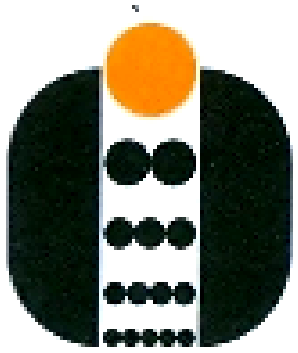
به نام خدا

نقش میکروبیوم دستگاه کوارش در بیماری های متابولیک و CKD

دکتر محمد محمدی

متخصص داروسازی بالینی

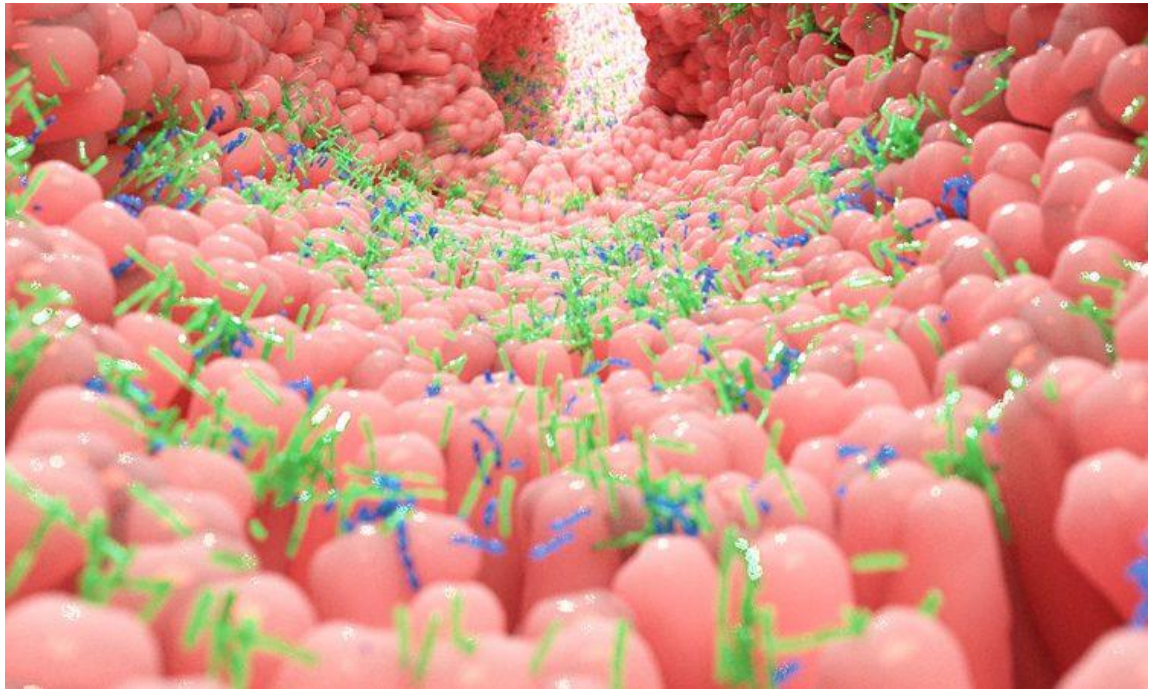
مدیر عامل شرکت فرا دارو

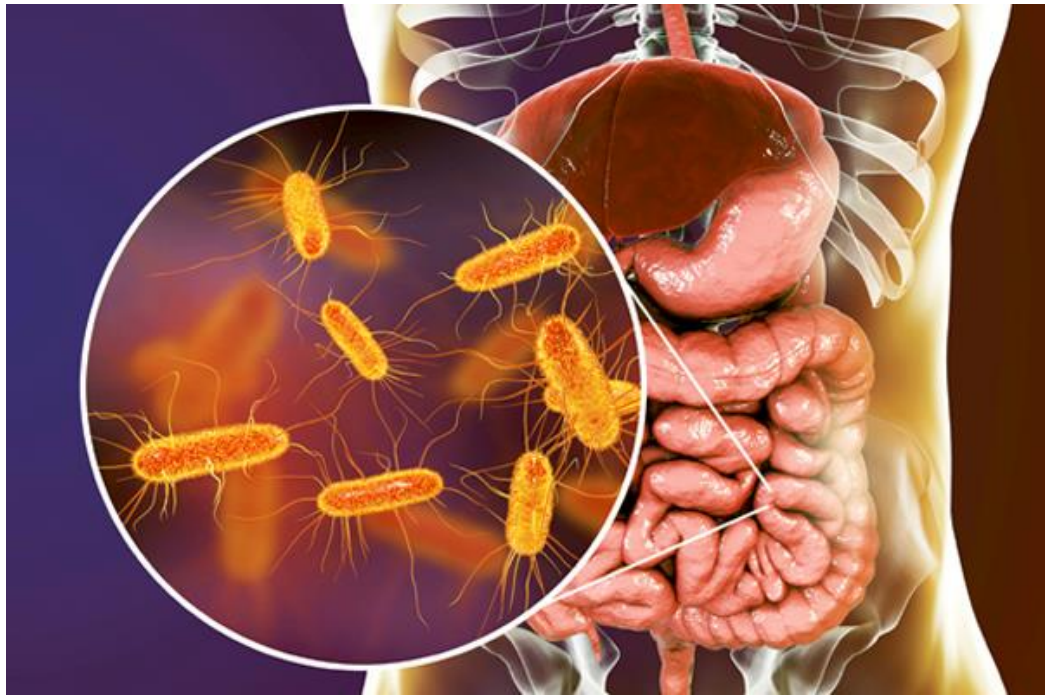


مرکز رشد واحدهای فناوری
فرآورده های دارویی

Tehran University of Medical Sciences (TUMS)

What is Microbiome?





Toxins increase water secretion

Bacteria destroy tight junction, invade mucosa

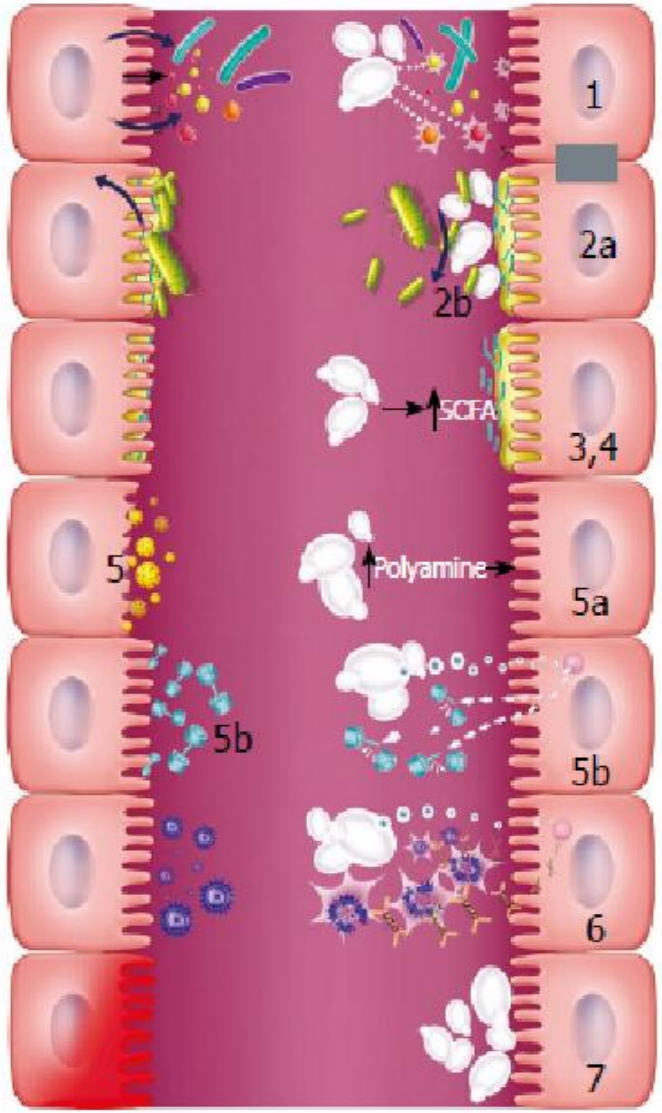
Intestinal flora depleted by antibiotics

Viral infection destroys mature enterocytes

Decrease in disaccharidase causes osmotic diarrhea

Decrease in IgA

Inflammation



Luminal action

1 Anti toxinic effect against
- (a) *C. difficile* toxins A and B (54 kDa protease)
- (b) Cholera toxin (120 kDa protein)
- (c) *E. coli* LPS (63 kDa protein phosphatase)

