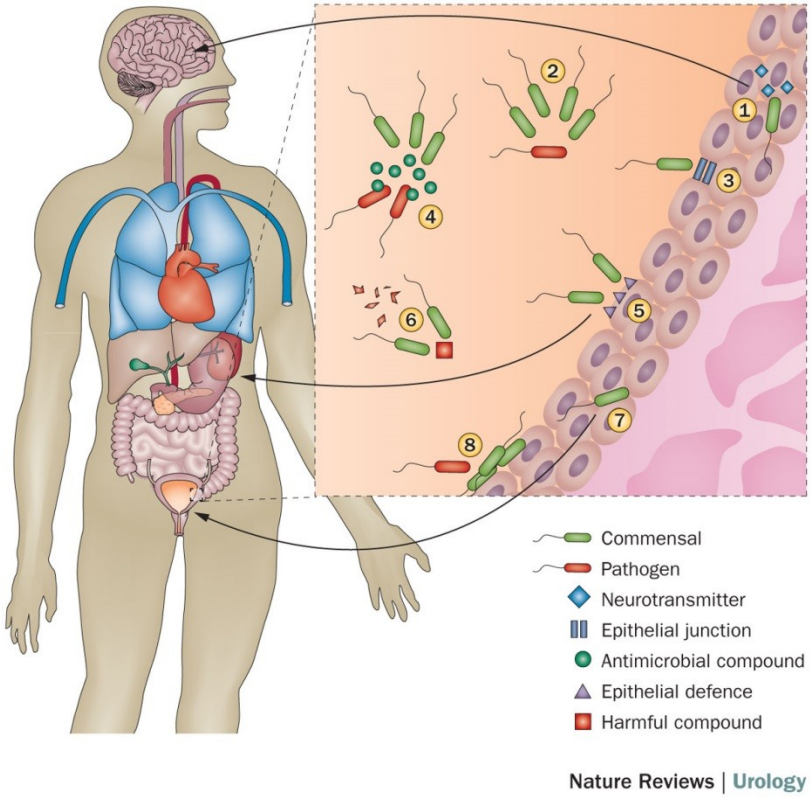
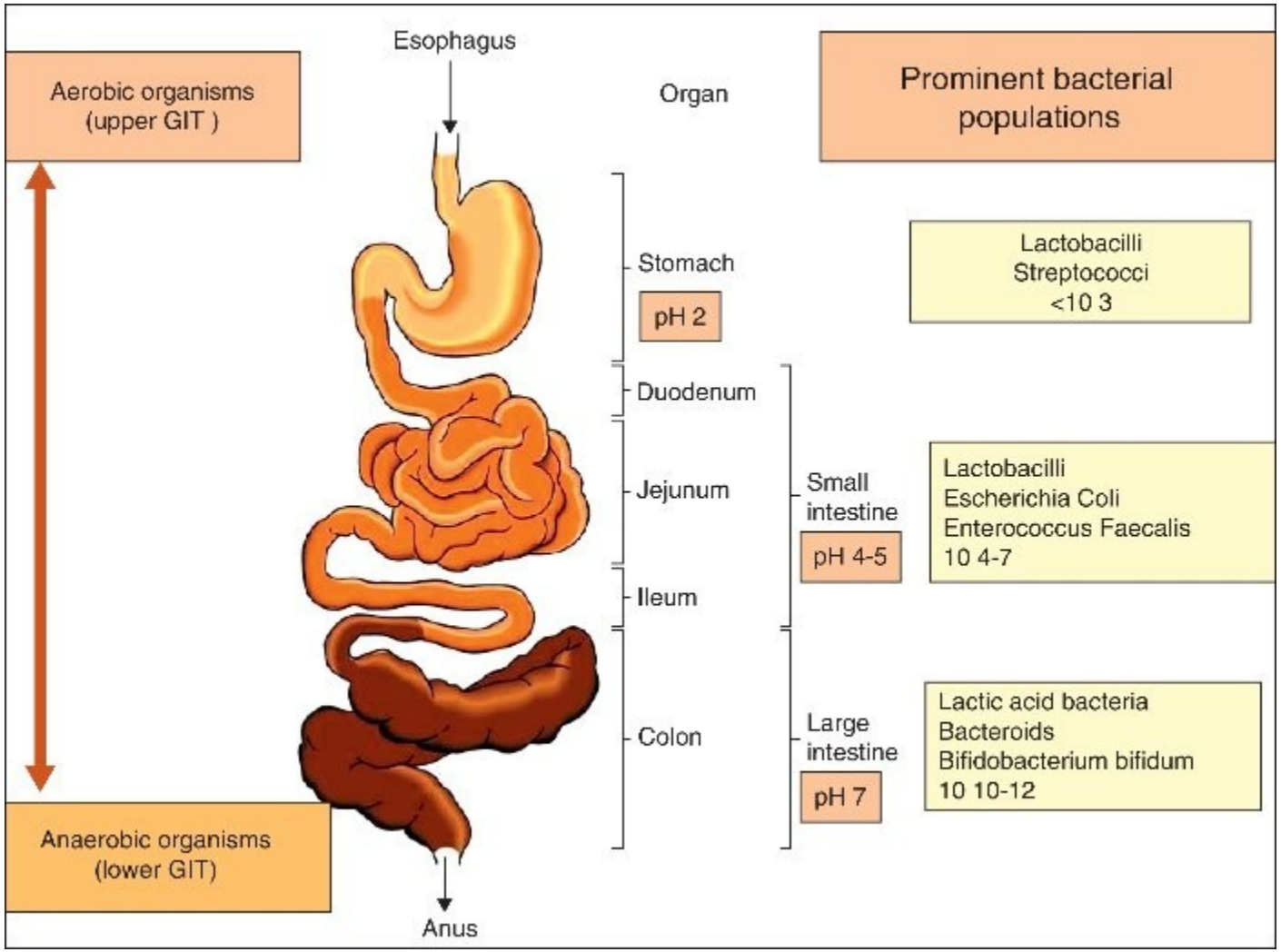
Metagenomika – mikrobiom člověka

Mikroflóra

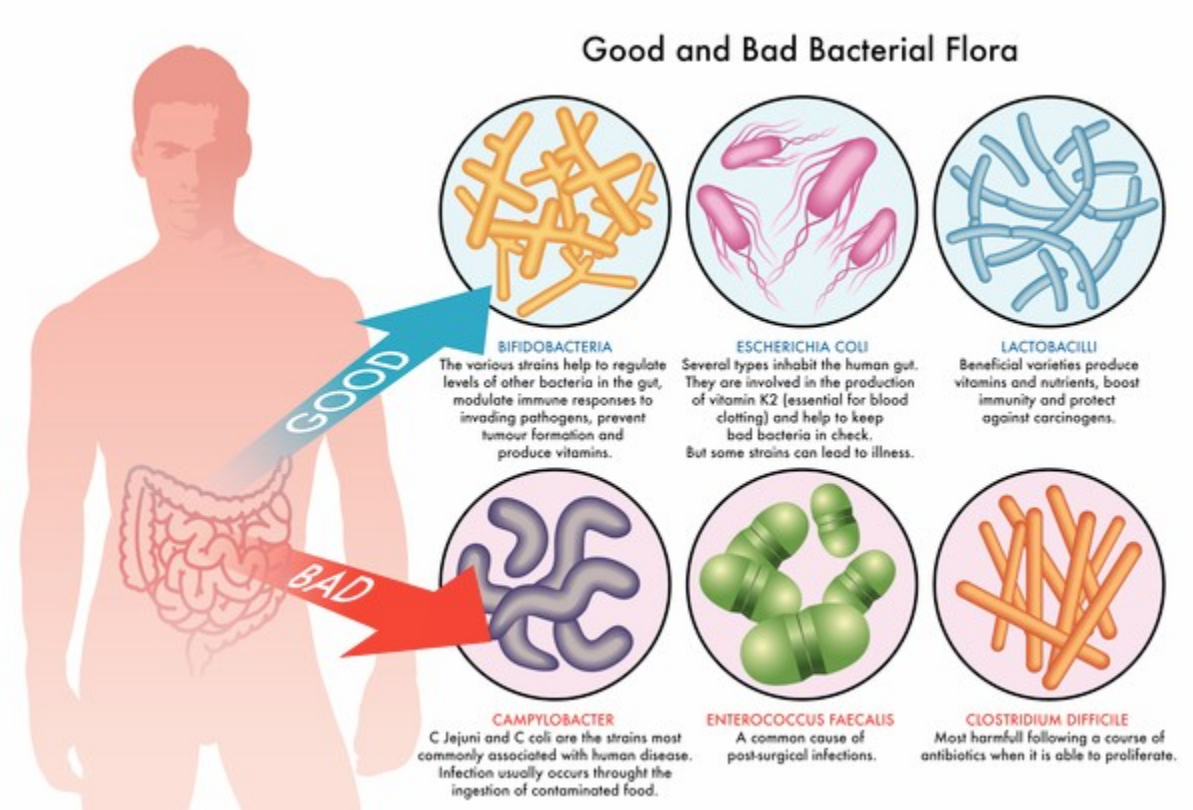


Whiteside, S. A. *et al.* (2015) The microbiome of the urinary tract—a role beyond infection
Nat. Rev. Urol. doi:10.1038/nrurol.2014.361

Mikroflóra v GI

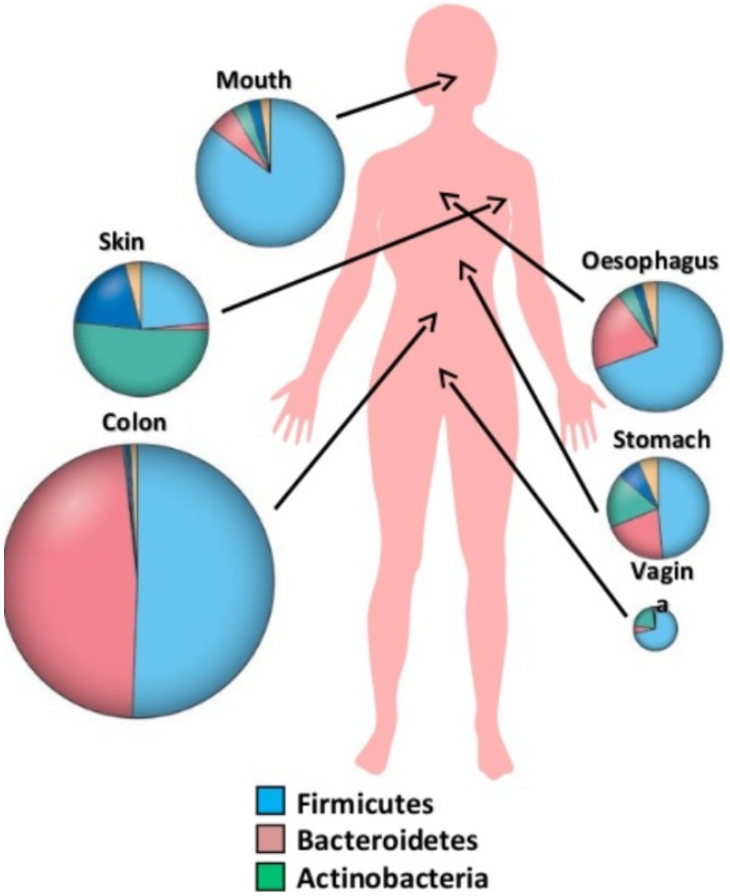


Mikroflóra


Good and Bad Bacterial Flora
GOOD
BAD
BIFIDOBACTERIA
The various strains help to regulate levels of other bacteria in the gut, modulate immune responses to invading pathogens, prevent tumour formation and produce vitamins.
ESCHERICHIA COLI
Several types inhabit the human gut. They are involved in the production of vitamin K2 (essential for blood clotting) and help to keep bad bacteria in check. But some strains can lead to illness.
LACTOBACILLI
Beneficial varieties produce vitamins and nutrients, boost immunity and protect against carcinogens.
CAMPYLOBACTER
C Jejuni and C coli are the strains most commonly associated with human disease. Infection usually occurs throught the ingestion of contaminated food.
ENTEROCOCCUS FAECALIS
A common cause of post-surgical infections.
CLOSTRIDIUM DIFFICILE
Most harmfull following a course of antibiotics when it is able to proliferate.

Mikroflóra

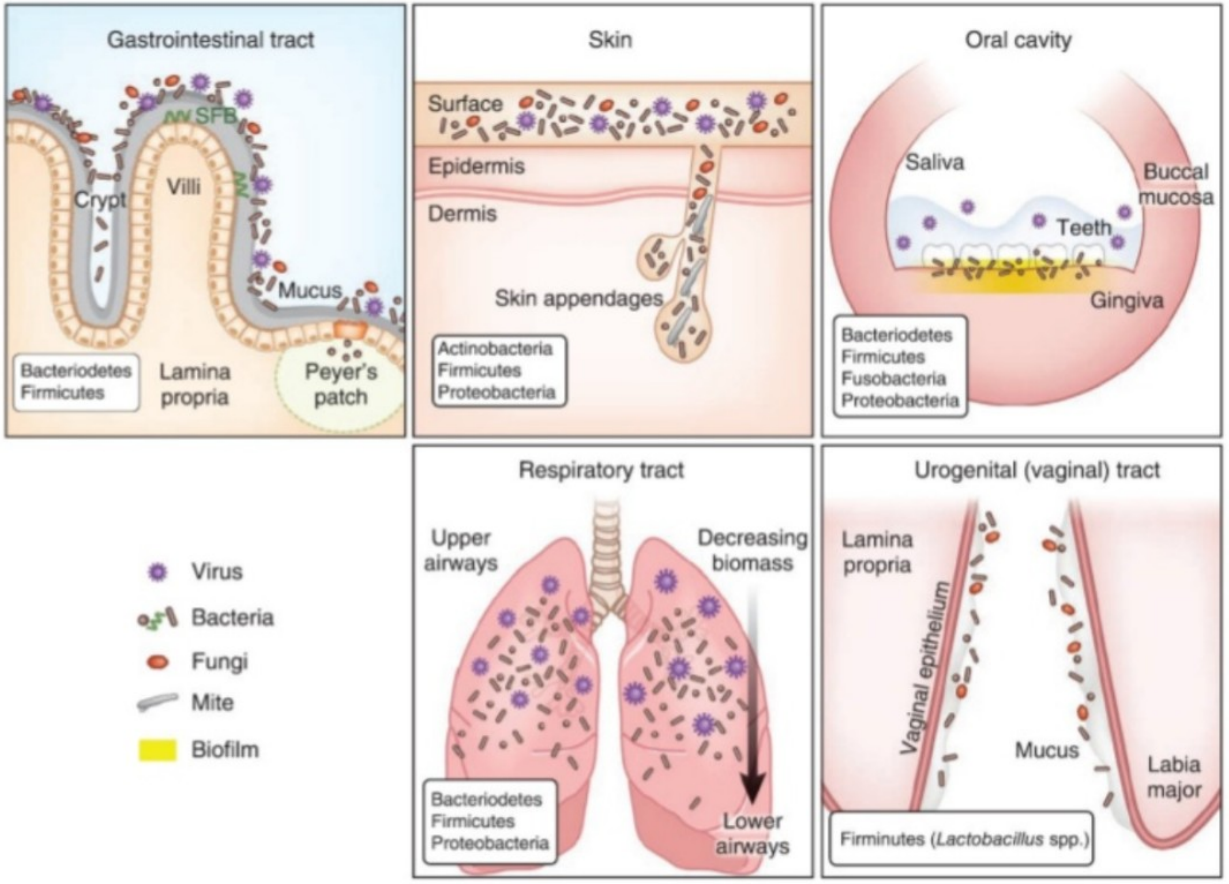
Humans have co-evolved with microbial partners



