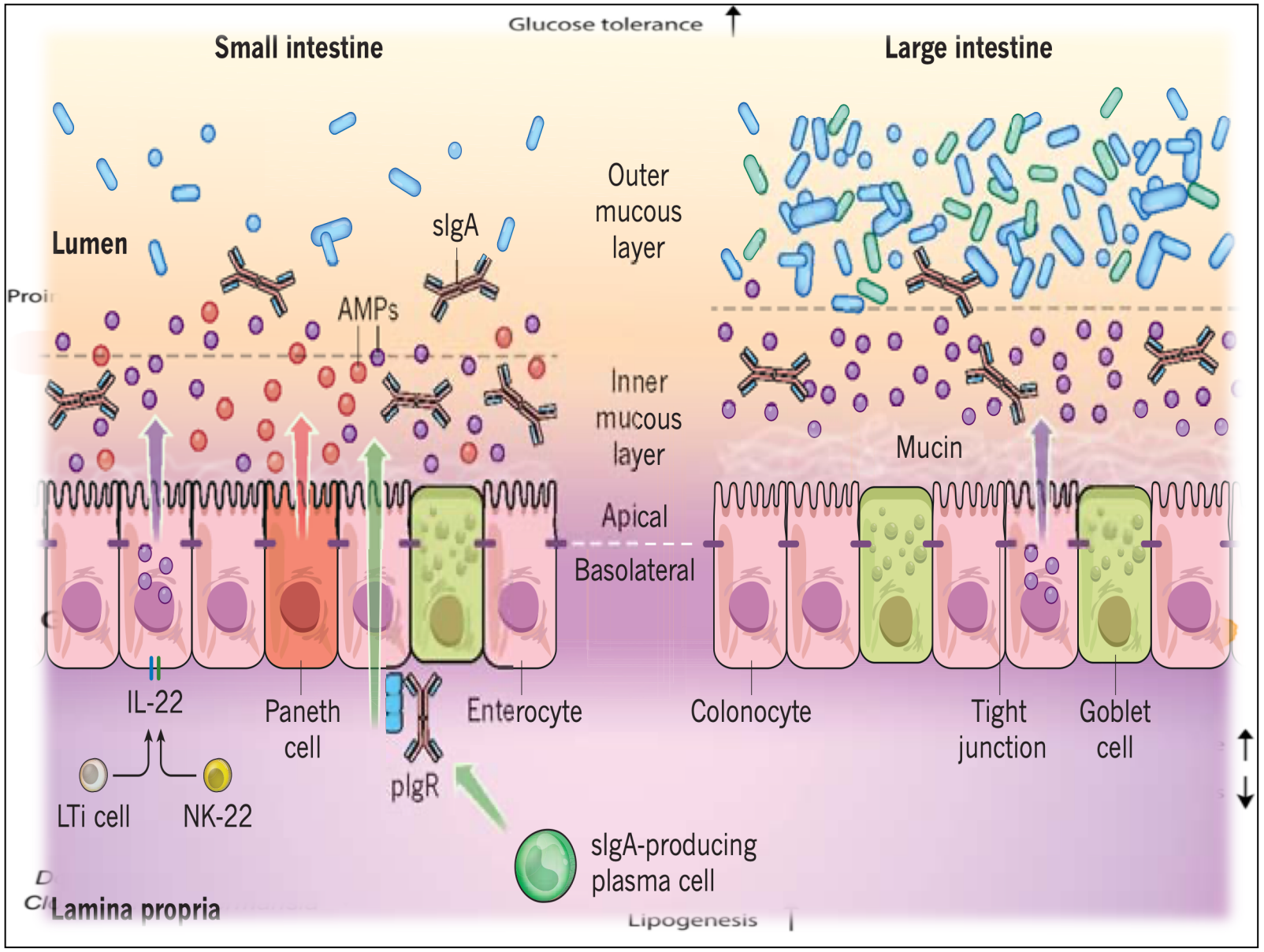
PSORIASIS: evidence suggests that psoriasis patients with gluten-related antibodies may benefit from a GFD, however, larger trials are still lacking.

MULTIPLE SCLEROSIS: The only clinical trial to have studied the effects of a GFD among patients with MS found positive results, however, the publication was subject to major limitations

Passali et al. Nutrients 2020

Poblocki et al. J. Clin. Med. 2021

Summary


Glucose tolerance
Small intestine
Large intestine
Lumen
sIgA
AMPs
Outer mucous layer
Inner mucous layer
Mucin
Apical
Basolateral
IL-22
Paneth cell
Enterocyte
Colonocyte
Tight junction
Goblet cell
pIgR
LTi cell
NK-22
sIgA-producing plasma cell
Lamina propria
Lipogenesis

Gluten avoidance may reduce beneficial gut bacteria thus affecting immune-metabolic responses in healthy people

Pay attention to unjustified GFD!