2 Antimicrobial activity
- (a) Preservation of tight junctions
- (b) Bacteria adhere to Sb, Sb decreases invasion

3 Modulation of intestinal flora

4 Metabolic activity: Sb increases short chain fatty acids, favors normal colonic function

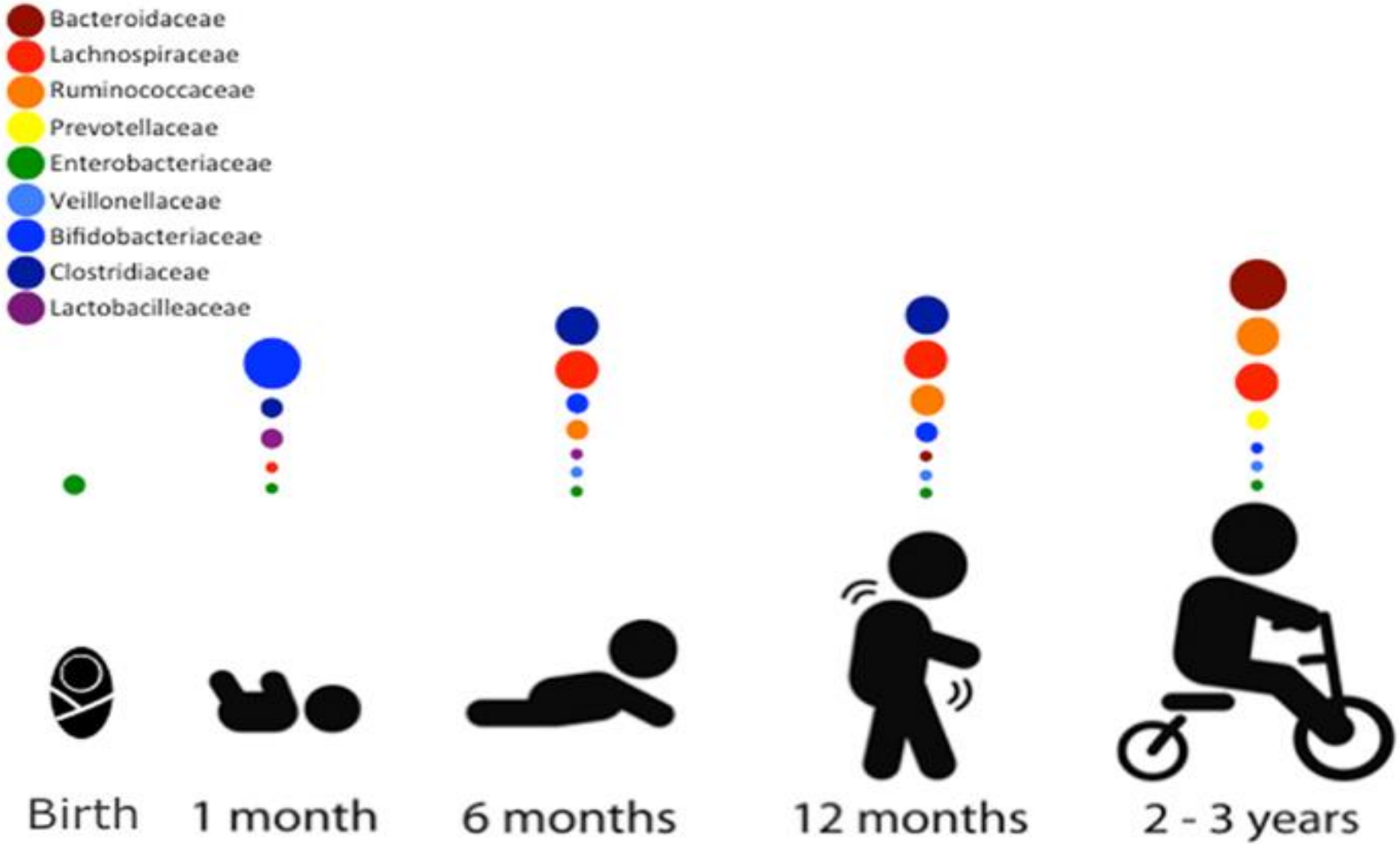
Trophic action

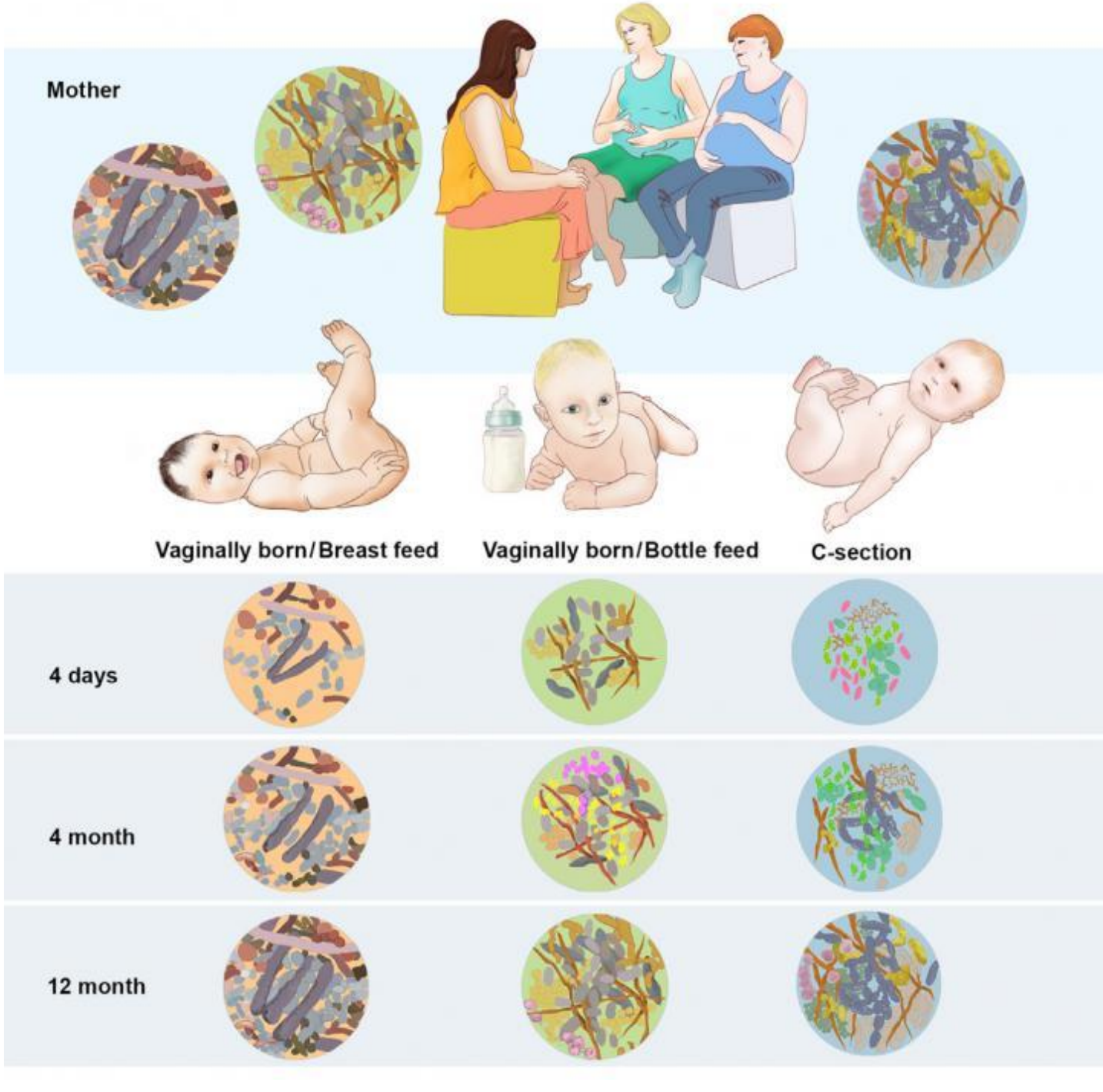
5 Enzymatic activity
- (a) Polyamines favor enterocyte maturation
- (b) Increased disaccharidase levels-beneficial in viral diarrhea

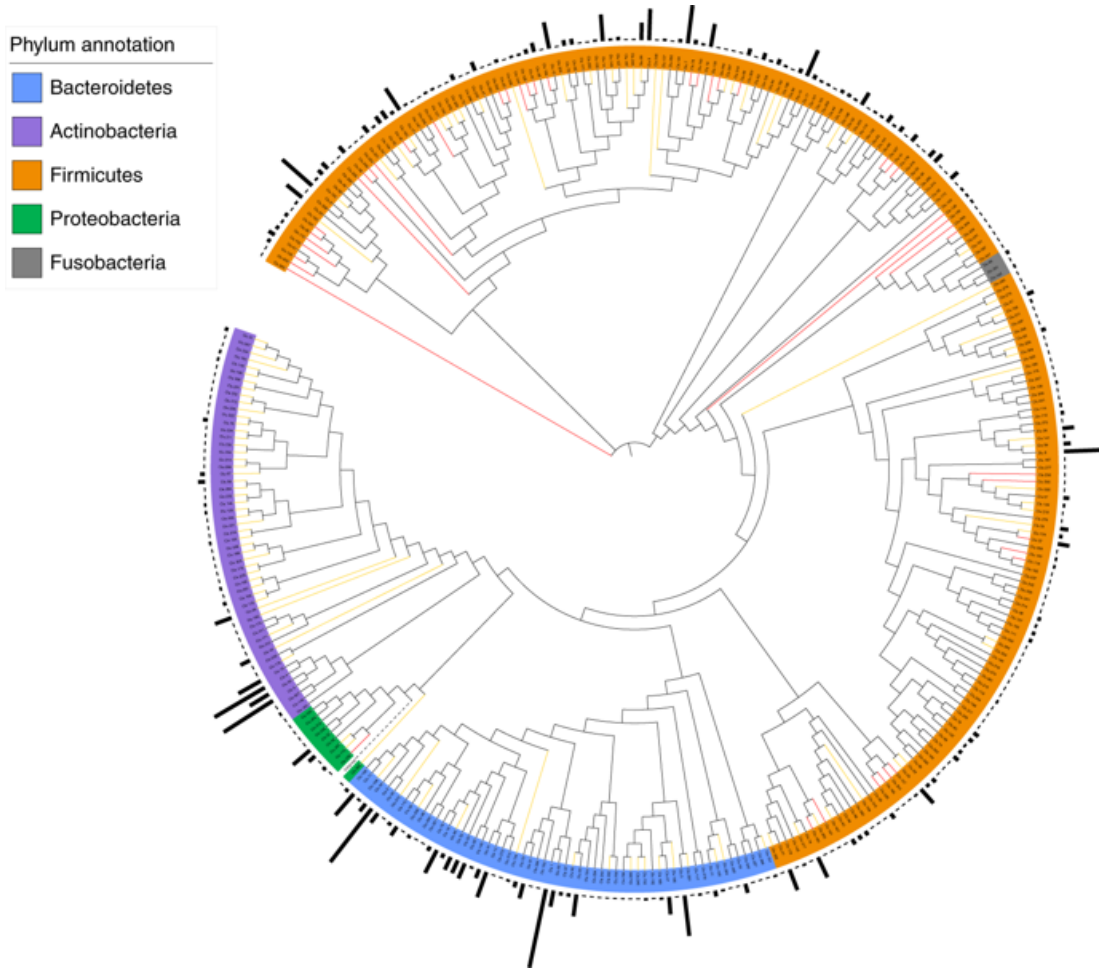
6 Increased sIgA levels increases immune defense in the gut

Mucosal action-antiinflammatory effect

7 Acts on the cellular signals and decreases synthesis of inflammatory cytokines


Bacteroidaceae
Lachnospiraceae
Ruminococcaceae
Prevotellaceae
Enterobacteriaceae
Veillonellaceae
Bifidobacteriaceae
Clostridiaceae
Lactobacilleaceae
Birth
1 month
6 months
12 months
2 - 3 years
Bacterial diversity
Interindividual variability


Mother
Vaginally born/Breast feed
Vaginally born/Bottle feed
C-section
4 days
4 month
12 month

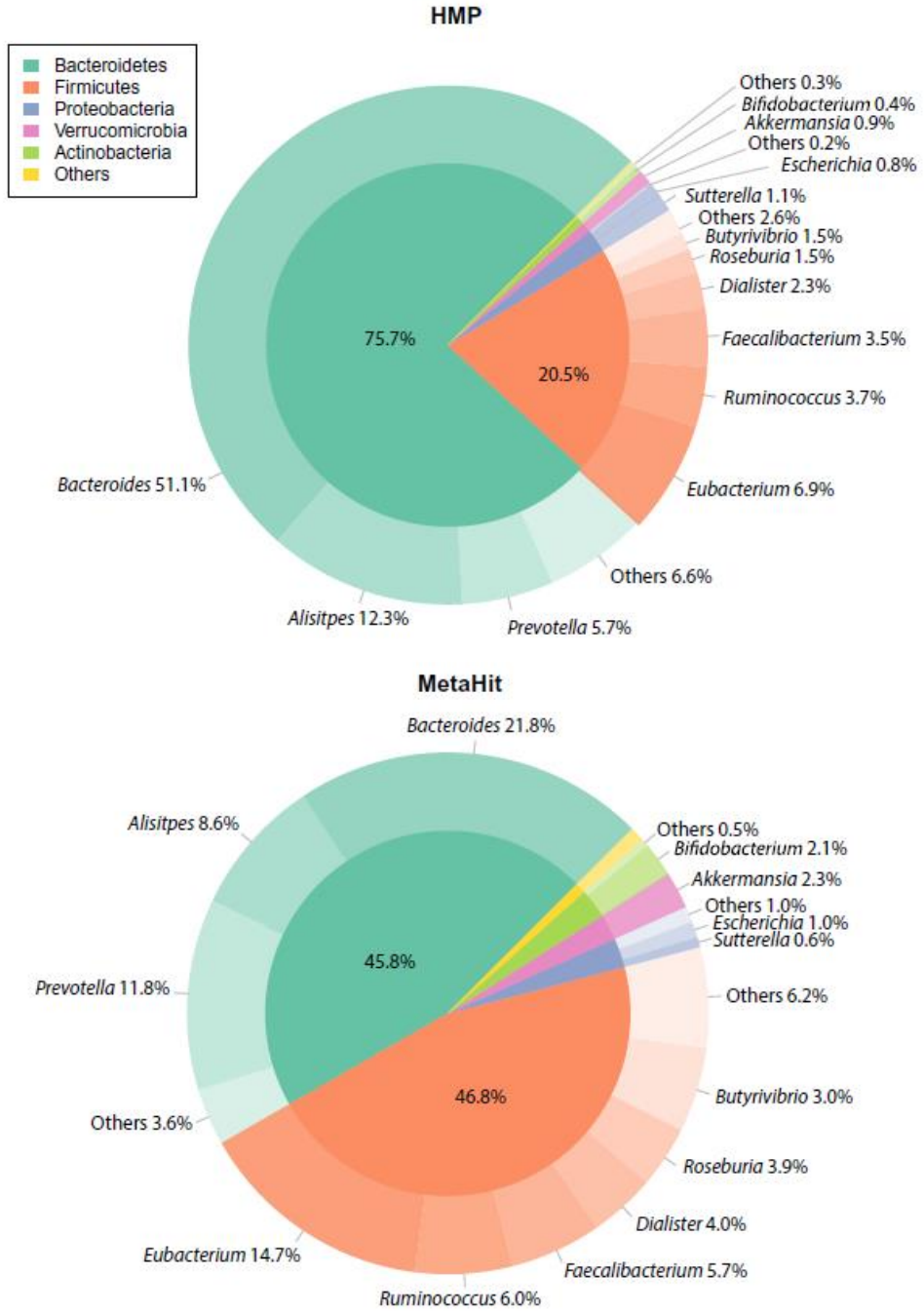


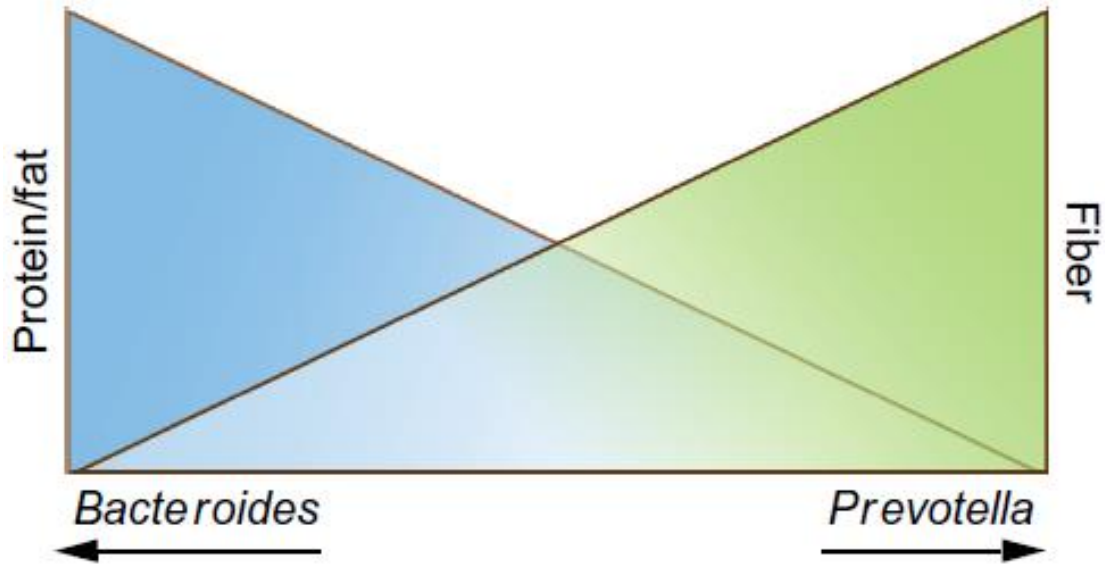
- **Further, the collective genomes of gut microbiota (microbiome) contain 100- to 150-fold more genes than our own genome**