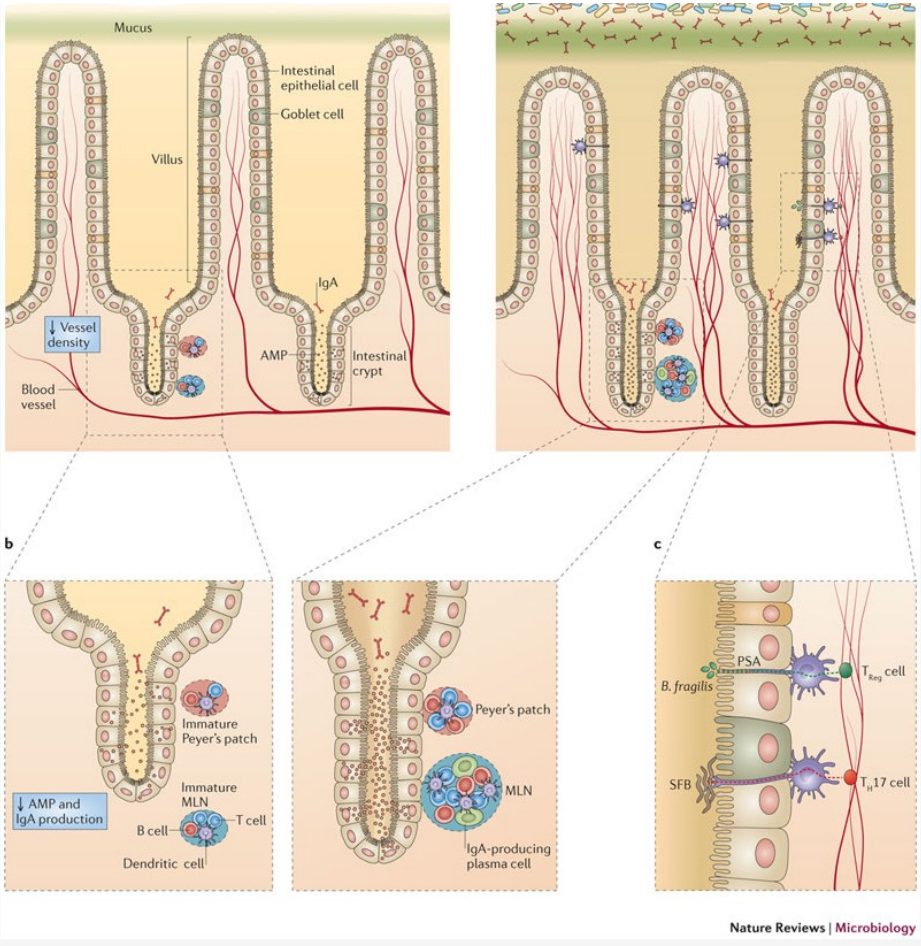
- We are a composite of species: bacteria, fungi, viruses, bacteriophages
- Microorganisms inhabit all barrier surfaces of the organism and outnumber the human cells by about 10 fold
- The total microbial DNA in our body (the microbiome) contains 100 times more genes than our 'own' human genome
- The microbiome is an integral part of our genetic landscape and plays a central role in the maintenance and control of host homeostasis
- The development of the immune system is dependent on interactions with the

Mikroflóra

Microorganisms inhabit all barrier surfaces of the organism

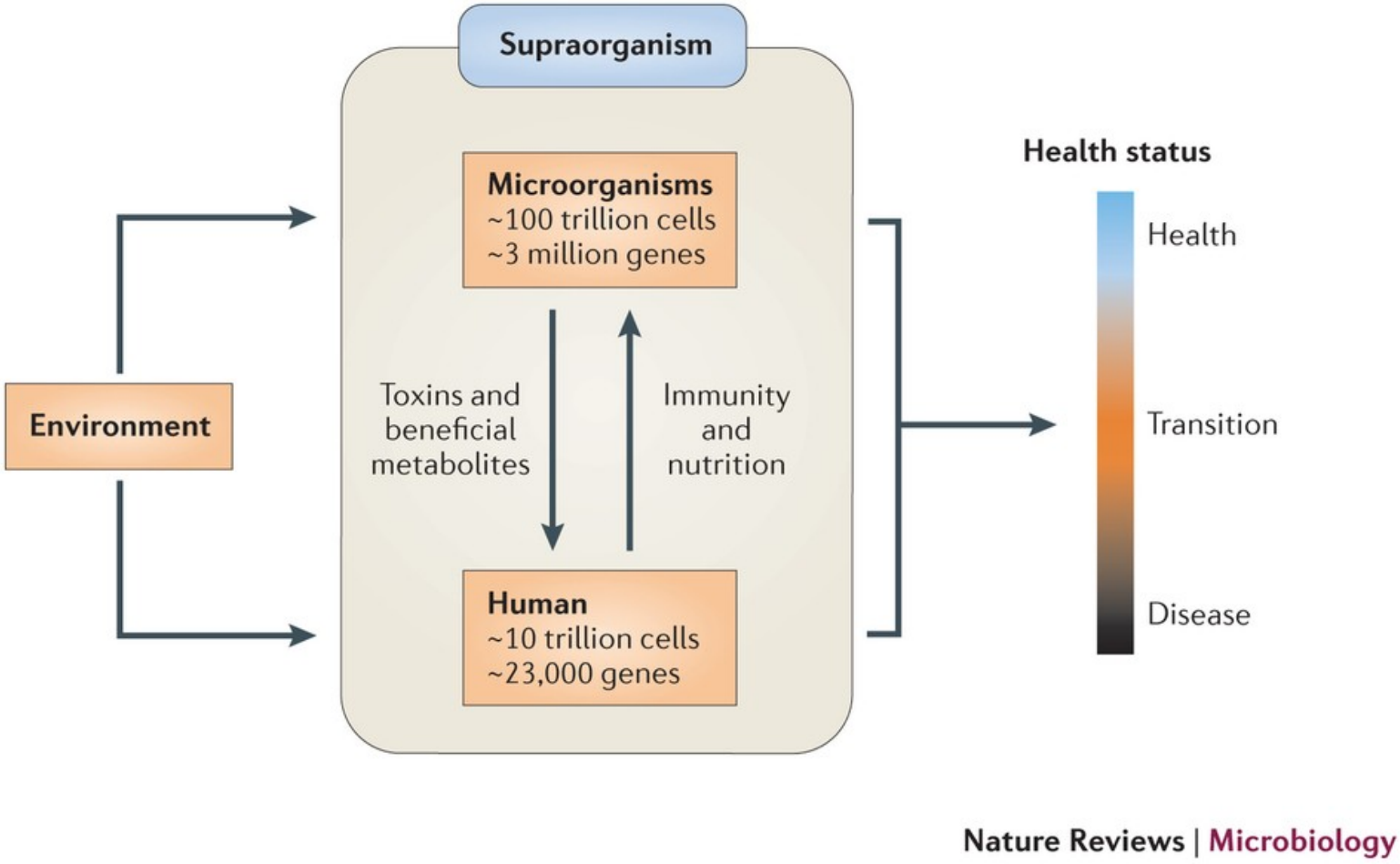


Mikroflóra a střevní stěna



The microbiota promotes substantial changes in gut morphology, including villus architecture, crypt depth, stem cell proliferation, blood vessel density, mucus layer properties and maturation of mucosa-associated lymphoid tissues. **a** | In germ-free mice, the villi in the distal small intestine are longer and thinner and have a less complex vascular network than the villi of conventionally raised animals. In the absence of bacteria, intestinal crypts are less deep and contain fewer proliferating stem cells. Furthermore, germ-free animals show reduced mucus thickness and altered mucus properties. **b** | Moreover, very few isolated lymphoid follicles, immature Peyer's patches and immature mesenteric lymph nodes (MLNs) are present under germ-free conditions, and levels of both immunoglobulin A (IgA) and antimicrobial peptides (AMPs) are lower than in conventionally raised animals. **c** | In conventionally raised mice, polysaccharide A (PSA) of *Bacteroides fragilis* is known to induce the expansion of $CD4^+CD25^+FOXP3^+$ regulatory T (T_{Reg}) cells, which have an anti-inflammatory effect and dampen immune responses. By contrast, segmented filamentous bacteria (SFB) have been shown to induce the expansion of T helper 17 (T_H17) cells, which a pro-inflammatory.

Mikroflóra


Supraorganism
Microorganisms
~100 trillion cells
~3 million genes
Environment
Toxins and beneficial metabolites
Immunity and nutrition
Human
~10 trillion cells
~23,000 genes
Health status
Health
Transition
Disease
Nature Reviews | Microbiology

NIH HUMAN MICROBIOME PROJECT

Login

REFERENCE GENOMES | MICROBIOME ANALYSIS | IMPACTS ON HEALTH | TOOLS & TECHNOLOGY | ETHICAL IMPLICATIONS | OUTREACH | HMPDACC DATA BROWSER

Feedback

Welcome to the Data Analysis and Coordination Center (DACC) for the National Institutes of Health (NIH) Common Fund supported Human Microbiome Project (HMP). This site is the central repository for all HMP data. The aim of the HMP is to characterize microbial communities found at multiple human body sites and to look for correlations between changes in the microbiome and human health. More information can be found in the menus above and on the NIH Common Fund site.

GET DATA

GET TOOLS

Current News

- August 2013
  NCI Symposium: Inflammation, Microbiota, and Cancer to be held in Bethesda, MD September 19-20
- July 2013
  Human Microbiome Science: Vision for the Future conference to be held in Bethesda, MD July 24-26
- May 2013
  Human Microbiome Consortium Virtual Meeting: Approaches in Microbiome Assembly

More News Items

Publications

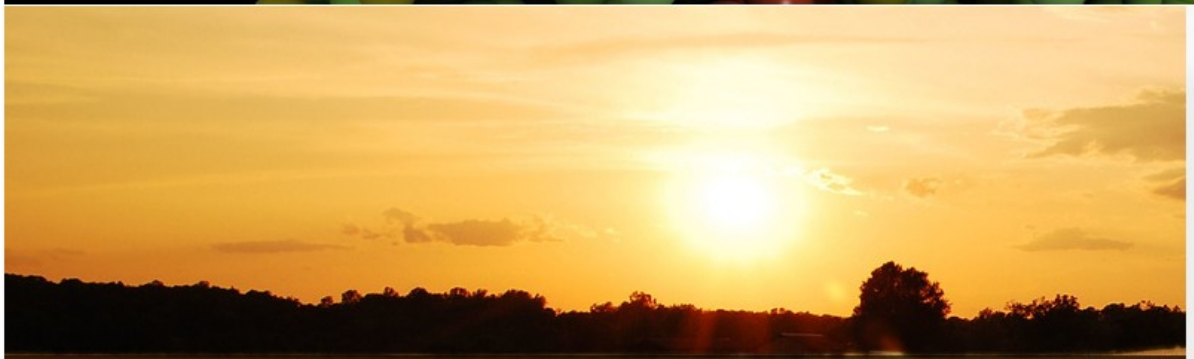
- Coverage theories for metagenomic DNA sequencing based on a generaliza...
- Development of a dual-index sequencing strategy and curation pipeline ...
- Propionibacterium acnes Strain Populations in the Human Skin Microbiom...

More Publications

Partner Resources

- NIH Common Fund
- NCBI HMP Data Repository

Areas of Interest



Outreach
We welcome feedback on all aspects of the HMP, and are soliciting recommendations for microbial reference genomes. Contact us for more information...

DACC Member Organizations

Related Sites

Please help us to improve the DACC website by taking our user survey!

View Survey

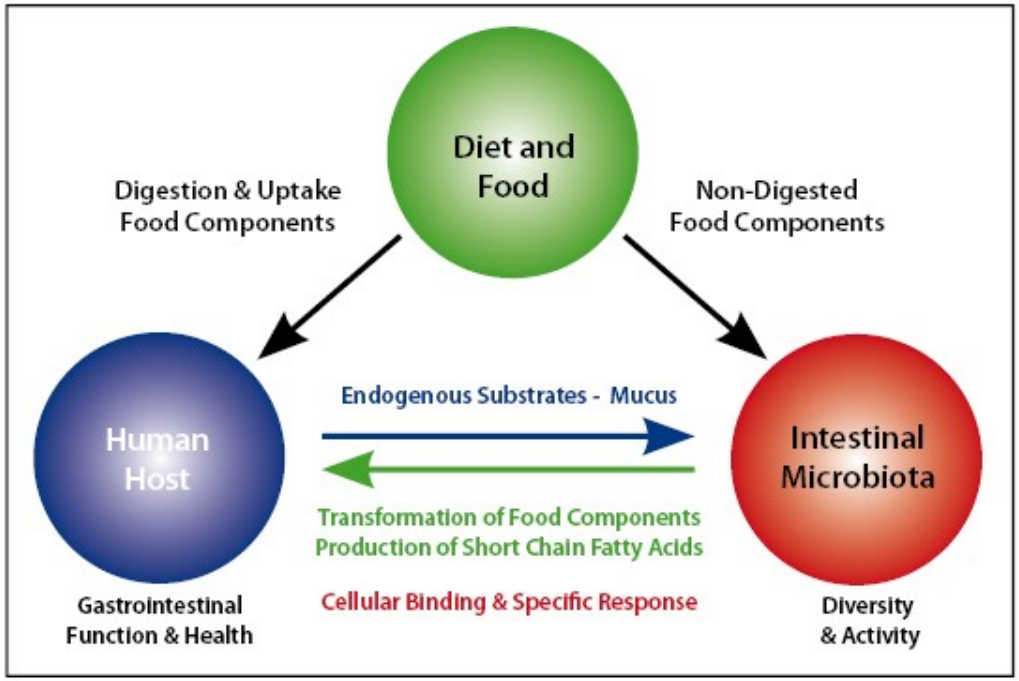
A new version of IMG/HMP M has been released, based on the new IMG4 system, and containing a larger reference genome base.