>10 000 000 genes

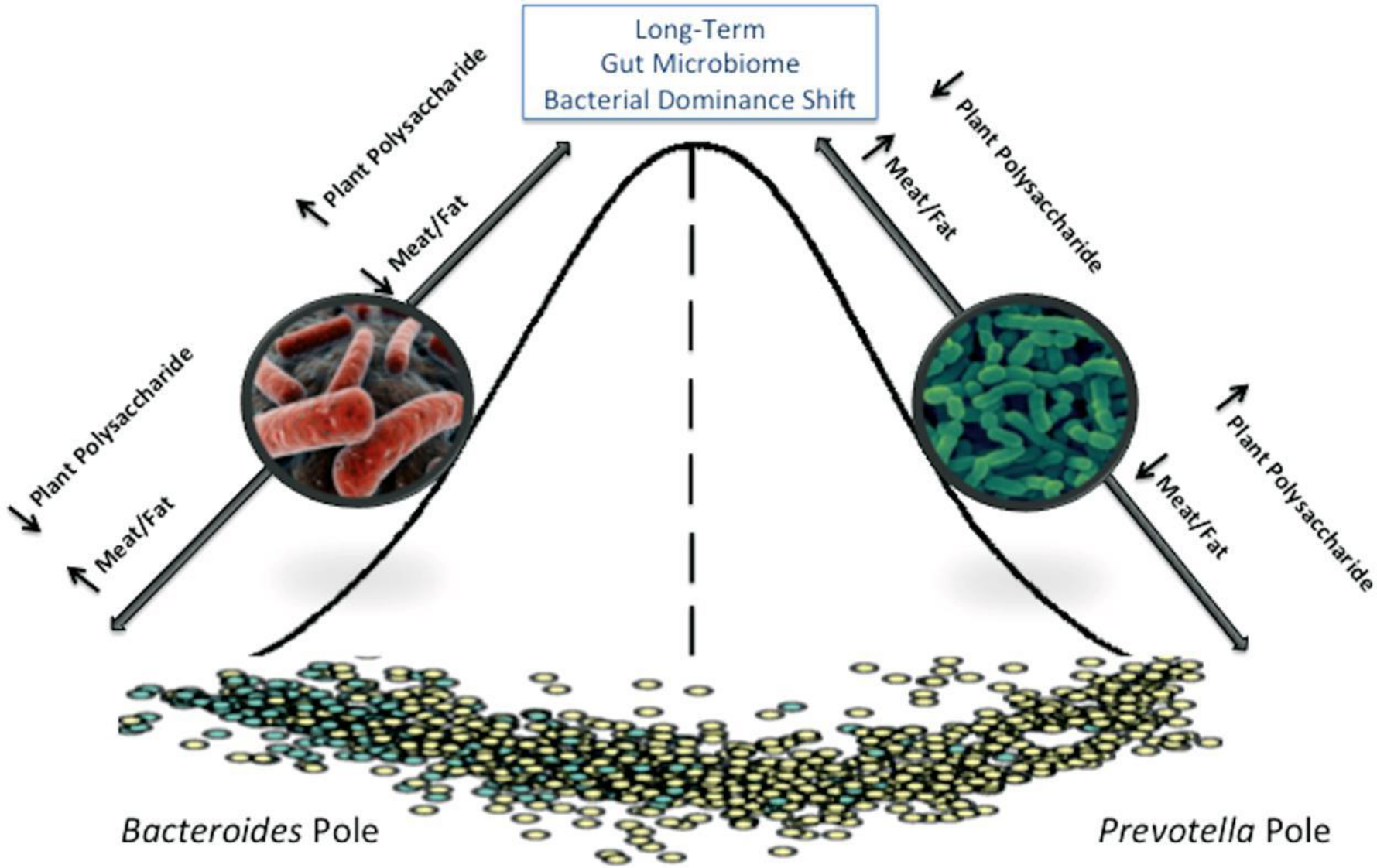
- Quantitative comparison of faecal microbiota in two healthy populations

- Comparisons between obese and lean individuals have demonstrated that obese individuals have increased levels of Firmicutes and reduced levels of Bacteroidetes



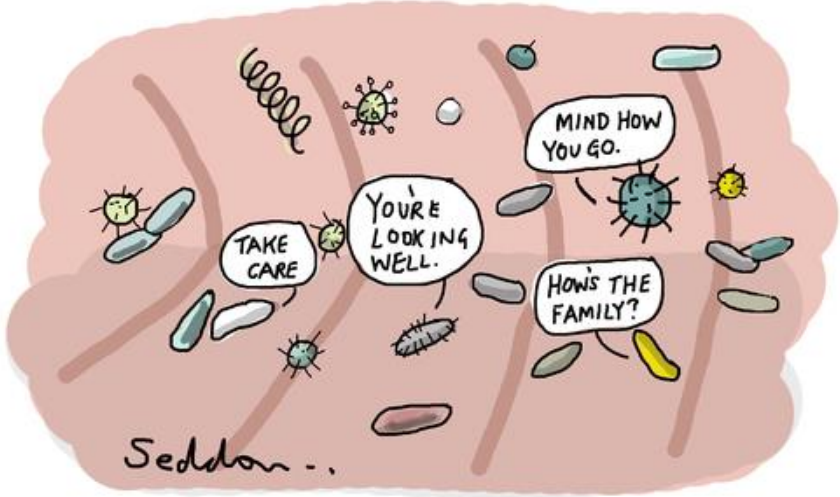


- Diet alters the gut microbiota. Dietary composition alters the proportions of Bacteroides and Prevotella, both of which belong to the phylum Bacteroidetes.
- Intake of an animal-based diet rich in protein/fat promotes higher Bacteroides levels, whereas intake of a plant-based diet rich in fiber shifts the microbiota towards higher Prevotella levels.

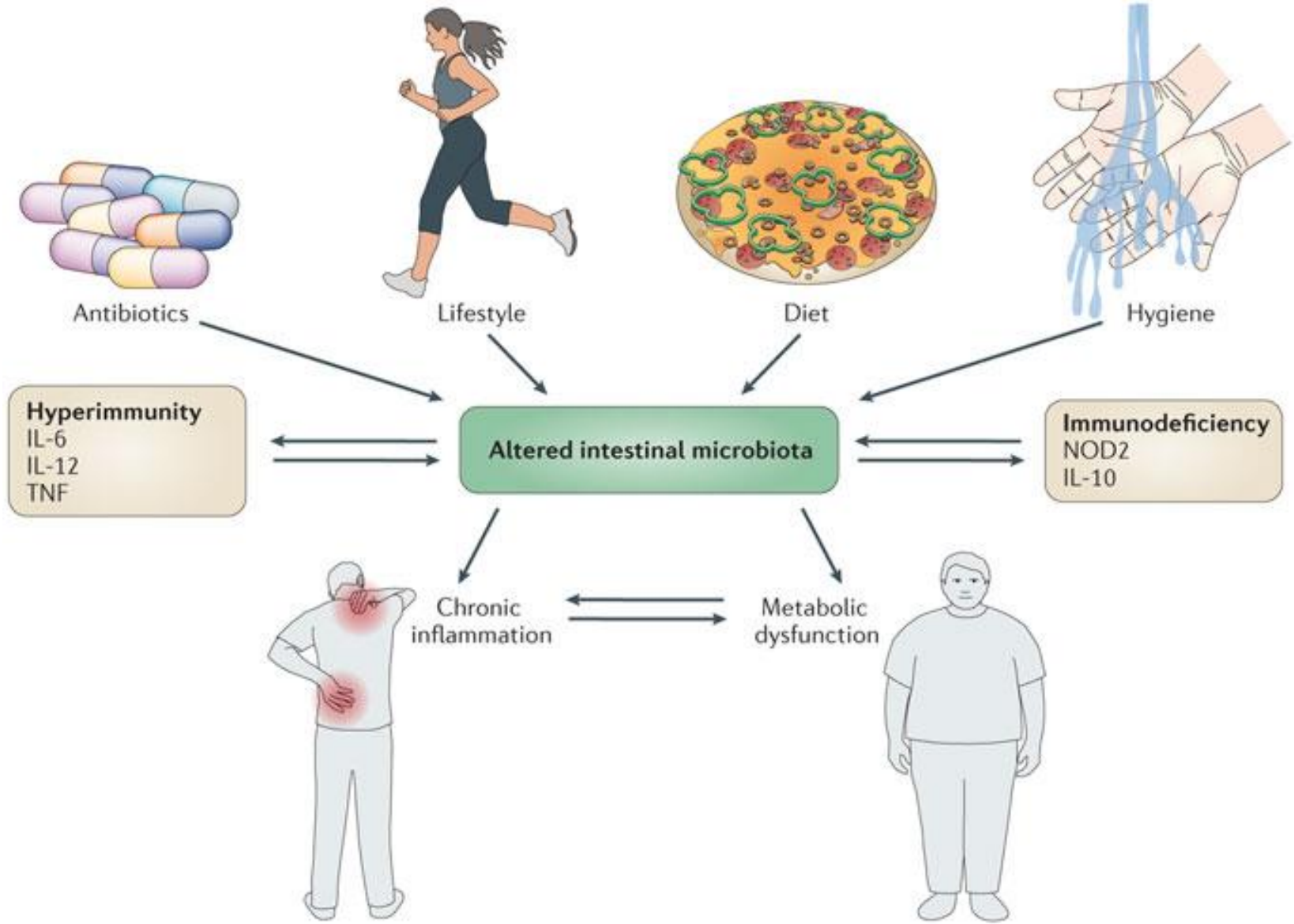

Long-Term
Gut Microbiome
Bacterial Dominance Shift
Plant Polysaccharide
Meat/Fat
Plant Polysaccharide
Meat/Fat
Meat/Fat
Plant Polysaccharide
Meat/Fat
Plant Polysaccharide
Bacteroides Pole
Prevotella Pole

FIRST IDEA

Research on alterations of the gut microbiota may provide insights into how the gut microbiota contributes to disease progression and whether it can be exploited as a novel diagnostic, prognostic and therapeutic target

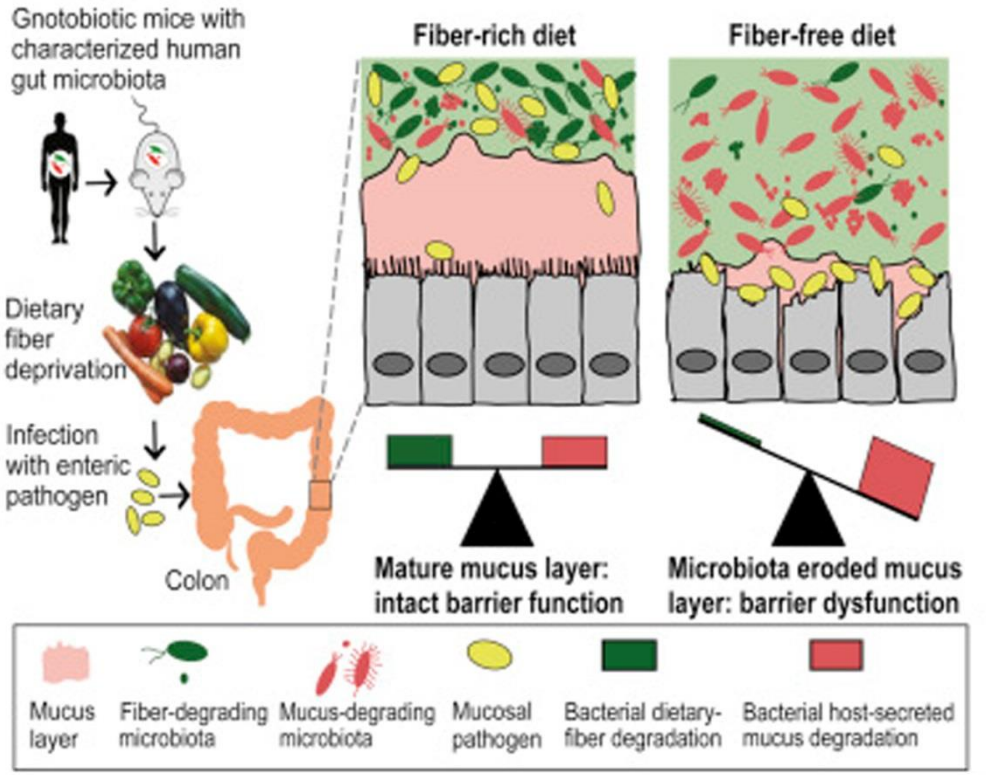


Friendly bacteria of the human gut.