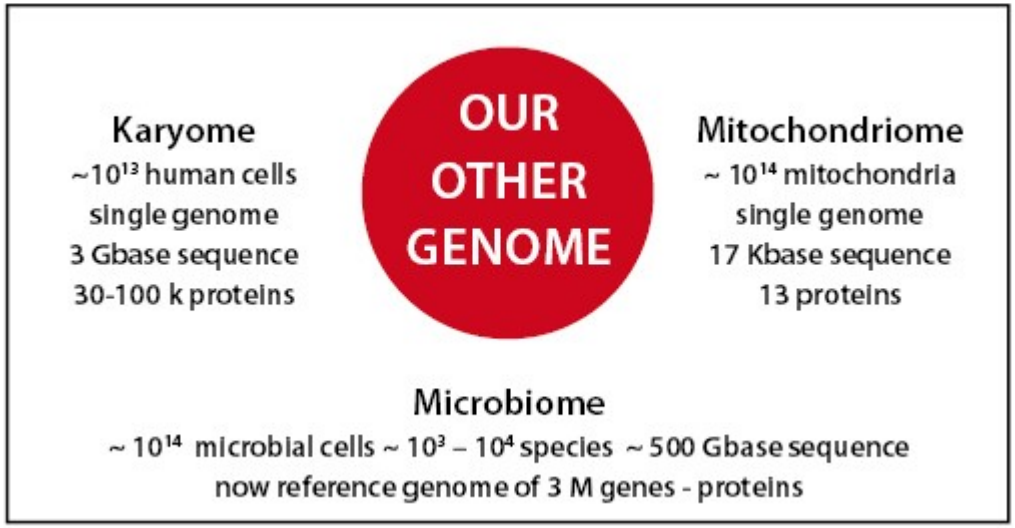
More Information

The DACC provides step-by-step tutorials, or walkthroughs, taking users through typical HMP analysis paths.

More Information

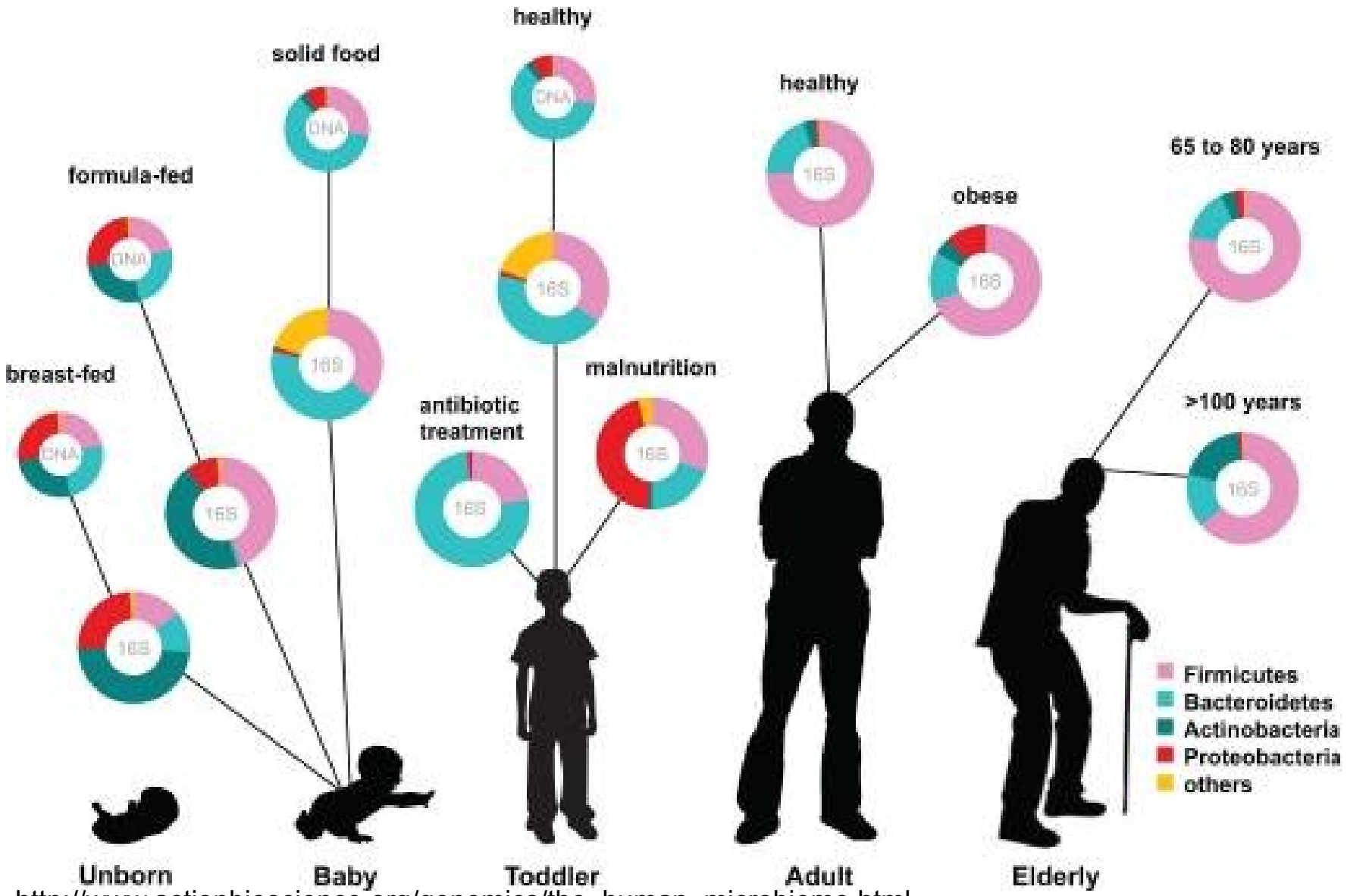
HMP





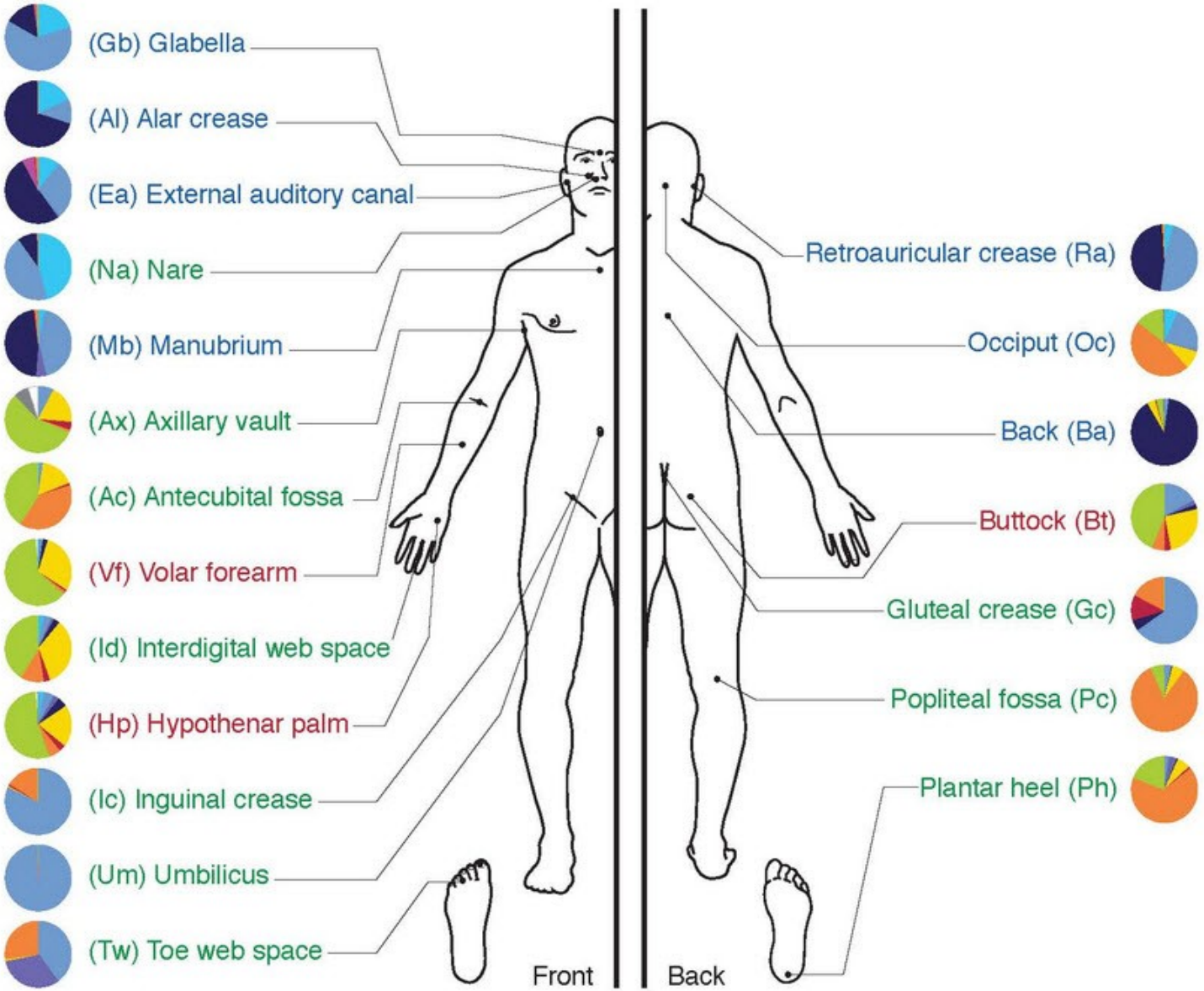
http://www.selfcarejournal.com/view.article.php?id=10088

HMP



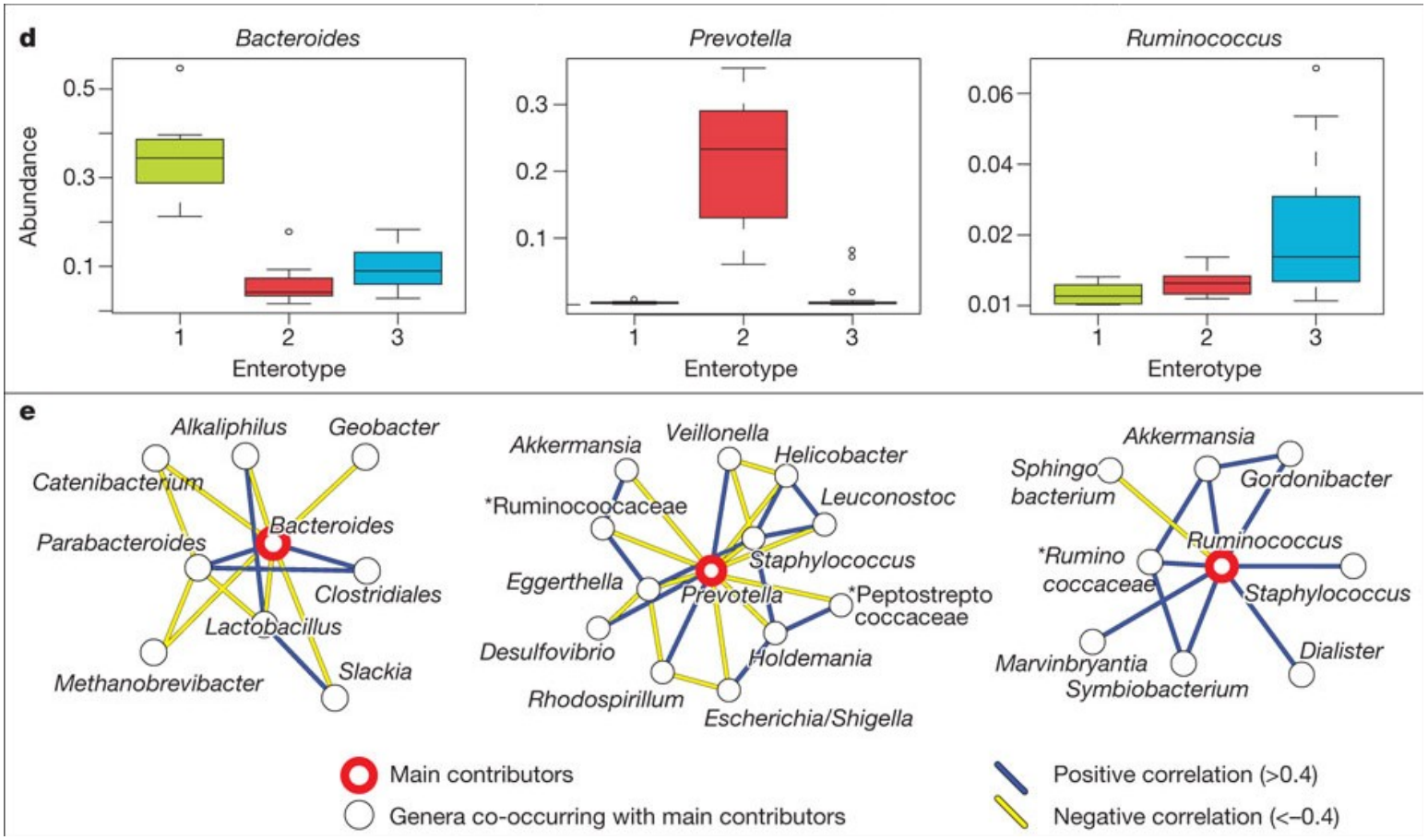
http://www.actionbioscience.org/genomics/the_human_microbiome.html