Antibiotics
Lifestyle
Diet
Hygiene
Hyperimmunity
IL-6
IL-12
TNF
Altered intestinal microbiota
Immunodeficiency
NOD2
IL-10
Chronic inflammation
Metabolic dysfunction

Investigations from studies

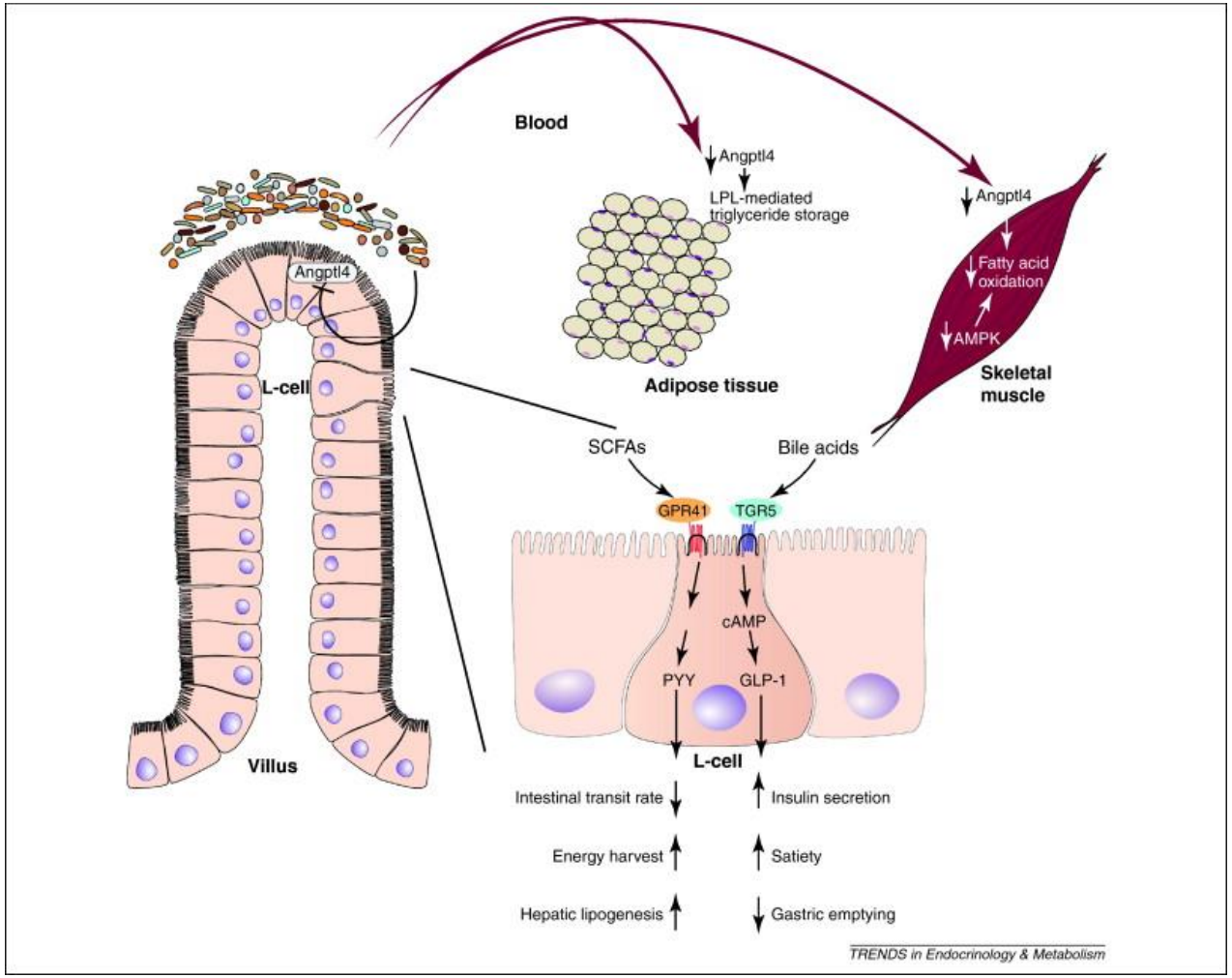
- Degrade polysaccharides
- Contribute 10% of daily energy requirements
- Asian/ African diets have higher fibre content, which may indicate a higher energy contribution from fibre fermentation to the host.



Credit: Desai MS e

- The reduced level of Angptl4 was associated with increased LPL activity in the white adipose tissue, supporting increased triglyceride incorporation into adipocytes

- Angptl4 was required for mediating microbiota-induced adiposity

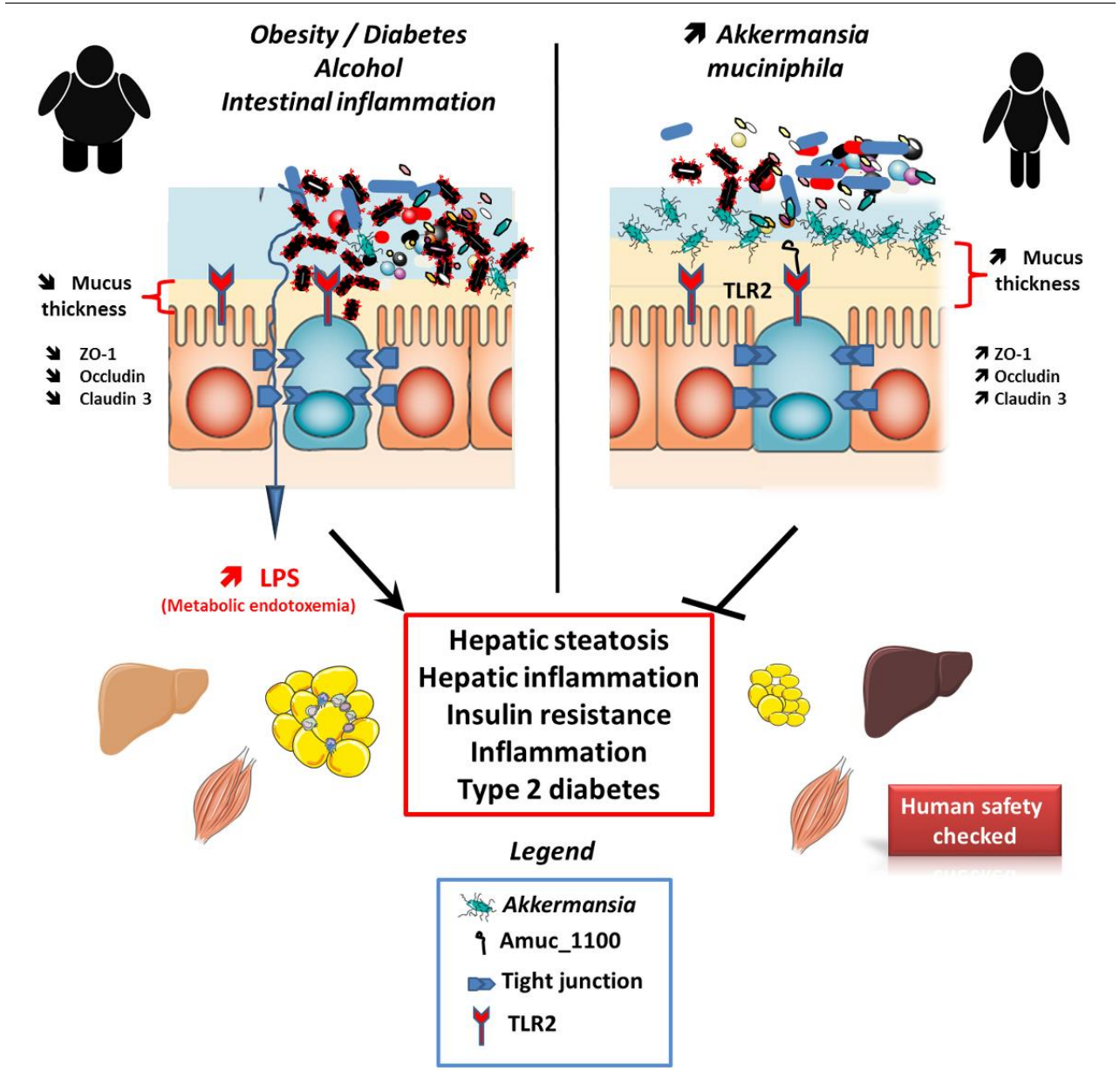


The gut microbiota and type 2 diabetes

- There are accumulating evidence to suggest that the microbiome may directly modulate insulin sensitivity in humans
- In patients with metabolic syndrome reduced the abundance of Gram-positive bacteria, such as butyrate-producing bacteria; this was associated with reduced insulin sensitivity, suggesting that the decreased levels of butyrate-producing bacteria observed in patients with type 2 diabetes may contribute to disease

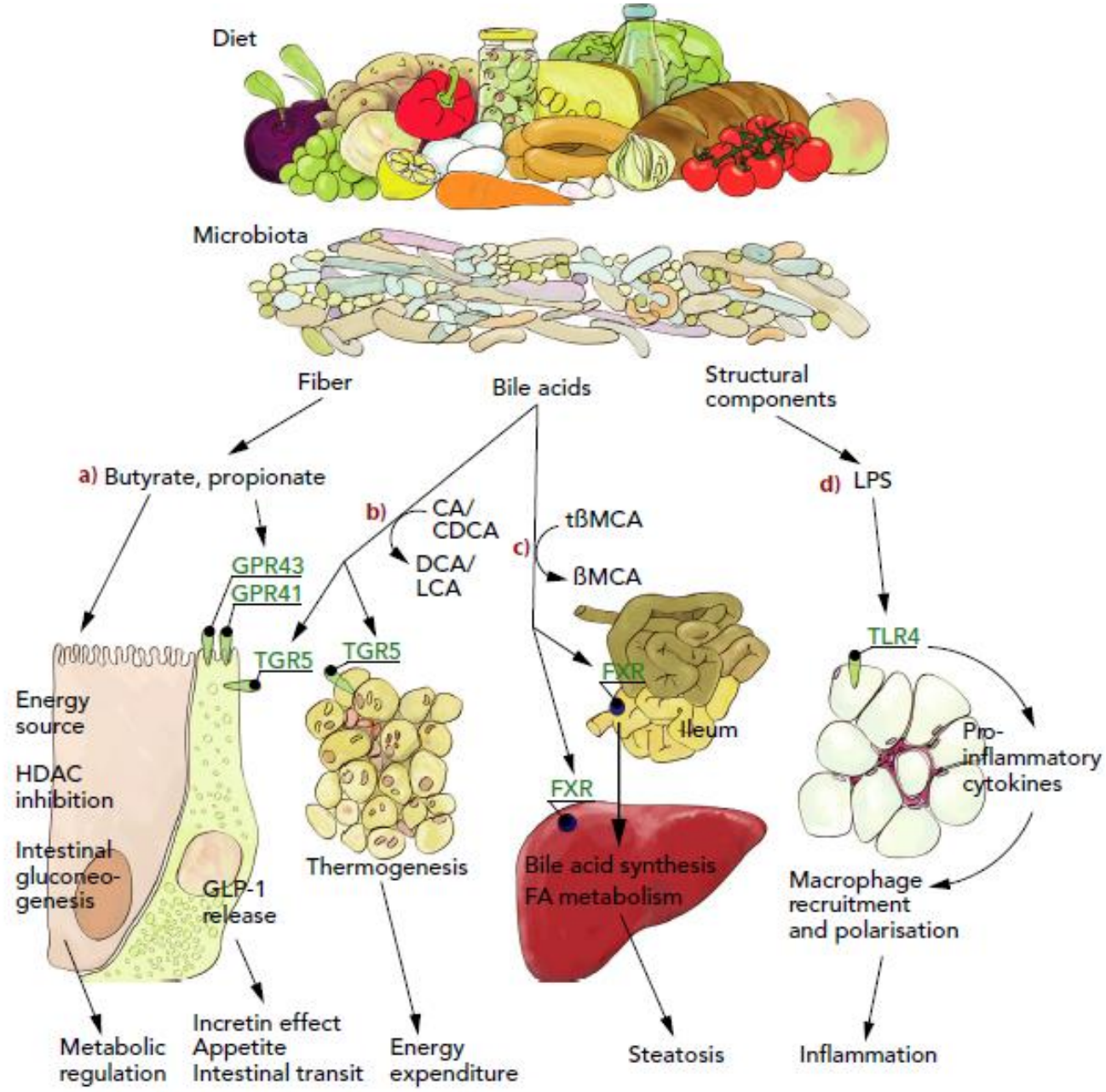
- Akkermansia muciniphila was associated with increased microbial diversity compared with subjects with more impaired metabolic status.

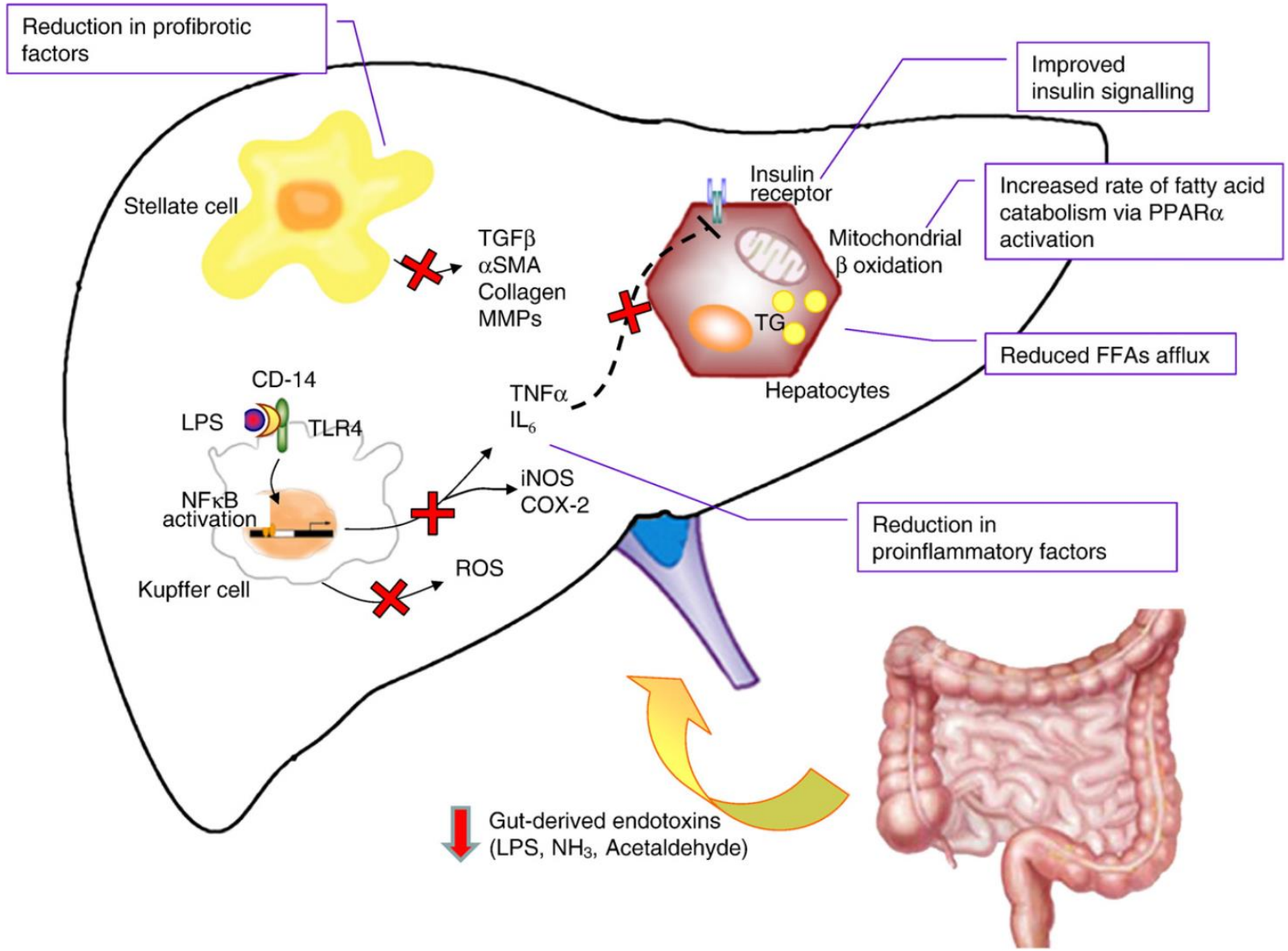
- Thus, there may be population-specific associations between A. muciniphila and type 2 diabetes.