HMP



http://www.actionbioscience.org/genomics/the_human_microbiome.html

HMP-Enterotypy

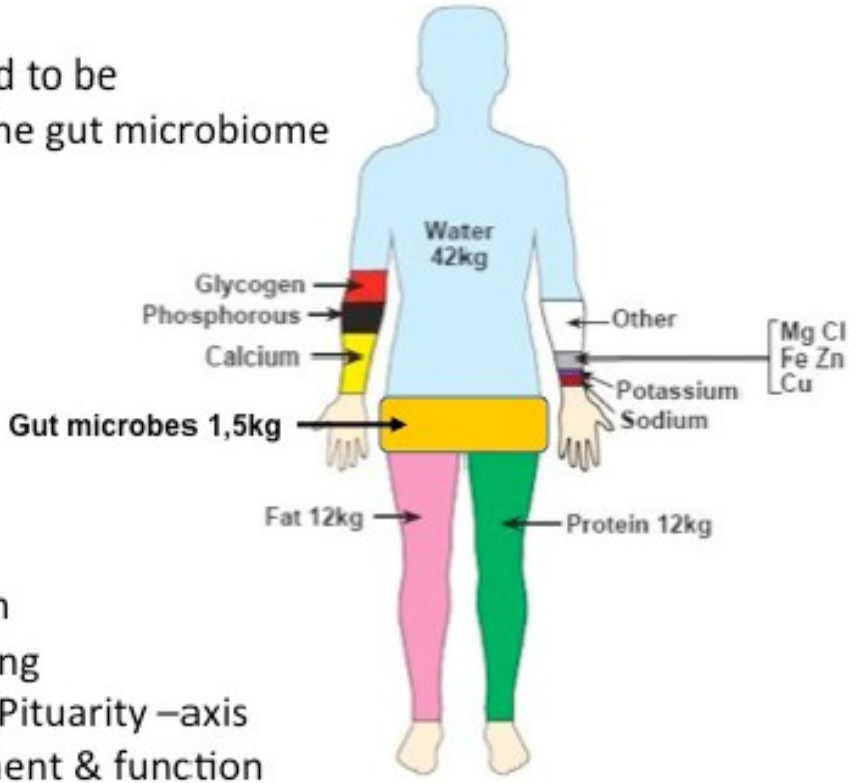


Aruguman et al., 2010, Nature

Microbiota a lidské zdraví

Organs reported to be
Influenced by the gut microbiome

GI-tract
Liver
Stomach
Immune System
Bone remodelling
Hypothalamus-Pituarity –axis
Brain development & function

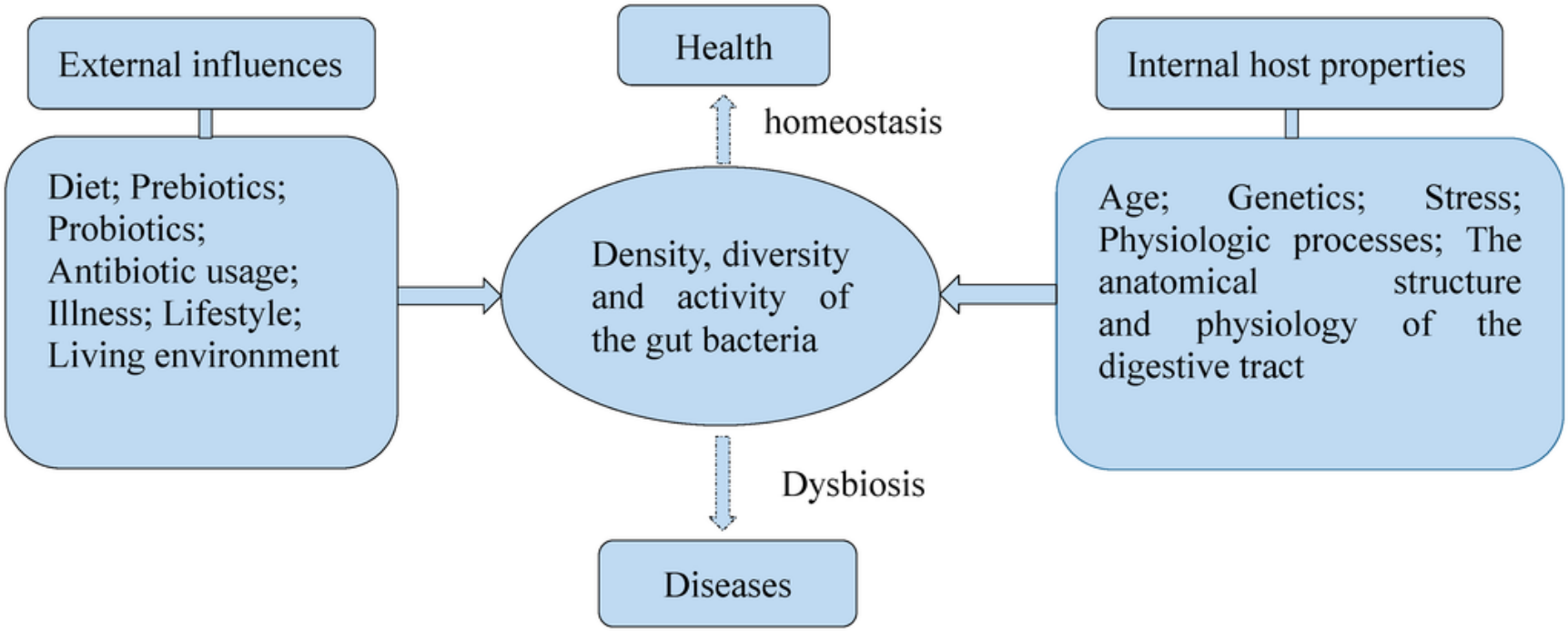


Diseases associated with an
Altered gut microbiome

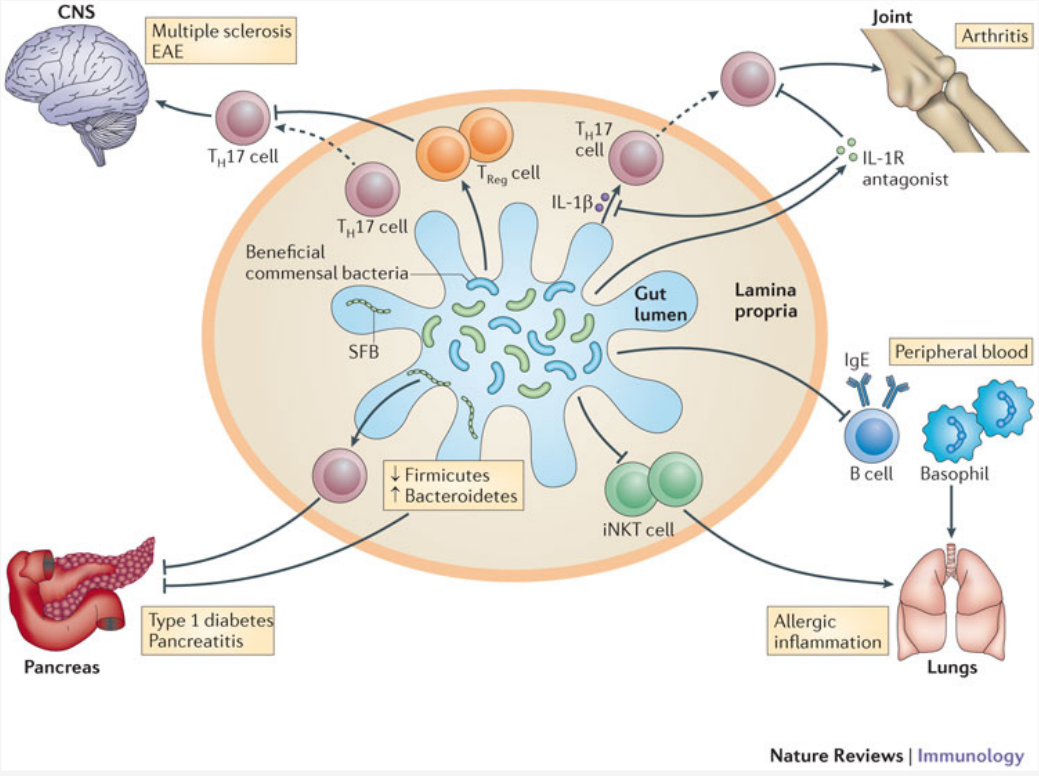
Obesity
Diabetes
Inflammatory Bowel Disease
Rheumatoid arthrithis
Stomach cancer
Colon cancer
Liver cancer

http://www.nccs.com.sg/Research/programmes/emergingtech/Pages/Microbiome.aspx

Microbiota a lidské zdraví



Mikrobiota a lidské zdraví



Segmented filamentous bacteria (SFB) colonization induces T helper 17 (T_H17) cell development in the intestine. These T_H17 cells might migrate to the periphery to affect systemic and central nervous system (CNS) immunity; increased intestinal T_H17 cells enhance the expansion of pathogenic autoantigen-specific T cells in the intestine and cause inflammation in the CNS. By contrast, 'beneficial' commensal bacteria can attenuate CNS inflammation through the induction of forkhead box P3 (FOXP3)$^+$ regulatory T (T_{Reg}) cells. Induced T_H17 cells can also promote autoimmune arthritis by facilitating autoantibody production by B cells (not shown). In addition, microbiota-induced interleukin-1β (IL-1β) signalling participates in the development of rheumatoid arthritis through the induction of T_H17 cells. The IL-1 receptor (IL-1R) antagonist blocks IL-1β signalling and abrogates joint inflammation. Balance in the microbial community also determines susceptibility to type 1 diabetes. A decreased Firmicutes/Bacteroidetes ratio as a result of a deficiency in myeloid differentiation primary-response protein 88 (MYD88) in non-obese diabetic mice is associated with an attenuated risk of type 1 diabetes. SFB-induced T_H17 cells protect the host against type 1 diabetes development by an unknown mechanism. Finally, exposure to microorganisms in neonatal, but not adult, life decreases the accumulation of invariant natural killer T (iNKT) cells in the gut, which results in protection against allergic inflammation in the lungs. In addition, microbial compounds stimulate peripheral B cells through B cell-intrinsic MYD88 signalling and inhibit IgE production. Decreased levels of peripheral IgE result in decreased numbers of basophils, and attenuate the risk of allergic airway inflammation. EAE, experimental autoimmune encephalomyelitis.

Mikrobiota a lidské zdraví

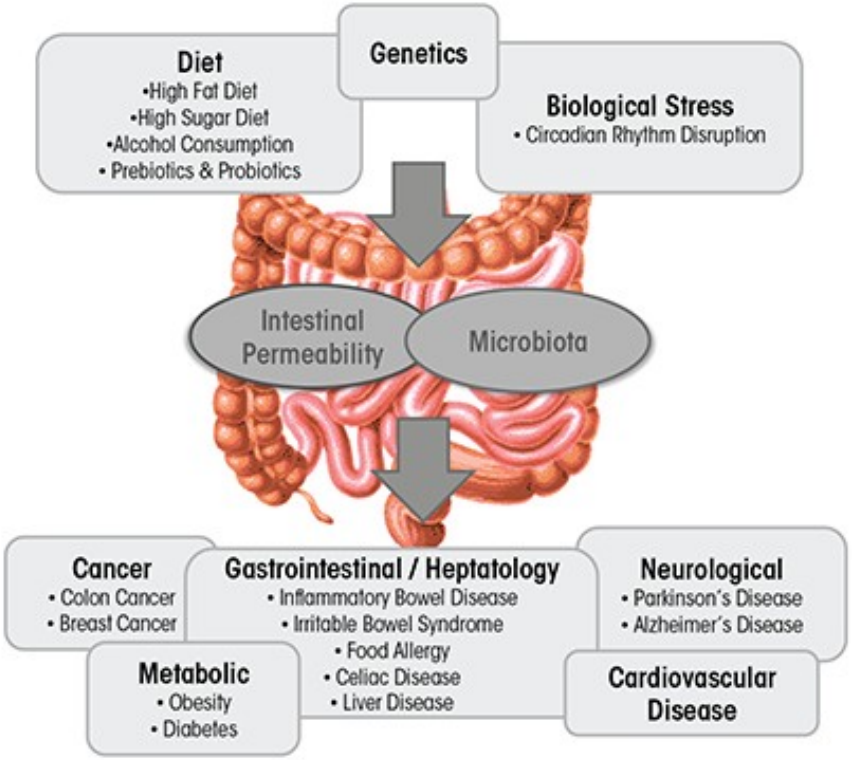
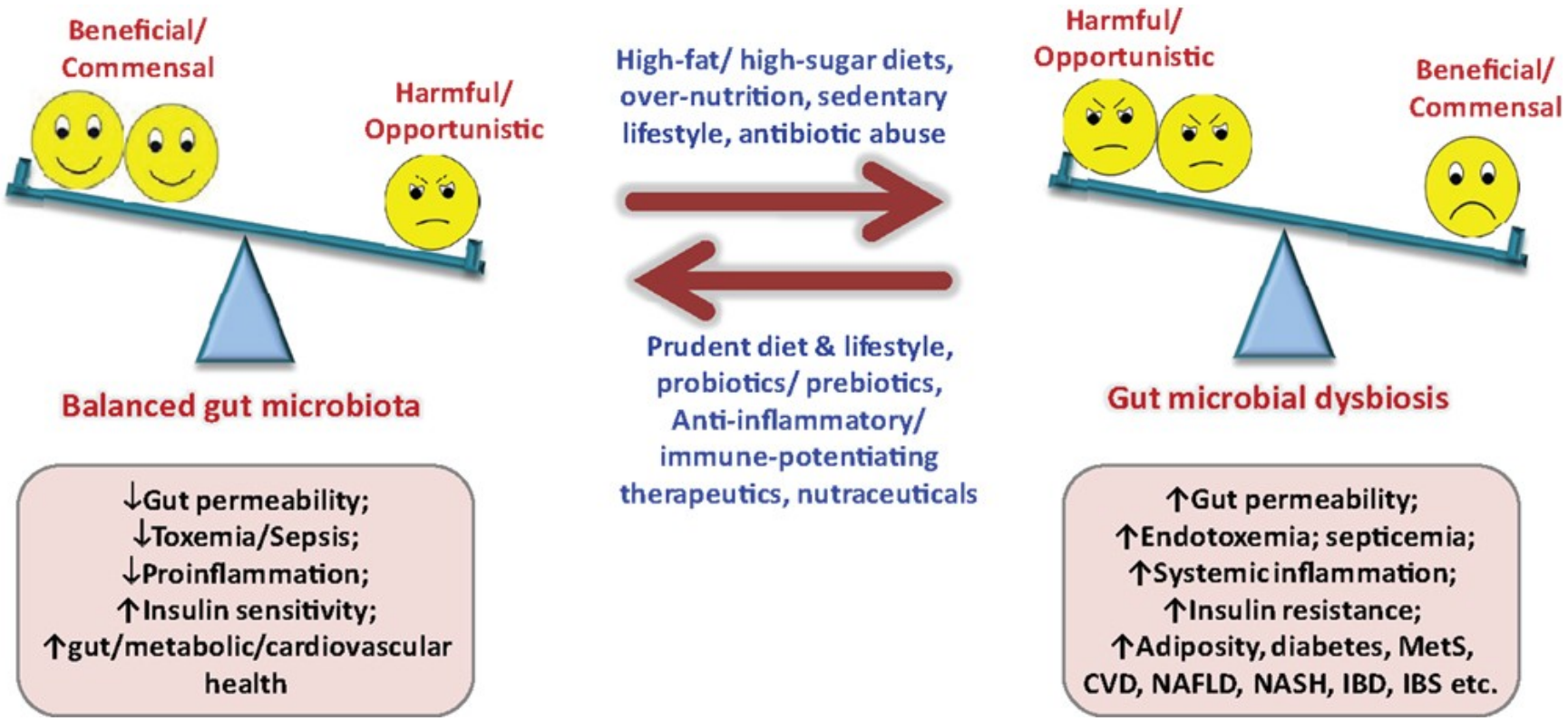


Figure 1 Disruption of intestinal microbiota homeostasis (dysbiosis) has been associated with these diseases (shown above). In addition, dysbiosis can be caused by environmental factors commonly encountered in Western societies, including diet, genetics, disruption of circadian rhythms, and alcoholic beverage consumption. Dysbiosis also can be prevented or treated with probiotics and prebiotics.