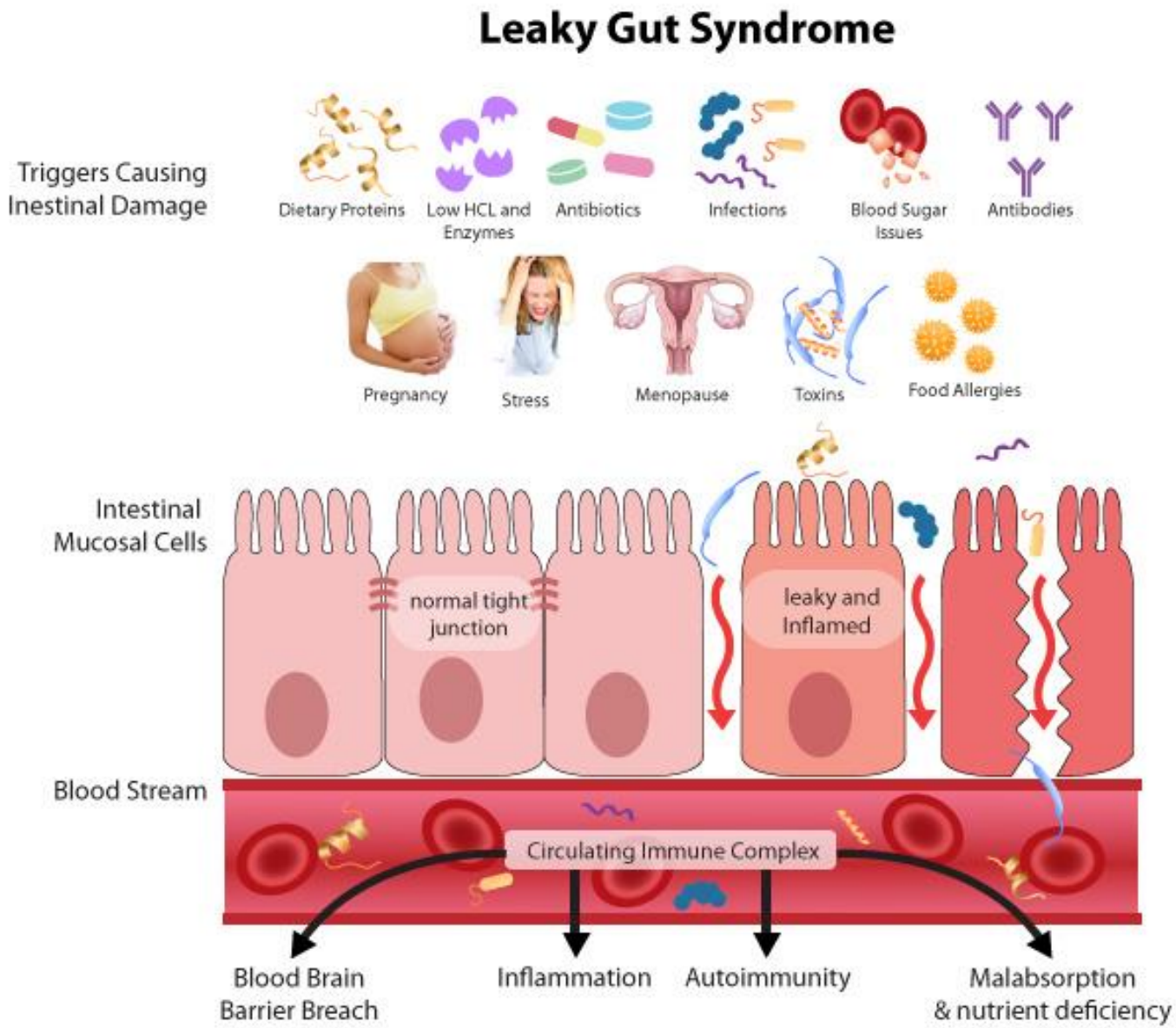


Microbial metabolites regulate metabolism in different tissues

Diet ⟷ **Microbiome**

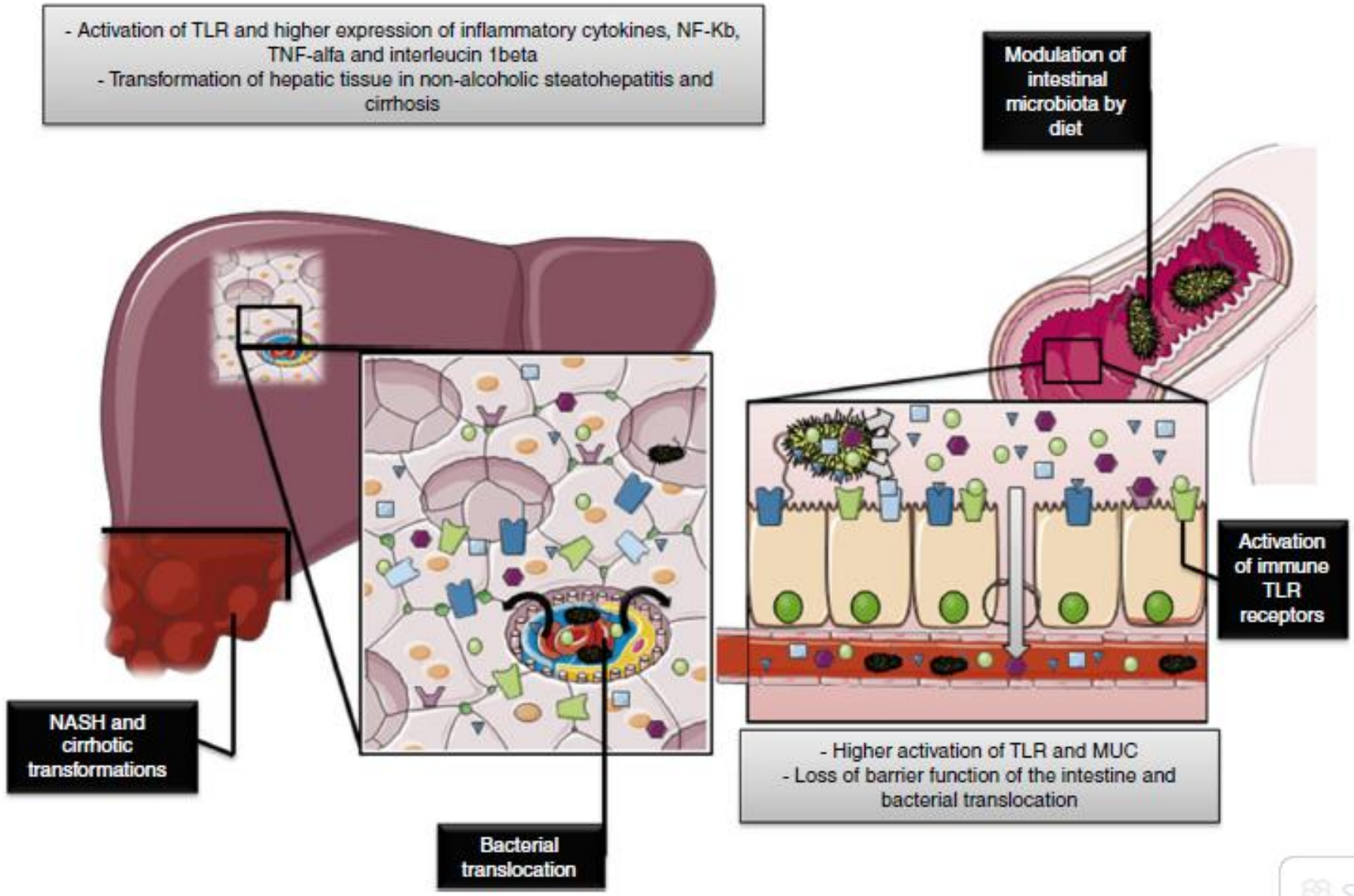


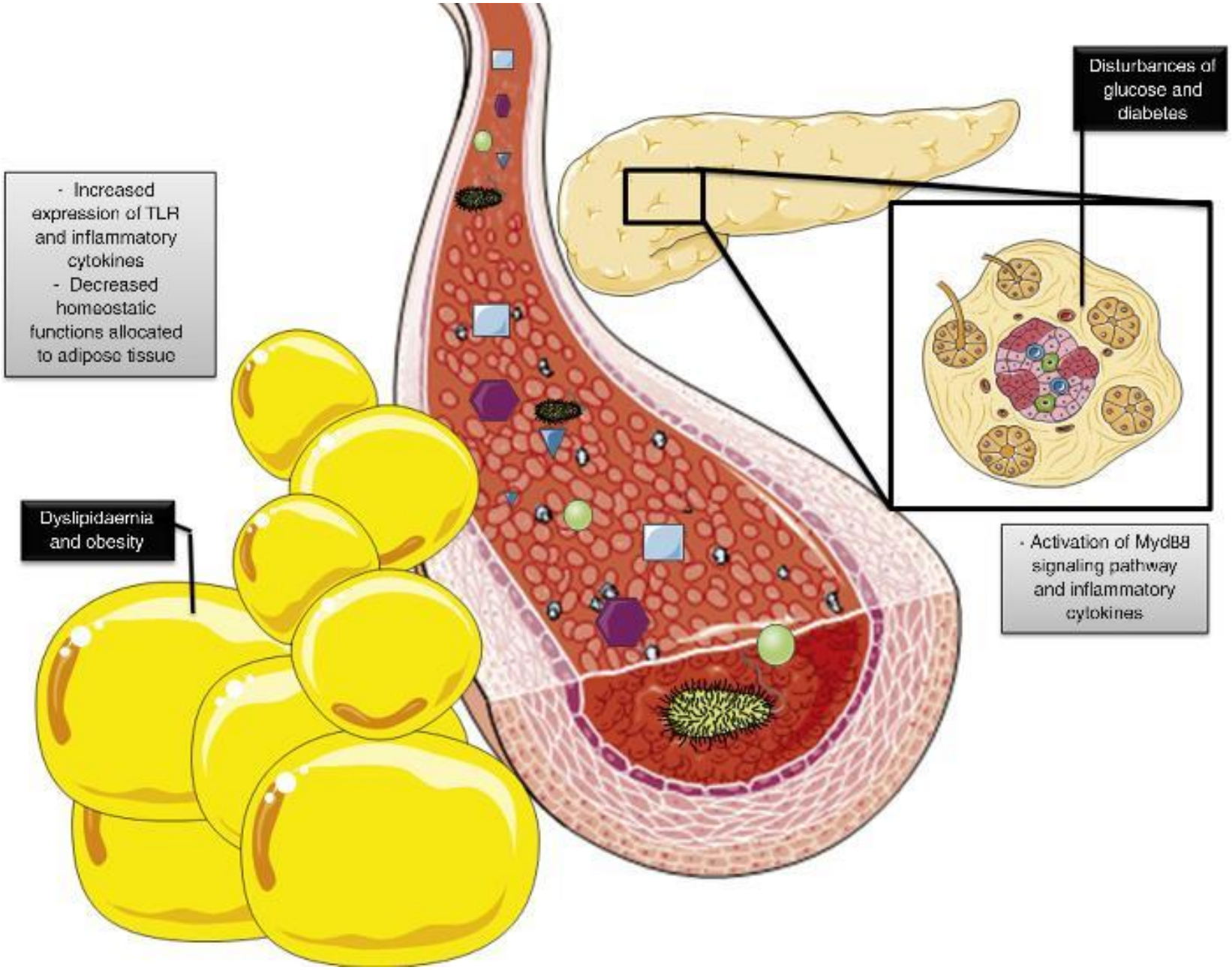

Reduction in profibrotic factors
Improved insulin signalling
Stellate cell
TGFβ
αSMA
Collagen
MMPs
Insulin receptor
Mitochondrial β oxidation
Increased rate of fatty acid catabolism via PPARα activation
TG
Reduced FFAs afflux
Hepatocytes
CD-14
LPS
TLR4
TNFα
IL6
NFκB activation
iNOS
COX-2
Reduction in proinflammatory factors
ROS
Kupffer cell
Gut-derived endotoxins (LPS, NH3, Acetaldehyde)


Leaky Gut Syndrome
Triggers Causing Inestinal Damage
Dietary Proteins
Low HCL and Enzymes
Antibiotics
Infections
Blood Sugar Issues
Antibodies
Pregnancy
Stress
Menopause
Toxins
Food Allergies
Intestinal Mucosal Cells
normal tight junction
leaky and Inflamed
Blood Stream
Circulating Immune Complex
Blood Brain Barrier Breach
Inflammation
Autoimmunity
Malabsorption & nutrient deficiency


CHOMP! MUNCH!
CRUNCH! CHOMP! MUNCH!
CHOMP!
CHOMP!
HEY! THEY'RE EATIN' US OUT OF HOUSE 'N HOME!
PROBIOTICS
BAD BACTERIA
ALNIJBET

NASH


- Activation of TLR and higher expression of inflammatory cytokines, NF-Kb, TNF-alfa and interleucin 1beta
- Transformation of hepatic tissue in non-alcoholic steatohepatitis and cirrhosis
Modulation of intestinal microbiota by diet
Activation of immune TLR receptors
NASH and cirrhotic transformations
Bacterial translocation
- Higher activation of TLR and MUC
- Loss of barrier function of the intestine and bacterial translocation


- Increased expression of TLR and inflammatory cytokines
- Decreased homeostatic functions allocated to adipose tissue
Dyslipidaemia and obesity
Disturbances of glucose and diabetes
- Activation of MyD88 signaling pathway and inflammatory cytokines

Obesity

GE Port J Gastroenterol. 2015;22(6):240–258

Portuguese Journal of Gastroenterology

www.elsevier.pt/ge

REVIEW ARTICLE

Systematic Review of the Relation Between Intestinal Microbiota and Toll-Like Receptors in the Metabolic Syndrome: What Do We Know So Far?

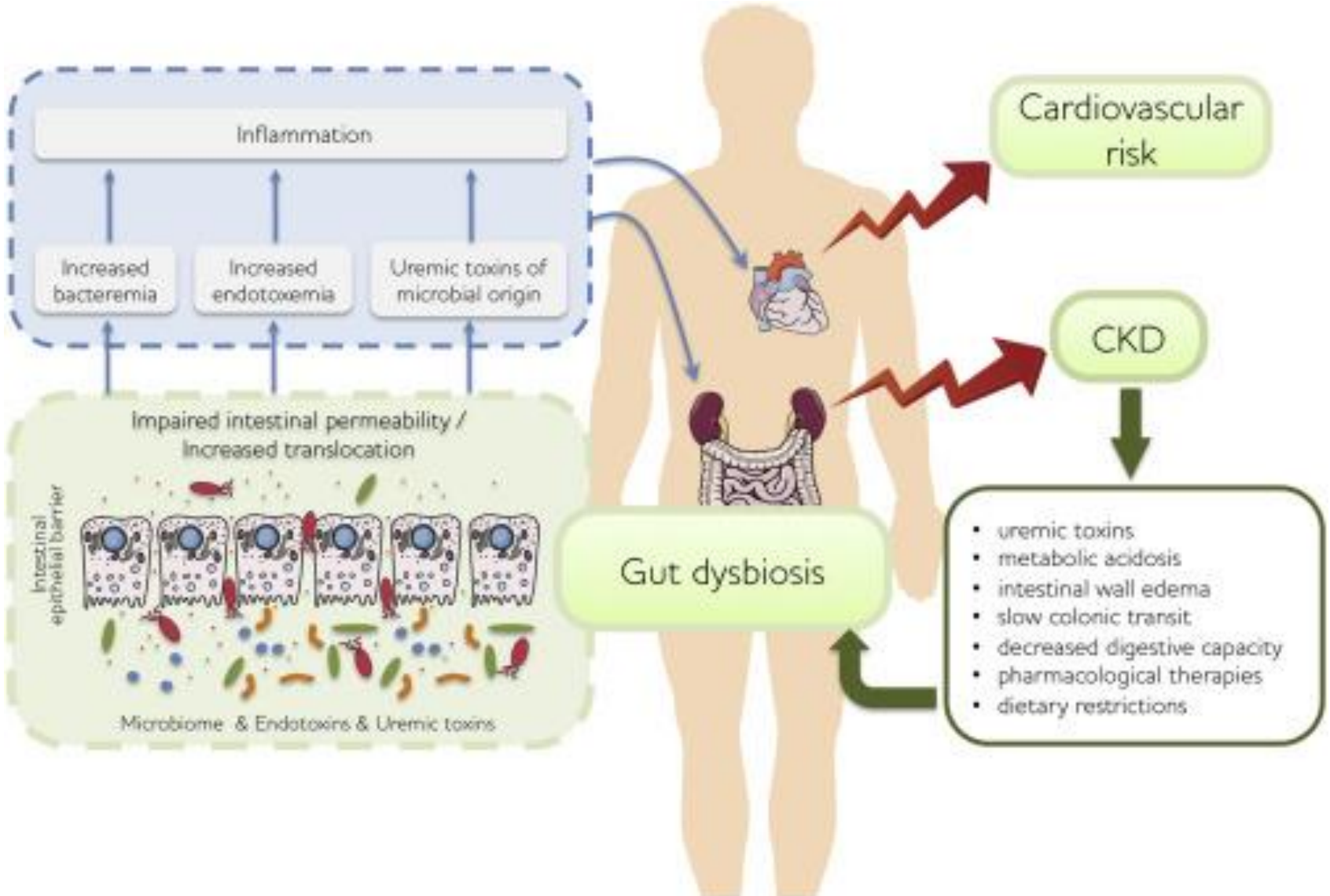
José Pedro Portela-Cidade[a,*], Marta Borges-Canha[a], Adelino Ferreira Leite-Moreira[a], Pedro Pimentel-Nunes[a,b,c]

TLR expression and metabolic syndrome: the importance of the innate immunity

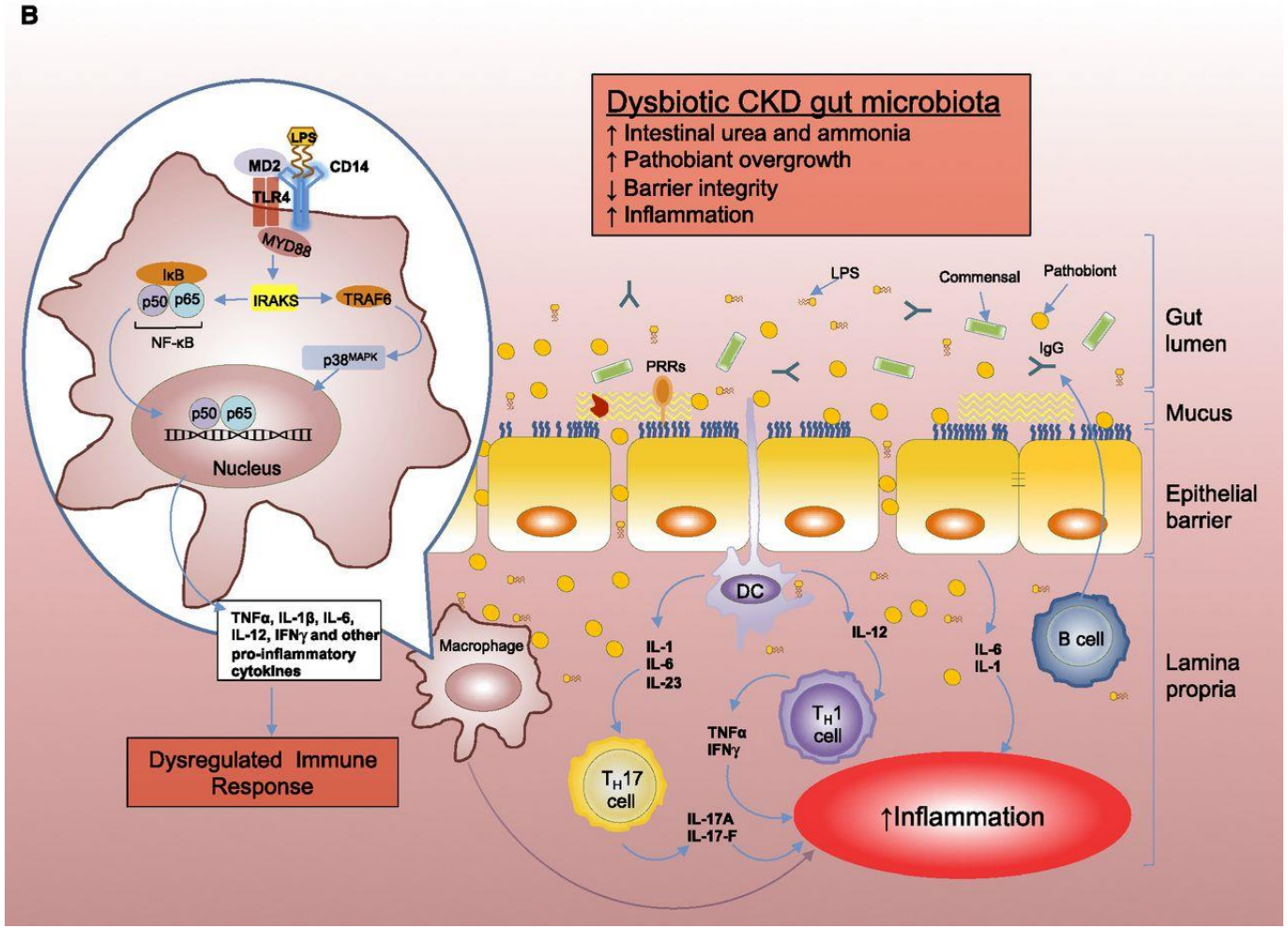
Table 2 Principal proposed mechanisms in the development of Metabolic Syndrome [here, ↑ represents an augment and ↓ a decrease].

	Toll-like receptor activation	Biochemical molecules expression	Intestinal microbiota modifications	Phenotypical/histological modifications
Diabetes	– ↑ TLR4 and TLR2 expression levels – ↑ MyD88 and TRIF signalling pathways	– ↑ Insulin levels – ↑ Leptin, MCP-1 and TNF-α expression levels – ↑ CD8+ T cells activation (↑ risk of diabetes type 1)	– ↑ *Firmicutes* and ↓ *Bacteroidetes* and *F. prausnitzii*	– Glucose intolerance, ↓ insulin sensitivity
Dyslipidaemia	– ↑TLR4 expression levels	– ↑ Saturated Fatty acids and ↓HDL cholesterol levels – ↓ Adiponectine levels – ↑ Lipoprotein lipase and ↓ fasting-induced adipocyte factor (Angpt14/Fiaf) activities	– ↑ *Firmicutes* and ↓ *Bacteroidetes*	– Obesity – Increased macrophage infiltration in adipose tissue – Smaller adipocytes
NASH	– ↑ TLR2 and TLR4, 5 and 9 expression levels	– ↑IL-1β, phospho-interleukin-1 receptor-associated kinase 1 and TNF-α expression levels – ↑ XBP-1, iNOS and NF-kB expression levels – ↑ Nlrp3, Nlrp6 and IL-18 expression levels – ↑MUC2 and 3 intestinal activity	– ↑ *Firmicutes*, *Porphyromonadaceae* and *Enterobacteriaceae* – ↓*Bacteroidetes*, *Lactobacilli* and *Bacteroides*	– Macrovesicular and microvesicular hepatic steatosis and hepatocellular ballooning – Obesity and glucose intolerance
Metabolic Syndrome	– ↑ TLR2 and TLR4 expression levels	– ↑IL-1β, MCP-1 and NF-kB expression levels; – ↑ Insulin levels and ↓ insulin sensitivity	– ↑ *Firmicutes*, *Desulfovibrionaceae*, and *Porphyromonadaceae* – ↓*Bacteroidetes* and *Bifidobacteria*	– Higher waist circumferences and body weight – Diabetes (with all above) – Dyslipidaemia (with all above) – NASH (with all above)

Gut Microbiome in Chronic Kidney Disease

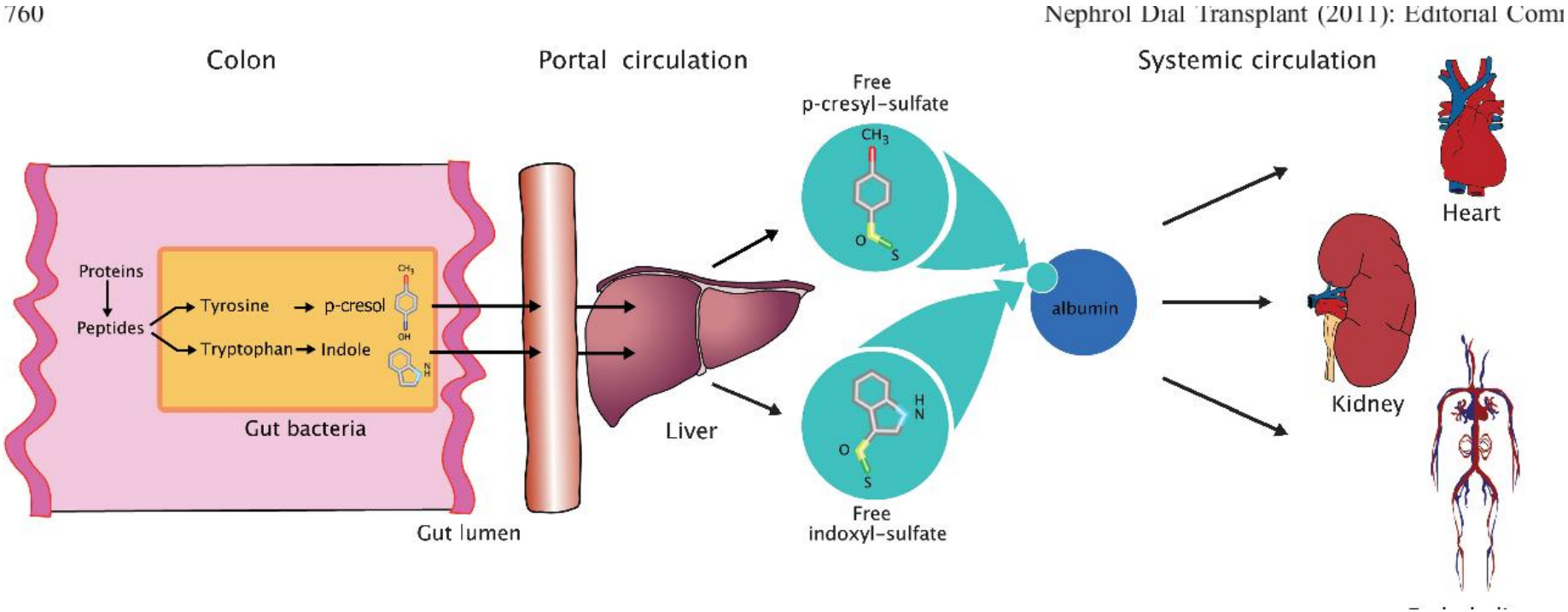


- The dysbiotic gut microbiome generates excessive amounts of uremic toxins, and the impaired intestinal barrier permits translocation of these toxins into the systemic circulation.



Microbiota and Uremic Toxins

- The large intestine has more diversity and quantity of bacteria and its place of the production of the most studied toxins, p-cresyl sulfate, and indoxyl sulfate

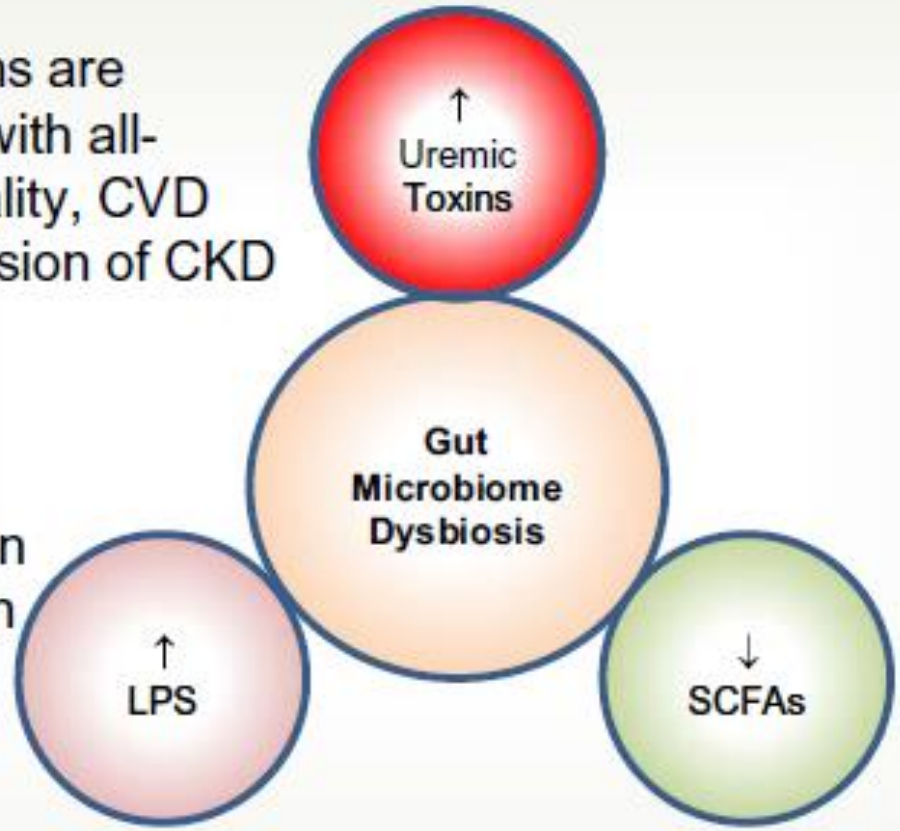


- The gut microbiota can ferment dietary fiber to yield SCFAs acetate and propionate (produced by Bacteroidetes phylum members) as well as butyrate (produced by bacteria of the Firmicutes phylum)

- In addition to their ability to moderate immune signaling and anti-inflammatory impact on both colonic epithelium and immune cells , SCFAs also have a vasorelaxant property in vitro as both butyrate and propionate can induce dilation of human colonic arteries.

- Interestingly, the SCFA olfactory receptor 78 (Olfr78) is expressed in the kidneys and regulates BP, as shown by BP reduction of about 20 mmHg following administration of propionate to normal mice

Uremic toxins are associated with all-cause mortality, CVD and progression of CKD



Endotoxin translocation causes inflammation in CKD; possible role in progression of atherosclerosis

SCFA may be involved in inflammation and blood pressure regulation

- Although no significant differences in the total amount of microorganisms, an increase in the proportion of aerobic bacteria to the detriment of anaerobic bacteria (especially Bifidobacterium and Lactobacillus) has been described.

- The expansion of these species increases the degradation of nitrogen compounds in worsen uremic state

- Recently, a greater emphasis has been given to the modulation of intestinal microbiota of CKD patients by oral supplementation with pre/probiotics or their combination (synbiotics), especially in inhibiting serum increase of uremic toxins, improving gastrointestinal symptoms and reversing or decreasing inflammation

Supplementation with gum arabic fiber increases fecal nitrogen excretion and lowers serum urea nitrogen concentration in chronic renal failure patients consuming a low-protein diet[1–4]

Donna Zimmaro Bliss, T Peter Stein, Charles R Schleifer, and R Gregg Settle

ABSTRACT In chronic renal failure (CRF), plasma concentrations of the products of protein metabolism are increased. Current dietary management is to prescribe a decrease in protein intake. The use of dietary fiber to increase fecal excretion of retained metabolites in CRF may be a beneficial adjunct to a low-protein diet (LPD). Colonic bacteria ferment dietary fiber, providing them with energy for growth and nitrogen incorporation, in turn, increasing nitrogen excretion in feces. Sixteen CRF patients consuming an LPD were randomly assigned to receive a supplement of a highly fermentable fiber, gum arabic (50 g/d), or a placebo (1 g pectin/d) in a prospective, single-blind, crossover design. Fecal bacterial mass and fecal nitrogen content were significantly increased during supplementation with gum arabic compared with the baseline LPD or supplementation with pectin. Serum urea nitrogen was significantly decreased during supplementation with gum arabic compared with the baseline LPD or supplementation with pectin. Nitrogen balance did not change significantly. *Am J Clin Nutr* 1996;63:392–8.

KEY WORDS Gum arabic, fiber, chronic renal failure treatment, dietary therapy

urea and other retained metabolites in CRF patients (14–18). The use of dietary fiber to increase fecal excretion of retained metabolites in CRF may be a beneficial adjunctive therapy. The purpose of this study was to determine whether supplementing an LPD with a highly fermentable fiber, gum arabic (19), would increase fecal nitrogen excretion and fecal bacterial mass and result in lower serum urea nitrogen concentrations.

SUBJECTS AND METHODS

Subjects

The study sample consisted of 20 adult volunteers (13 males and 7 females) with CRF who had been treated with an LPD for $\geq$ 4 mo. Sixteen subjects (10 males and 6 females) completed the study protocol. Subjects were excluded from participating if they had a history of liver disease, were on dialysis, had undergone renal transplantation, were pregnant or lactating, or had active gastrointestinal bleeding. The participation of three subjects was discontinued for the following reasons: stroke and

CJASN ePress. Published on January 15, 2016 as doi: 10.2215/CJN.05240515

Article

Synbiotics Easing Renal Failure by Improving Gut Microbiology (SYNERGY): A Randomized Trial

Megan Rossi,†‡ David W. Johnson,*†‡ Mark Morrison,†§ Elaine M. Pascoe,* Jeff S. Coombes,‖ Josephine M. Forbes,*†¶ Cheuk-Chun Szeto,** Brett C. McWhinney,†† Jacobus P.J. Ungerer,†† and Katrina L. Campbell*†‡

Abstract

Background and objectives The generation of key uremic nephrovascular toxins, indoxyl sulfate (IS), and p-cresyl sulfate (PCS), is attributed to the dysbiotic gut microbiota in CKD. The aim of our study was to evaluate whether synbiotic (pre- and probiotic) therapy alters the gut microbiota and reduces serum concentrations of microbiome–generated uremic toxins, IS and PCS, in patients with CKD.

Design, setting, participants, & measurements Predialysis adult participants with CKD (eGFR=10–30 ml/min per 1.73 m^2) were recruited between January 5, 2013 and November 12, 2013 to a randomized, double–blind, placebo–controlled, crossover trial of synbiotic therapy over 6 weeks (4-week washout). The primary outcome was serum IS. Secondary outcomes included serum PCS, stool microbiota profile, eGFR, proteinuria-albuminuria, urinary kidney injury molecule-1, serum inflammatory biomarkers (IL-1β, IL-6, IL-10, and TNF-α), serum oxidative stress biomarkers (F_2-isoprostanes and glutathione peroxidase), serum LPS, patient-reported health, Gastrointestinal Symptom Score, and dietary intake. A prespecified subgroup analysis explored the effect of antibiotic use on treatment effect.