Mikrobiota a lidské zdraví



Vývoj mikroflóry

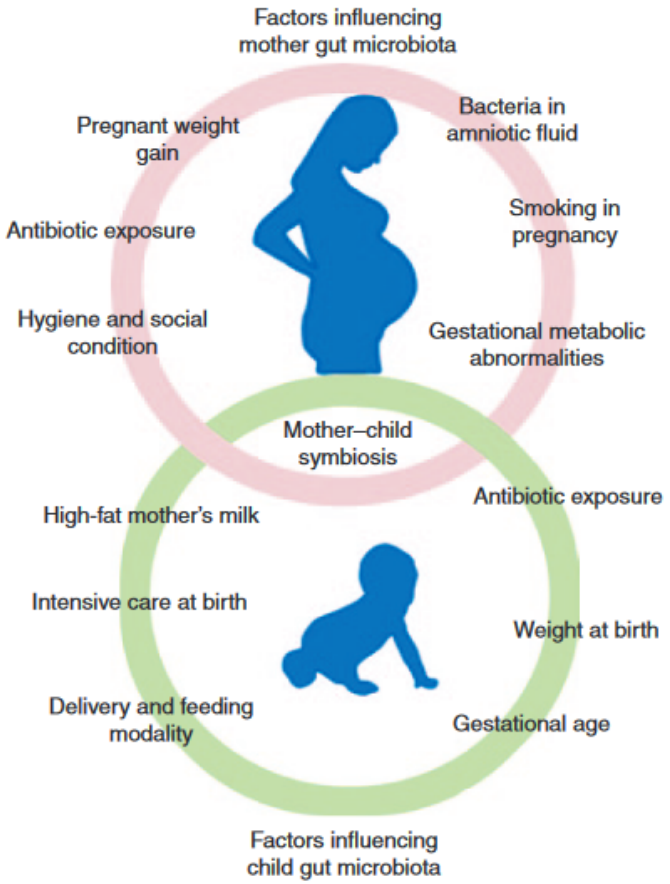
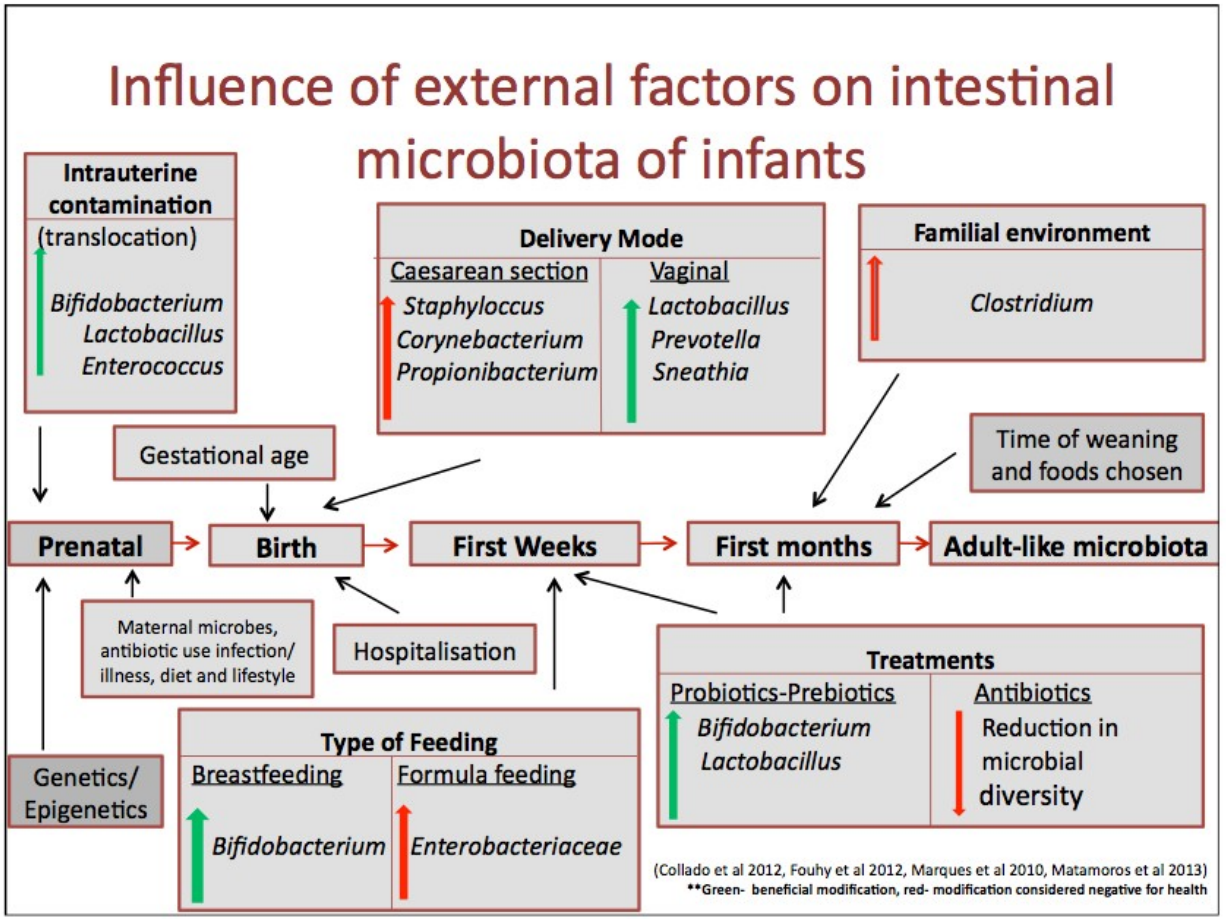


Figure 5. Mother–child symbiosis elements affecting the onset and modulation of the newborn gut microbiota. Based on the complex mother–child symbiosis, a plethora of factors affecting child gut microbiota actually resides in maternal physiology, hence preparing a "dynamic" baseline for the following interventions of external stimuli on newborn gut microbiota. An incorrect maternal behavior (e.g., smoking and weight gain in pregnancy), poor social condition, and diseases during pregnancy can negatively influence the newborn gut microbiota composition. Furthermore, environmental factors, such as delivery and feeding modality, can significantly drive the newborn gut microbiota.

Vývoj mikroflóry



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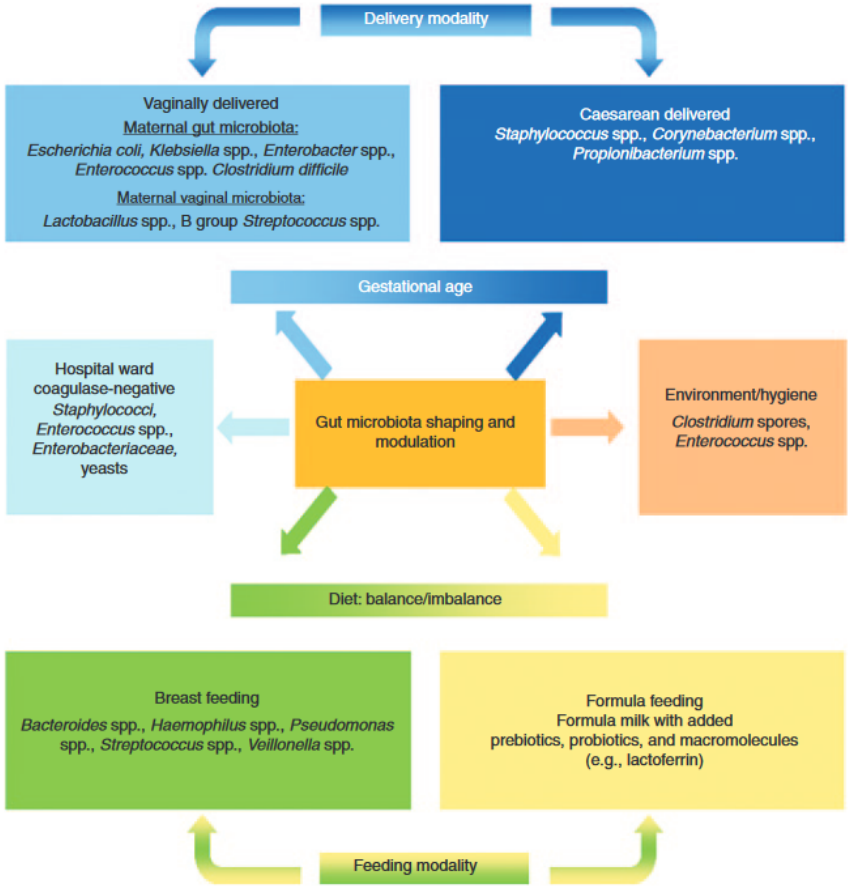
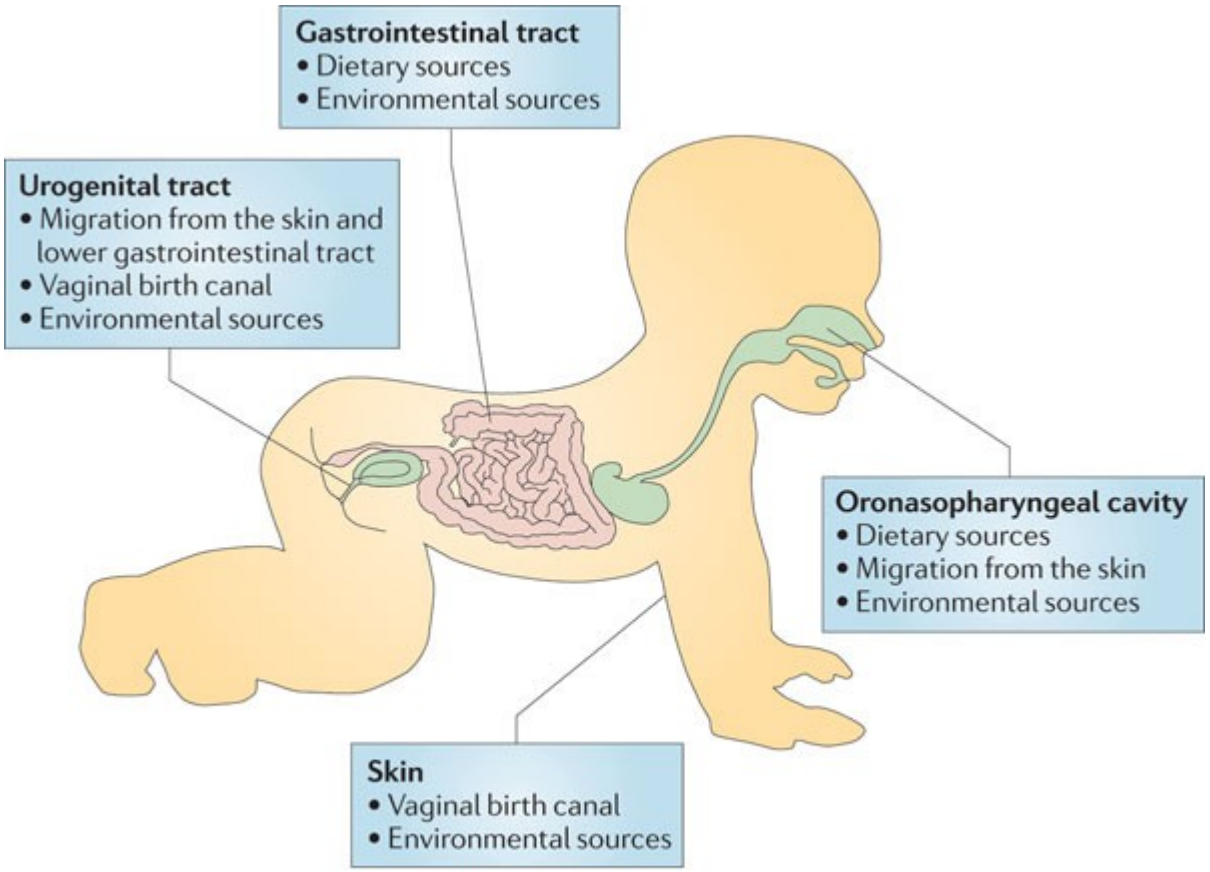


Figure 4. Illustration of the main determinants of variability affecting the gut microbiota ecosystem. During early life, several external factors, such as delivery mode, feeding modality, environmental influences, antibiotic exposure, and functional food intake, can affect microbiota shaping and composition. Vaginally born babies acquire bacterial communities that resemble their mother's vaginal microbiota, while Caesarean delivered babies harbor bacterial communities that are similar to the skin surface communities of the mothers. Additionally, breast-fed newborns show a more uniform and stable bacteria population compared with formula-fed newborns. Moreover, the environment during delivery, antibiotic treatment, and hygiene measures can influence the composition of the gut microbiota in neonates. Finally, the intake of functional foods, containing probiotic, prebiotic, or bioactive proteins (e.g., lactoferrin), modify the gut microbiota, reducing pathogen growth.

Vývoj mikroflóry



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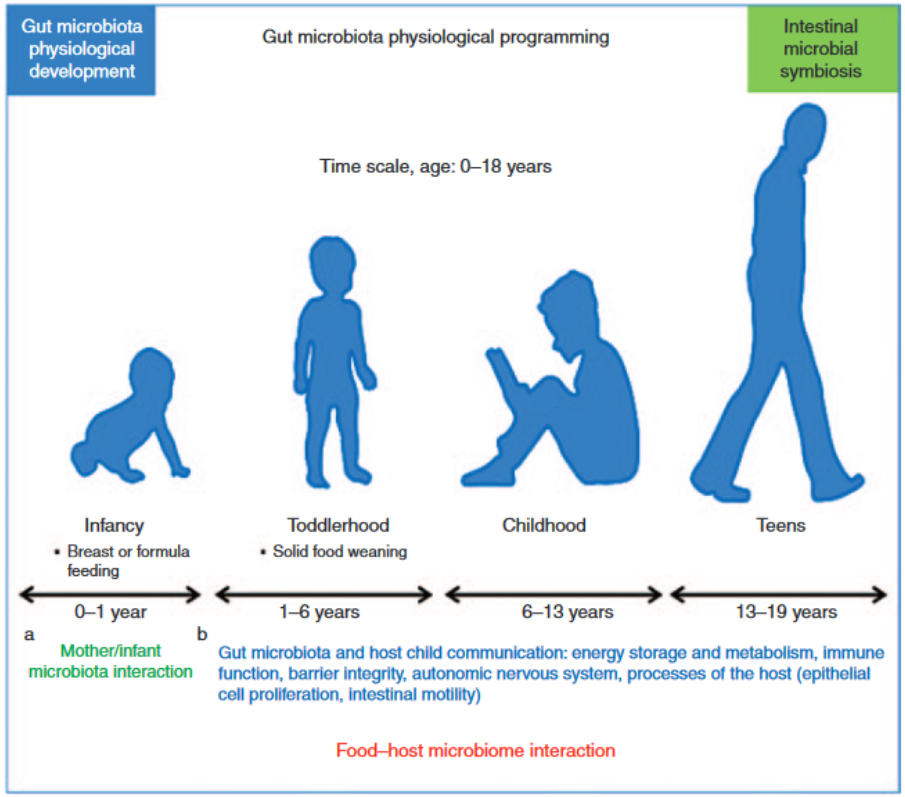

Figure 6. Physiological conditions of the gut microbiota during age of development from birth to adulthood. In the pediatric age scale, 0–18 y has been divided for convenience into 4 main groups, representing a scheme of child development stages in which birth, feeding, and environmental, social, biological, and genetic factors progressively influence the entire individual psychosomatic development, intimately connected to the gut microbiota onset and modulation. During infancy, external factors, such as delivery mode and feeding modality (breast or formula feeding), in the context of the mother/infant axis, electively and massively exert the first substantial action on the gut microbiota onset and further modulation. During toddlerhood, the intake of solid food and the maturation of immune system profoundly modify the gut microbiota profiles toward adult gut microbiota setting. During childhood and in teens, the maturation of hormonal and sexual development, social behavior, and adult-like diet and lifestyle changes continue to affect, but to a lesser extent, the gut microbiota shaping. Scheme of age scale 0–18 y and physiological programming and gut microbiota: (**a**), from 0 to 1 y infant gut interacts with mother; (**b**), from 1 to 19 y, child gut microbiota plays a crucial role in energy storage and metabolism, immune function, barrier integrity, autonomic nervous system development, epithelial cell proliferation, and intestinal motility.

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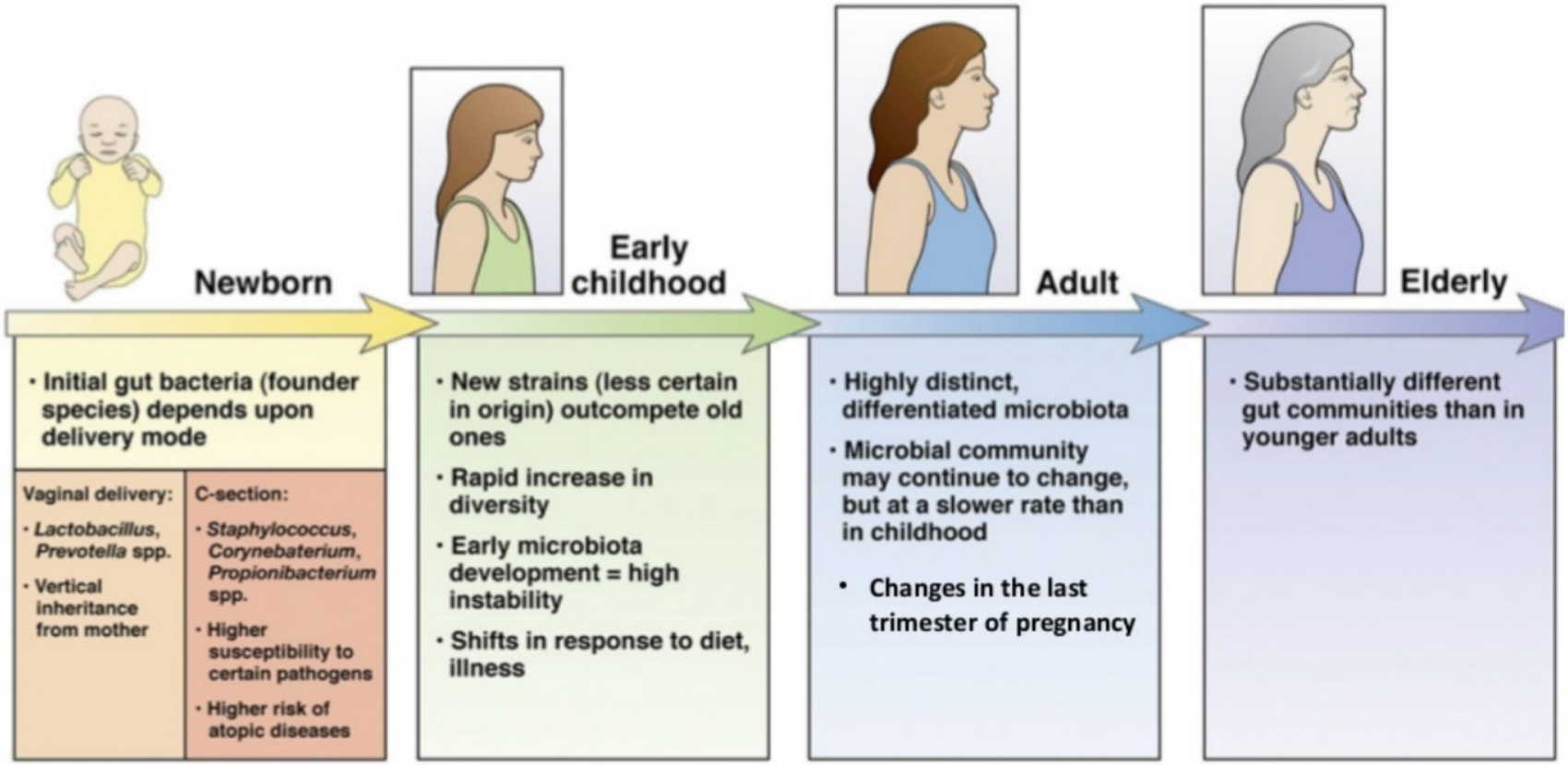
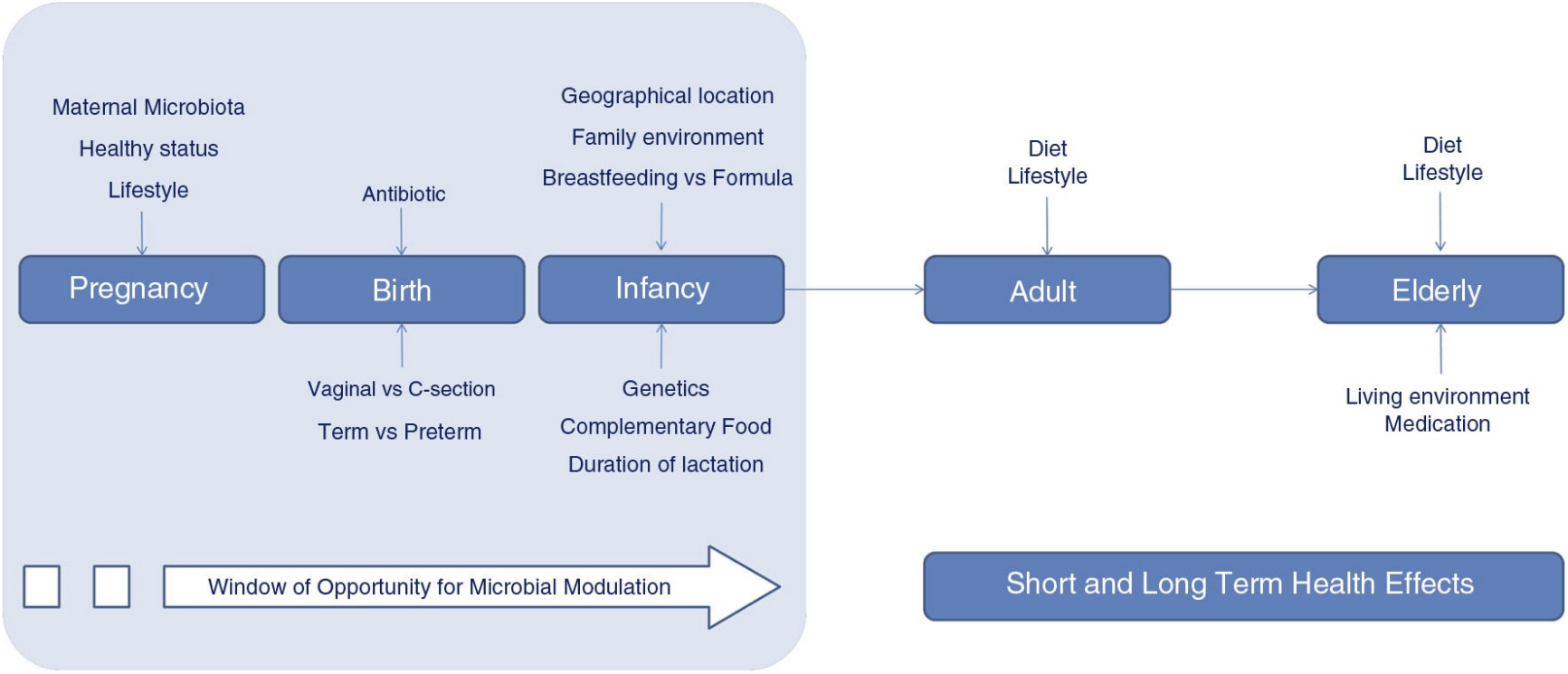


Dominguez-Bello MG, Blaser MJ, Ley RE, Knight R.

Vývoj mikroflóry



Narušená mikroflóra - důsledky

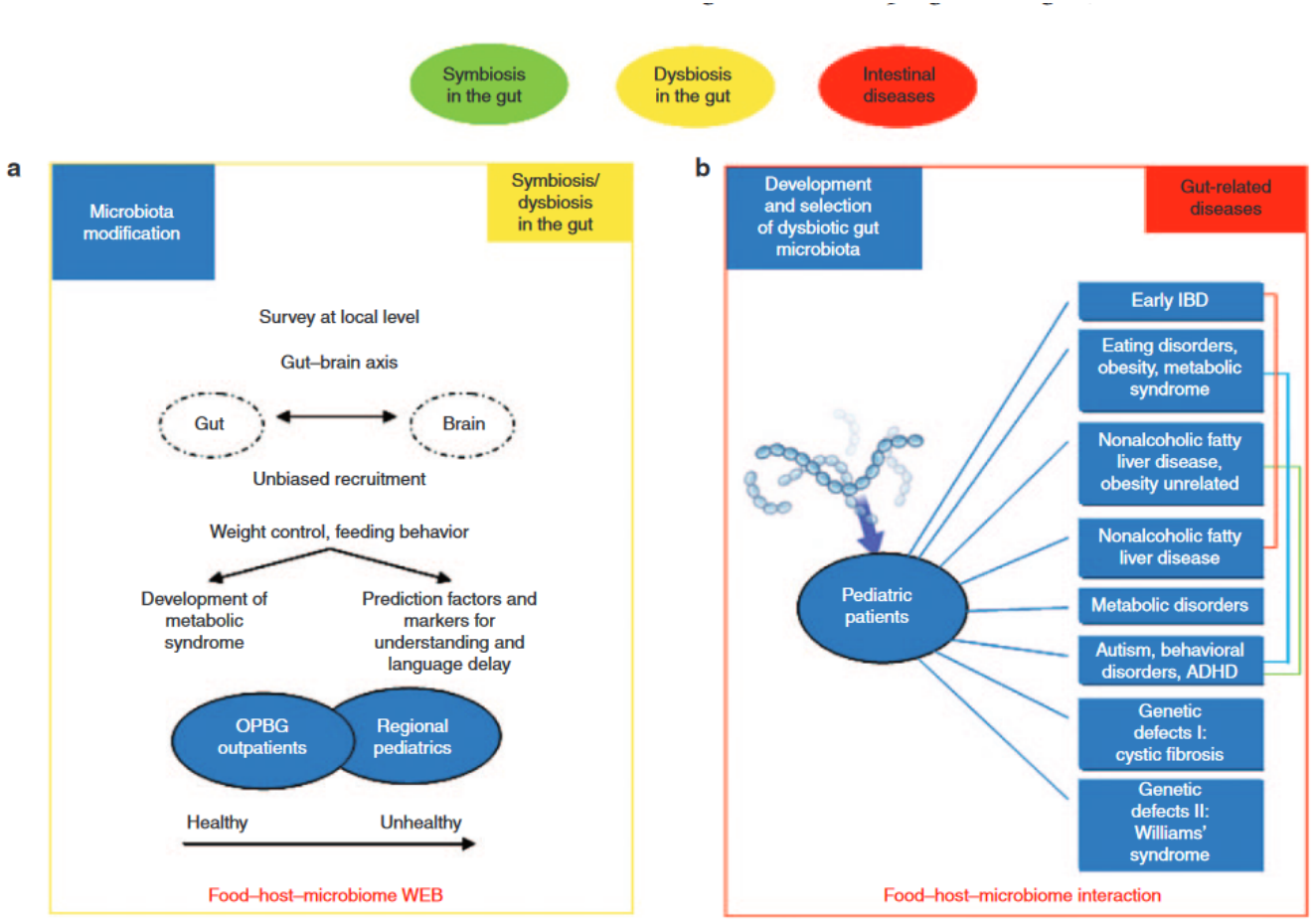
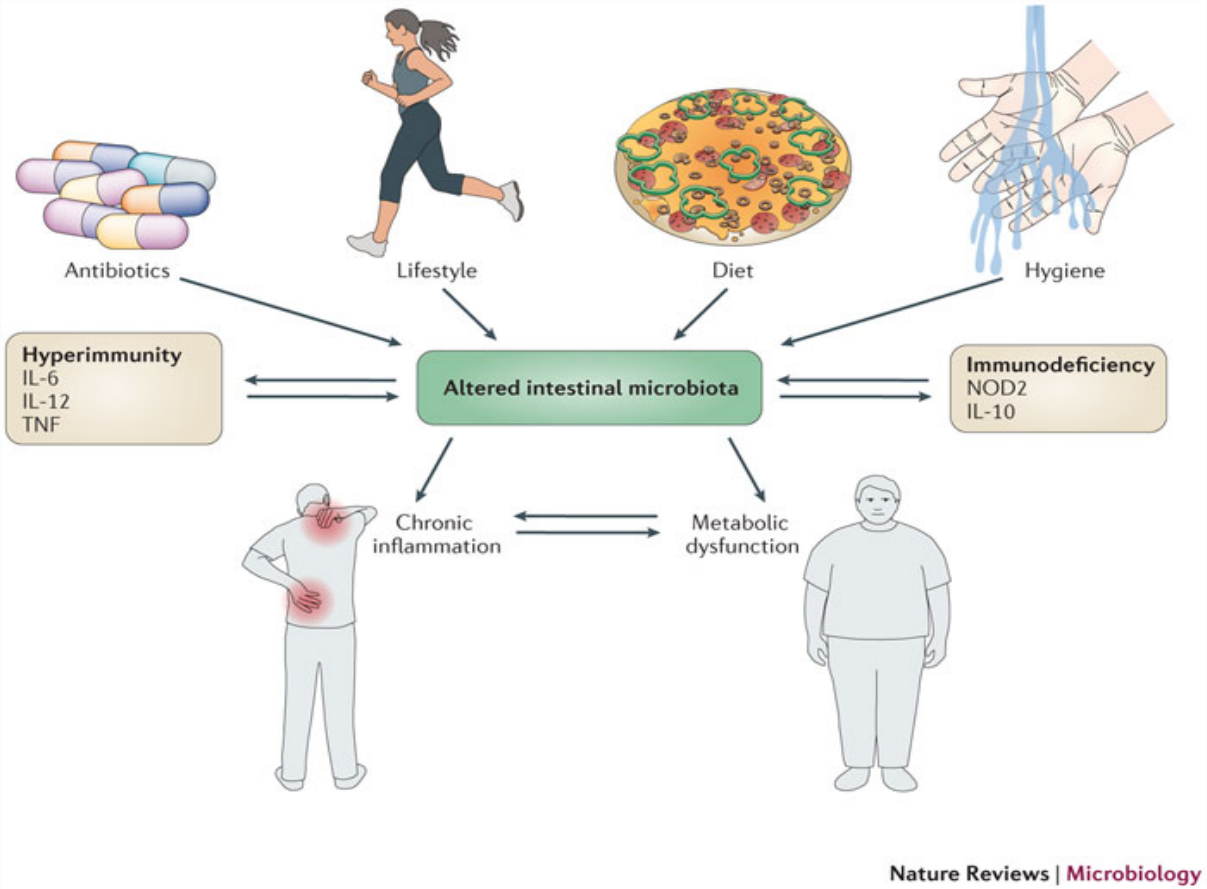