Results Of 37 individuals randomized (age =69±10 years old; 57% men; eGFR=24±8 ml/min per 1.73 m^2), 31 completed the study. Synbiotic therapy did not significantly reduce serum IS (−2 μmol/L; 95% confidence interval [95% CI], −5 to 1 μmol/L) but did significantly reduce serum PCS (−14 μmol/L; 95% CI, −27 to −2 μmol/L). Decreases in both PCS and IS concentrations were more pronounced in patients who did not receive antibiotics during the study (n=21; serum PCS, −25 μmol/L; 95% CI, −38 to −12 μmol/L; serum IS, −5 μmol/L; 95% CI, −8 to −1 μmol/L). Synbiotics also altered the stool microbiome, particularly with enrichment of *Bifidobacterium* and depletion of *Ruminococcaceae*. Except for an increase in albuminuria of 38 mg/24 h (P=0.03) in the synbiotic arm, no changes were observed in the other secondary outcomes.

Conclusion In patients with CKD, synbiotics did not significantly reduce serum IS but did decrease serum PCS and favorably modified the stool microbiome. Large–scale clinical trials are justified.

Clin J Am Soc Nephrol 11: ●●●–●●●, 2016. doi: 10.2215/CJN.05240515

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Table 1 Therapeutic interventions targeting gut microbiome

Author/Ref	Population	(*n*)	Intervention	Study design	Duration	Result
Probiotic						
Hida et al. 1996 [7]	HD	25	*B. infantis, L. acidophilus, E. faecalis*	Single-center, observational trial	4 weeks	↓ Indican in feces and serum ↓ p-cresol in feces
Simenhoff et al. 1996 [50•]	HD	8	*L. acidophilus*	Single-center, observational trial	One course	↓ Dimethylamine ↓ Nitrosodim-ethylamine
Takayama et al. 2003 [51]	HD	22	*B. longum* strain (JCM008)	Single-center, non-randomized, placebo controlled trial	5 weeks	↓ IS
Taki et al. 2005 [52]	HD	27	*B. longum*	Single-center, non-randomized, placebo controlled trial	3 months	↓ Homocysteine, IS, and triglycerides
Natarajan et al. 2014 [53]	HD	22	*S. thermophilus, L. acidophilus, B. longum* (KB 19, KB 27, KB 31)	Single-center, double-blind, placebo controlled, randomized cross-over trial	2 months	↑ Quality of life, Trend ↓ of serum indoxyl glucuronide and C-reactive protein
Wang et al. 2015 [54]	PD	39	*B.bifidum, B.catenulatum, B. longum, L. plantarum* (A218, A302, A101, A87)	Single-center, double-blind, placebo controlled, randomized trial	6 months	↓ Serum TNF-α, IL-5, IL-6, and LPS; preservation of residual renal function
Ando et al. 2003 [55]	CKD patients all stages	27	*B. longum*	Single-center, observational trial	6 months	Slowing of the progression of kidney disease
Ranganathan et al. 2009 [56]	CKD stage 3–4	13	*L. acidophilus, S. thermophilus, and B. longum* (KB31, KB27, KB35)	Single-center, prospective, randomized, double-blind, cross-over, placebo-controlled trial	6 months	↓ BUN ↓ Uric acid concentration ↑ Quality of life

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META-ANALYSIS

Effects of probiotics on nonalcoholic fatty liver disease: A meta-analysis

Yan-Yan Ma, Lin Li, Chao-Hui Yu, Zhe Shen, Li-Hua Chen, You-Ming Li

- Four randomized trials involving 134 NAFLD/NASH patients were included. The results showed that probiotic therapy significantly decreased alanine aminotransferase (ALT), aspartate transaminase (AST), total-cholesterol (T-chol), high density lipoprotein (HDL), tumor necrosis factor (TNF)-α and homeostasis model assessment of insulin resistance (HOMAIR)
- **CONCLUSION:** Probiotic therapies can reduce liver aminotransferases, total-cholesterol, TNF-α and improve insulin resistance in NAFLD patients. Modulation of the gut microbiota represents a new treatment for NAFLD.

Hypertension
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Effect of Probiotics on Blood Pressure: A Systematic Review and Meta-Analysis of Randomized, Controlled Trials

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- **9 trials were included.**
- **Probiotic consumption significantly changed systolic BP by −3.56 mm Hg (95% confidence interval, −6.46 to −0.66) and diastolic BP by −2.38 mm Hg (95% confidence interval, −2.38 to −0.93) compared with control groups**
- **Multiple species of probiotics are consumed, the duration of intervention is ≥8 weeks**

Effects of Probiotics on Cholesterol Reduction

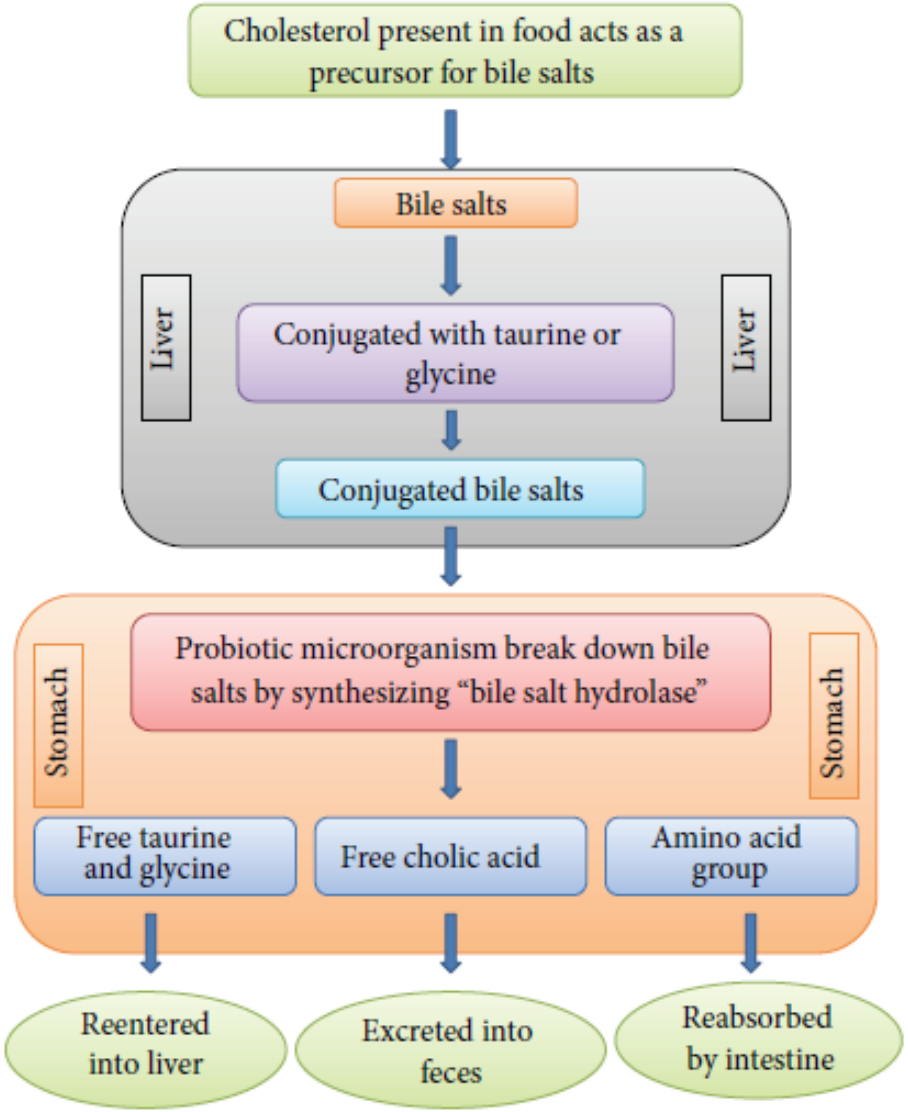

Table 1: Human studies considering probiotics and body weight.

Study	Population	Conclusion	Reference
A DB, RPCT to investigate the impact of a *L. rhamnosus* CGMCC1.3724 (LPR) supplementation on weight loss and maintenance.	125 obese adults (48 male and 77 female) aged 18-55 years.	LPR supplementation can accentuate body-weight loss and seems to help obese women to maintain healthy body weight.	[27]
A DB, randomized, prospective study to evaluate the impact of perinatal probiotic intervention (*L. rhamnosus* GG - ATCC 53103) on childhood growth patterns and the development of overweight during a 10-year follow-up.	159 women before delivery and 113 children were measured at the ages of 3, 6, 12 and 24 months and 4, 7 and 10 years.	Early gut microbiota modulation with probiotics may modify the growth pattern of the child by restraining excessive weight gain during the first years of life.	[29]
A multicenter, DB, RPCT to evaluate the effects of the probiotic L. *gasseri* SBT2055 (LG2055) - originated from the human gut - on abdominal adiposity, body weight and other body measures.	87 healthy adults (59 men/ 28 women) with BMI of 24.2-30.7 kg/m^2 and abdominal visceral fat area (81.2-78.5 cm^2).	LG2055 consumption promoted a significant reduction in abdominal adiposity, BMI, waist and hip circumference.	[33]
A DB, RPCT parallel pilot study to evaluate the effects of a hypocaloric diet supplemented with a probiotic cheese containing L. plantarum strain TENSIA on obese hypertensive patients.	25 obese hypertensive patients.	The hypocaloric diet supplemented with a probiotic cheese helped to reduce BMI.	[45]
A DB, RPCT to assess the beneficial effects on MetS of functional yogurt NY-YP901 (Namyang Dairy Product Co. Ltd and Nutra R&BT Inc., Seoul, Korea) supplemented with Streptococcus thermophilus, L. acidophilus, B. infantis.	101 healthy adults (70 women and 31 men), 20-65 years.	The functional yogurt NY-YP901 with probiotics reduced body weight and BMI.	[50]

Table 2: Human studies considering probiotics and blood lipids.

Table 2: Human studies considering probiotics and blood lipids.

Study	Population	Conclusion	Reference
A DB, RPCT to investigate the effect of L. salivarius Ls-33 on a series of biomarkers related to inflammation and the MetS.	50 obese adolescents (28 female and 22 male), 12-15 years.	No evidence of any beneficial effect on lipid profile.	[13]
A DB, RPCT to assess the cholesterol-lowering clinical efficacy and safety of microencapsulated L. reuteri NCIMB 30242 supplemented in a yogurt formulation.	114 healthy hypercholesterolaemic adult men and women, 18-74 years.	Microencapsulate L. reuteri yoghurt consumption decreased LDL-C, TC and non-HDL-C.	[28]
A DB, RCT to investigate the effects of probiotic (L. acidophilus La5 and B. lactis Bb12) and conventional yogurt on the lipid profile.	60 adults (23 men and 37 women) with T2D and LDL-C > 2.6 mmol/L, 30-60 years.	Probiotic yogurt improved TC and LDL-cholesterol.	[35]
A RPCT to verify and compare the effects of probiotic (L. casei subsp. casei) and conventional yoghurt on the plasma lipid profile.	33 healthy, non-smoking, normocholesterolemic women, 22-29 years.	The total/HDL and LDL/HDL-C ratios improved in both probiotic and conventional yogurt intake.	[36]
A DB, RPCT to assess the beneficial effects on MetS of functional yogurt NY-YP901 (Namyang Dairy Product Co. Ltd and Nutra R&BT Inc., Seoul, Korea) supplemented with Streptococcus thermophilus, L. acidophilus, B. infantis.	101 healthy adults (70 women and 31 men), 20-65 years.	The functional yogurt NY-YP901 with probiotics reduced LDL-C.	[50]
A triple blind, randomized study to test the effect of probiotic (L. acidophilus La5 and B. lactis Bb12) and conventional yogurt on the lipid profile.	90 women, 19-49 years.	Decrease in cholesterol, increase in HDL-C, decrease in total:HDL-C ratio) were observed in both yogurt groups.	[51]
A single-blind, RCOT to compare the effect of consuming probiotic yogurt (L. acidophilus and B. lactis) with that of ordinary yogurt on serum cholesterol level.	14 adults (10 men and 4 women) 40-64 years with mild to moderate hypercholesterolemia.	Cholesterol-lowering effect.	[52]
A single-blind, RPCT to investigate the effect of probiotic capsules (L. acidophilus DDS-1 and B. longum UABL-14) on plasma lipid concentrations.	55 normocholesterolemic adults (33 premenopausal women and 22 men), 18-36 years.	No evidence of any beneficial effect on plasma lipids.	[53]
A single-center, DB, placebo-controlled study to assess the effects of PCC® L. fermentum on LDL cholesterol and other lipid fractions.	44 adults (16 men and 28 women) 30-75 years.	No major effect of Lactobacillus fermentum on serum lipids.	[54]
A single-blind, parallel group study to demonstrate the effect of milk fermented by B. longum strain BL1 on blood lipids.	32 healthy males with serum TC levels within the range of 220 to 280 mg/dl. 35-52 years.	B. longum yogurt lowered serum TC, especially in subjects with moderate hypercholesterolemia.	[55]
A randomized, DB, placebo-and compliance-controlled, parallel study to investigate the effect of a probiotic milk product containing the culture CAUSIDO® and of two alternative products on risk factors for cardiovascular disease.	70 healthy, weight-stable, overweight and obese adults (20 men and 50 women) 18-55 years.	CAUSIDO® culture reduced LDL-cholesterol.	[56]

Thanks for your attention