Figure 3. Strategies for dysbiosis controlling at epidemiological level for the major diseases related to the gut microbiota alterations. (**a**) The description of potential dysbiosis "types" in childhood must include rigorous criteria for unbiased recruitment rules, reflecting individual multiplicity and different development baselines. The definition of these types, obtainable by epidemiological surveys, may throw light onto complex physiological networks, such as the gut–brain axis, linking behavioral and food-related endophenotypes to obesity mechanisms. (**b**) The development and selection of dysbiotic gut microbiota can lead to gut-related diseases occurring during infancy and childhood: IBD, eating disorders, obesity, metabolic syndrome, nonalcoholic fatty liver disease, metabolic disorders, autism, behavioral disorders, attention deficit/hyperactivity disorder (ADHD), and genetic defects, such as cystic fibrosis and Williams' syndrome. IBD, inflammatory bowel disease; OPBG, Bambino Gesù Children's Hospital.

Faktory ovlivňující mikroflóru



The composition of the gut microbiota is influenced by various environmental factors, including the use of antibiotics, lifestyle, diet and hygiene preferences. The host's genetic disposition also has a role: hyperimmunity (owing to over-representation of pro-inflammatory mediators such as interleukin-6 (IL-6), IL-12 or tumour necrosis factor (TNF)) or immunodeficiency (owing to mutations in regulatory immune proteins such as NOD2 (nucleotide-binding oligomerization domain protein 2) or IL-10) can influence the gut microbiota composition. In turn, dysbiosis affects levels of immune mediators and induces both chronic inflammation and metabolic dysfunction.

Faktory ovlivňující mikroflóru

What can damage Gut Flora

- Antibiotics
- Steroids, The Pill
- Other Drugs
- Stress
- **Poor Diet**
- Infections
- Disease
- Bottle Feeding
- Old Age
- Pollution
- Radiation
- Alcohol
- Toxic Chemicals
- Dental Work

Komplexnost mikroflóry

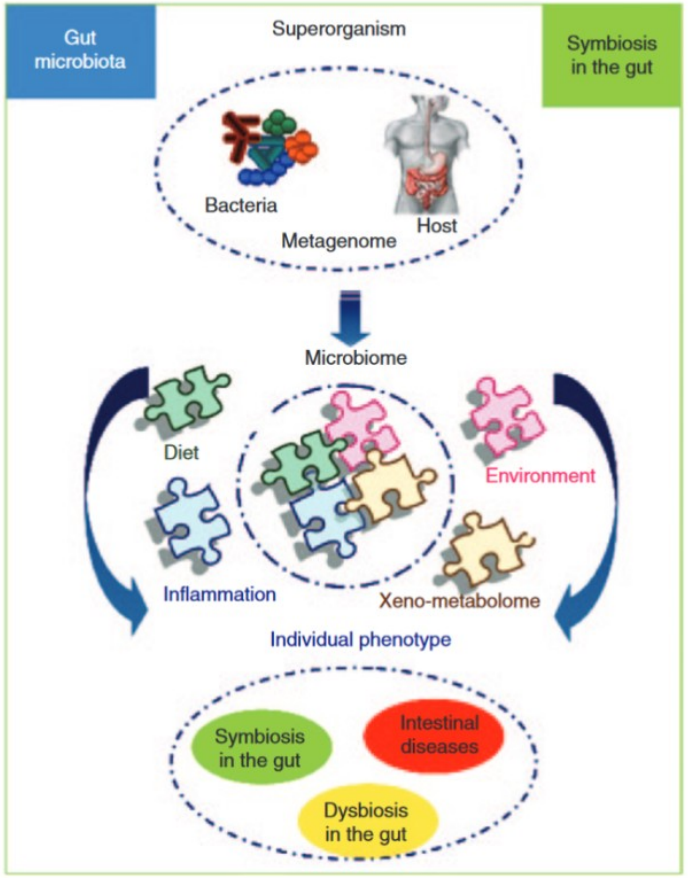
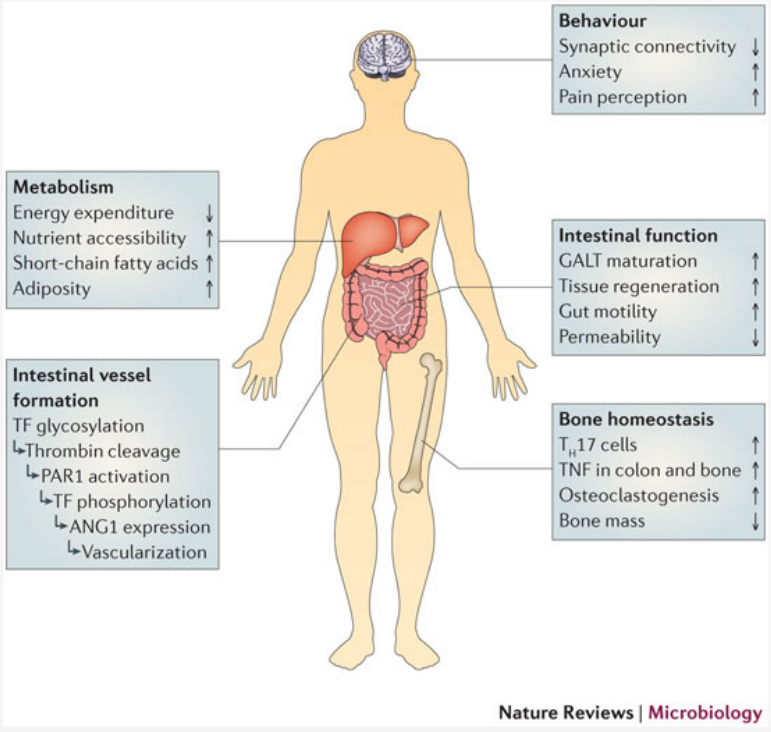


Figure 1. Graphical representation of the superorganism, its interactions with the various variability determinants, and related individual phenotypes. The largest microbiome is located in our gastrointestinal tract, and it is influenced by several external factors, such as diet, inflammation stage, environment, and xeno-metabolome. Each microbiome constitutes an individual phenotype, able to describe symbiosis-, dysbiosis-, and disease-related gut conditions.

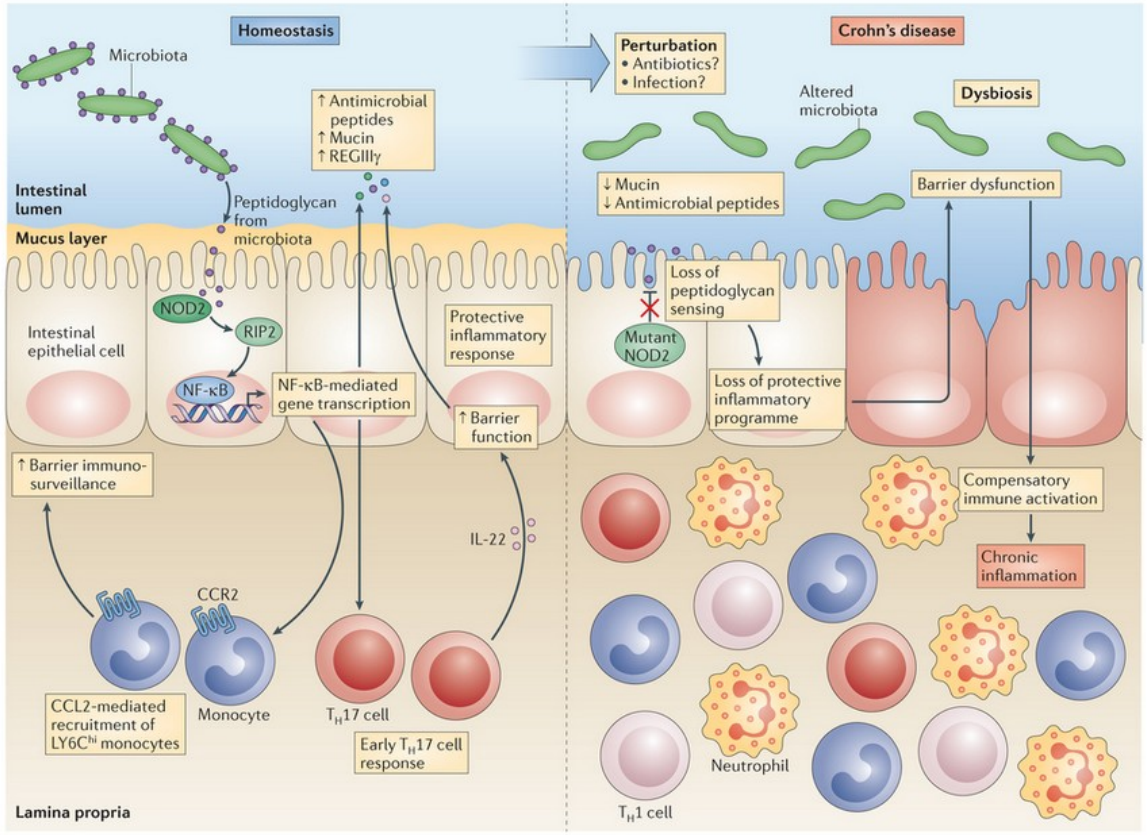
Mikrobiota a imuinitní systém



The gut microbiota has been shown to affect several aspects of host physiology; arrows represent either stimulatory or inhibitory effects of the gut microbiota on host physiological processes. The microbiota has been shown to influence intestinal function in the host, promoting gut-associated lymphoid tissue (GALT) maturation, tissue regeneration (in particular of the villi) and gut motility, and reducing the permeability of epithelial cells lining the gut, thus promoting barrier integrity. Similarly, the gut microbiota influences the morphogenesis of the vascular system surrounding the gut. This is associated with increased glycosylation of tissue factor (TF), which leads to cleavage of thrombin, in turn activating proteinase-activated receptor 1 (PAR1). This then phosphorylates TF to promote epithelial expression of angiopoietin 1 (ANG1), which promotes increased vascularization. Changes in the microbiota composition or a complete lack of a gut microbiota has been shown to affect metabolism, behaviour and tissue homeostasis, suggesting that the microbiota also regulates these processes. Specifically, the gut microbiota can influence the host's nervous system, decreasing synaptic connectivity and promoting anxiety-like behaviour and pain perception. In the case of host metabolism, the gut microbiota has been shown to facilitate energy harvest from the diet, to modulate host metabolism (for example, by decreasing energy expenditure) and to promote host adiposity. Finally, the gut microbiota can influence tissue homeostasis, for example decreasing bone mass by promoting the function of osteoclasts (which cause bone resorption) and increasing the numbers of pro-inflammatory T helper 17 (T_H17) cells.

Nemoci spojené s narušenou mikroflórou

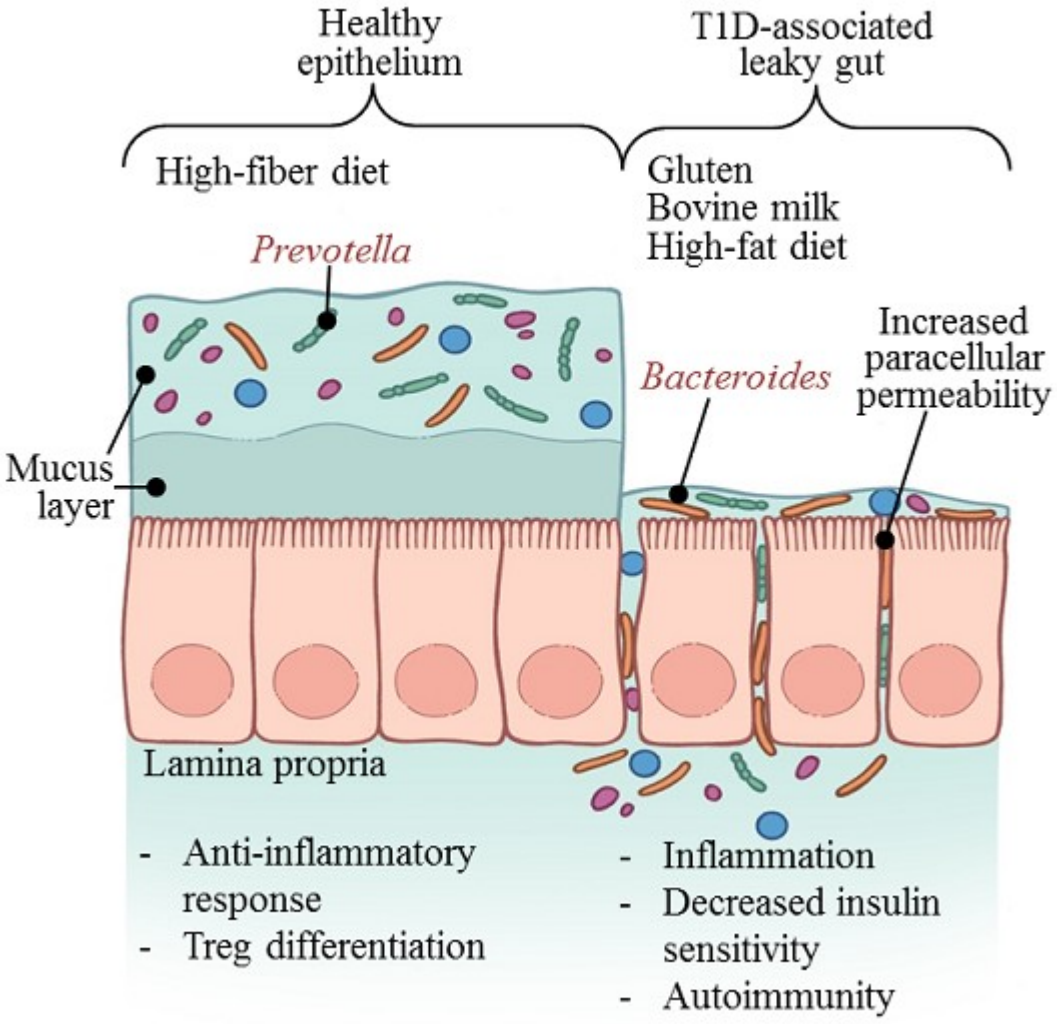
Mikroflóra a Crohnova choroba



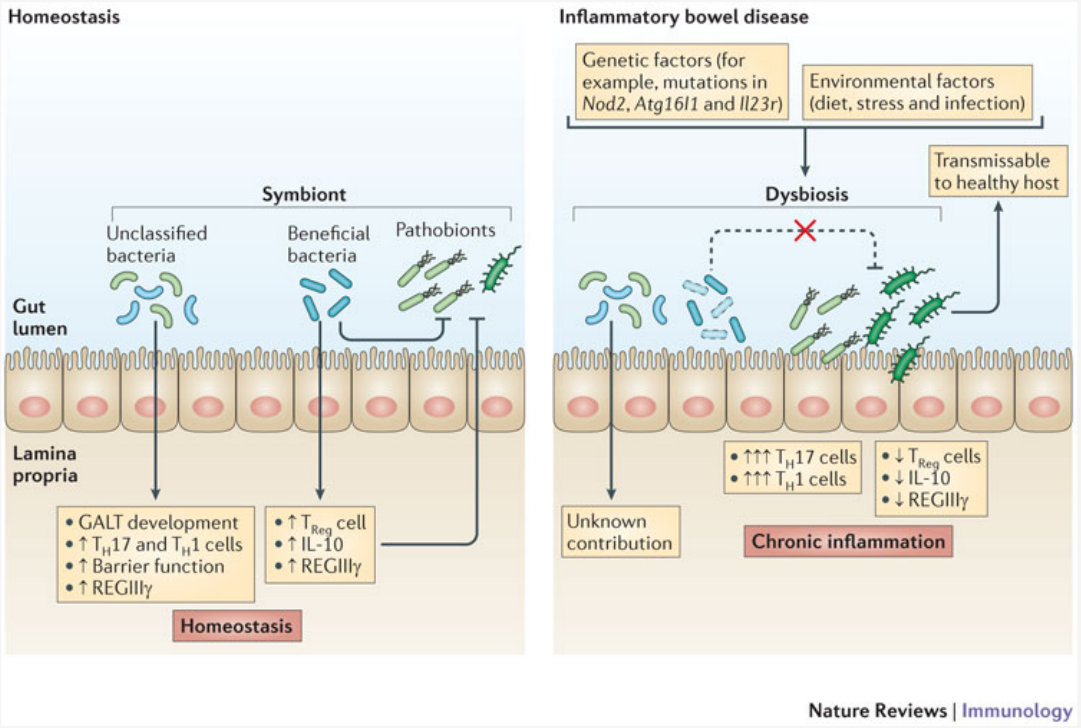
Nature Reviews | Immunology

NOD2 (nucleotide-binding oligomerization domain-containing protein 2) has a key role in intestinal homeostasis by detecting peptidoglycan that is released from the gut microbiota and by driving a physiological inflammatory programme through the kinase receptor-interacting protein 2 (RIP2), leading to nuclear factor-κB (NF-κB) activation. This programme includes stimulating the production of antimicrobial peptides and mucin, which together restrain the microbiota and maintain a physical distance between the microorganisms and the gut epithelial cells (left panel). An early T helper 17 (T_H17) cell response enhances barrier protection by inducing the production of interleukin-22 (IL-22) and regenerating islet-derived protein IIIγ (REGIIIγ), and the CC-chemokine ligand 2 (CCL2)-mediated recruitment of LY6C^{hi} monocytes enhances barrier surveillance. In Crohn's disease that is associated with *NOD2* mutations (right panel), some perturbation, which may include antibiotics or an infection, alters the protective inflammatory programme and leads to a breakdown in the intestinal barrier and potentially to dysbiosis. Compensatory immune activation through other pathways then drives chronic inflammation. CCR2, CC-chemokine receptor 2.

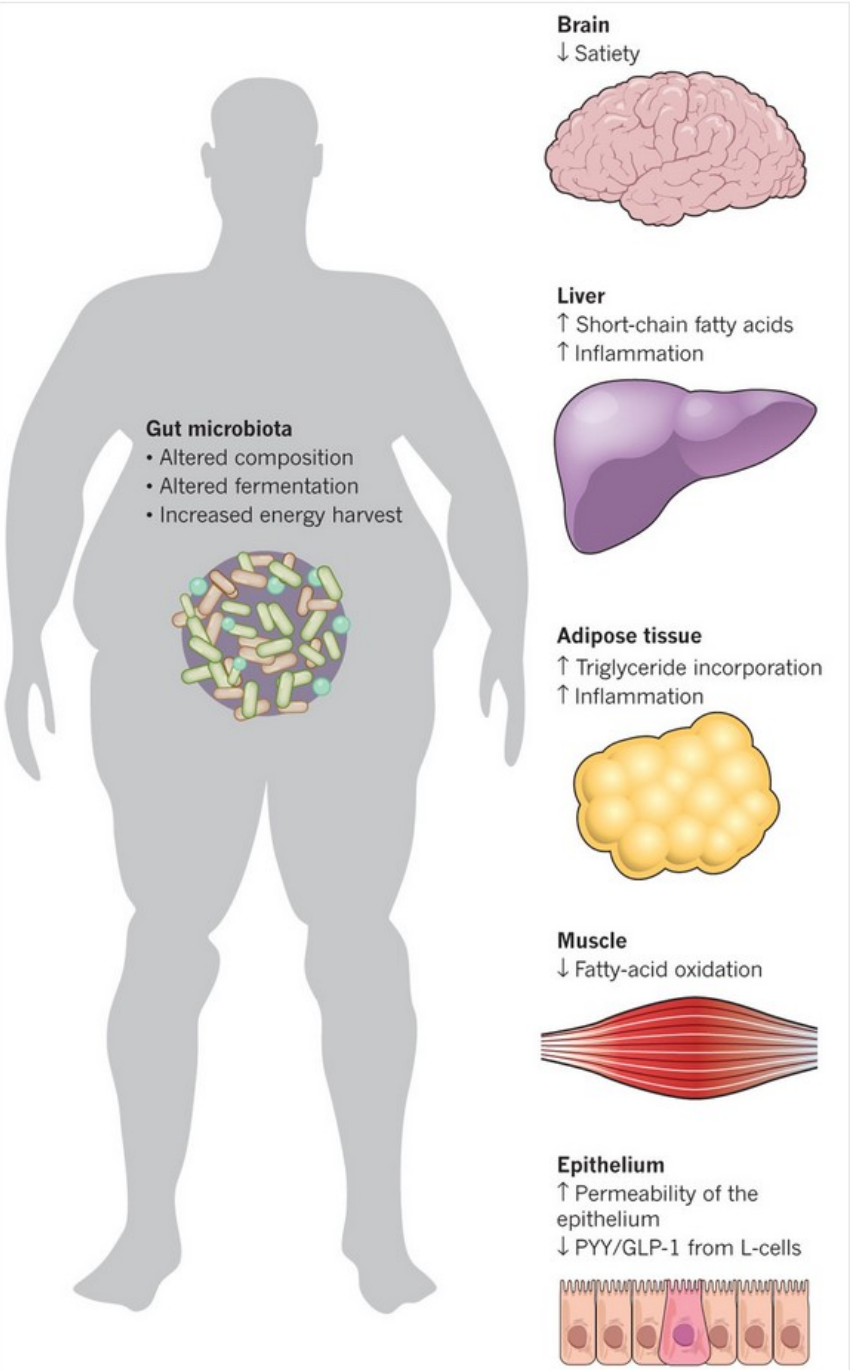
Leaky Gut


Healthy epithelium
T1D-associated leaky gut
High-fiber diet
Gluten
Bovine milk
High-fat diet
Prevotella
Bacteroides
Increased paracellular permeability
Mucus layer
Lamina propria
- Anti-inflammatory response
- Treg differentiation
- Inflammation
- Decreased insulin sensitivity
- Autoimmunity

IBS

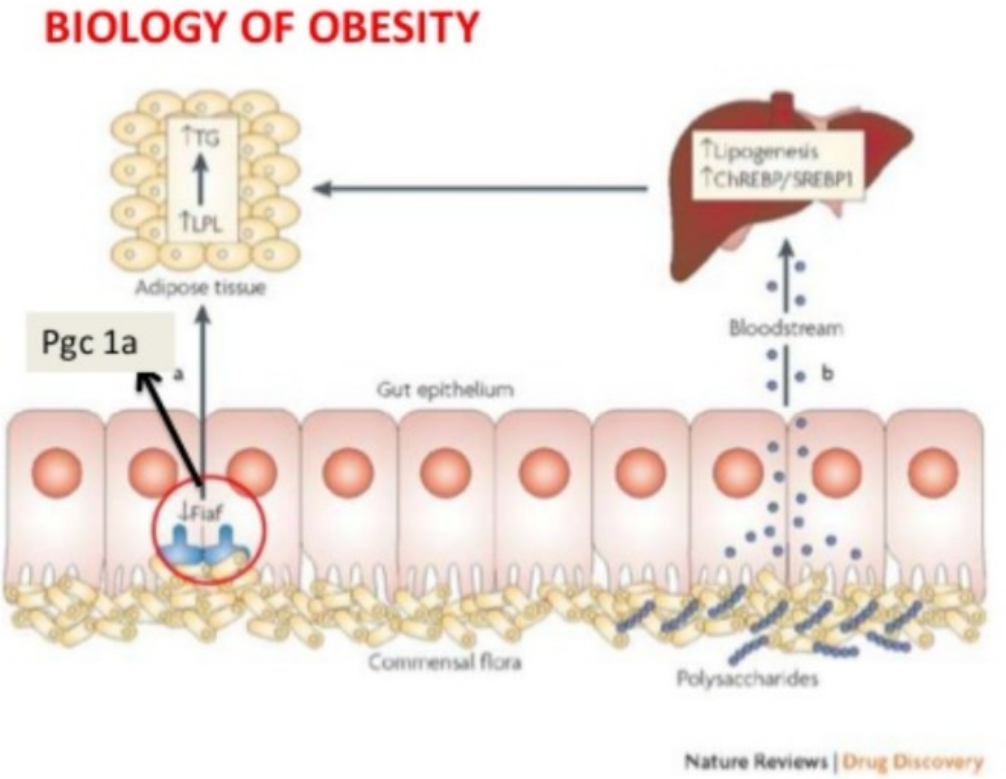


During homeostasis (left-hand side), the gut microbiota has important roles in the development of intestinal immunity. Beneficial subsets of commensal bacteria tend to have anti-inflammatory activities. Pathobionts that are colitogenic are directly suppressed by beneficial commensal bacteria partly through the induction of regulatory immune responses, involving regulatory T (T_{Reg}) cells, interleukin-10 (IL-10) and regenerating islet-derived protein 3γ (REGIIIγ). In inflammatory bowel disease (IBD) (right-hand side), a combination of genetic factors (for example, mutations in nucleotide-binding oligomerization domain 2 (*Nod2*), autophagy-related gene 16-like 1 (*Atg16l1*) and interleukin-23 receptor (*Il23r*)) and environmental factors (such as infection, stress and diet) result in disruption of the microbial community structure, a process termed dysbiosis. Dysbiosis results in a loss of protective bacteria and/or in the accumulation of colitogenic pathobionts, which leads to chronic inflammation involving hyperactivation of T helper 1 (T_H1) and T_H17 cells. Dashed line shows that that the suppression of pathobionts by beneficial bacteria is diminished. In certain contexts, pathobionts can be transferred to the host and can cause disease without the host having a predisposing genetic susceptibility. It is unknown whether unclassified bacteria have a role in the pathogenesis of IBD. GALT, gut-associated lymphoid tissue.



Alterations to the composition and metabolic capacity of gut microbiota in obesity promote adiposity and influence metabolic processes in peripheral organs, such as the control of satiety in the brain; the release of hormones from the gut (shown as PYY and GLP-1); and the synthesis, storage or metabolism of lipids in the adipose tissue, liver and muscle. Microbial molecules also increase intestinal permeability, leading to systemic inflammation and insulin resistance.

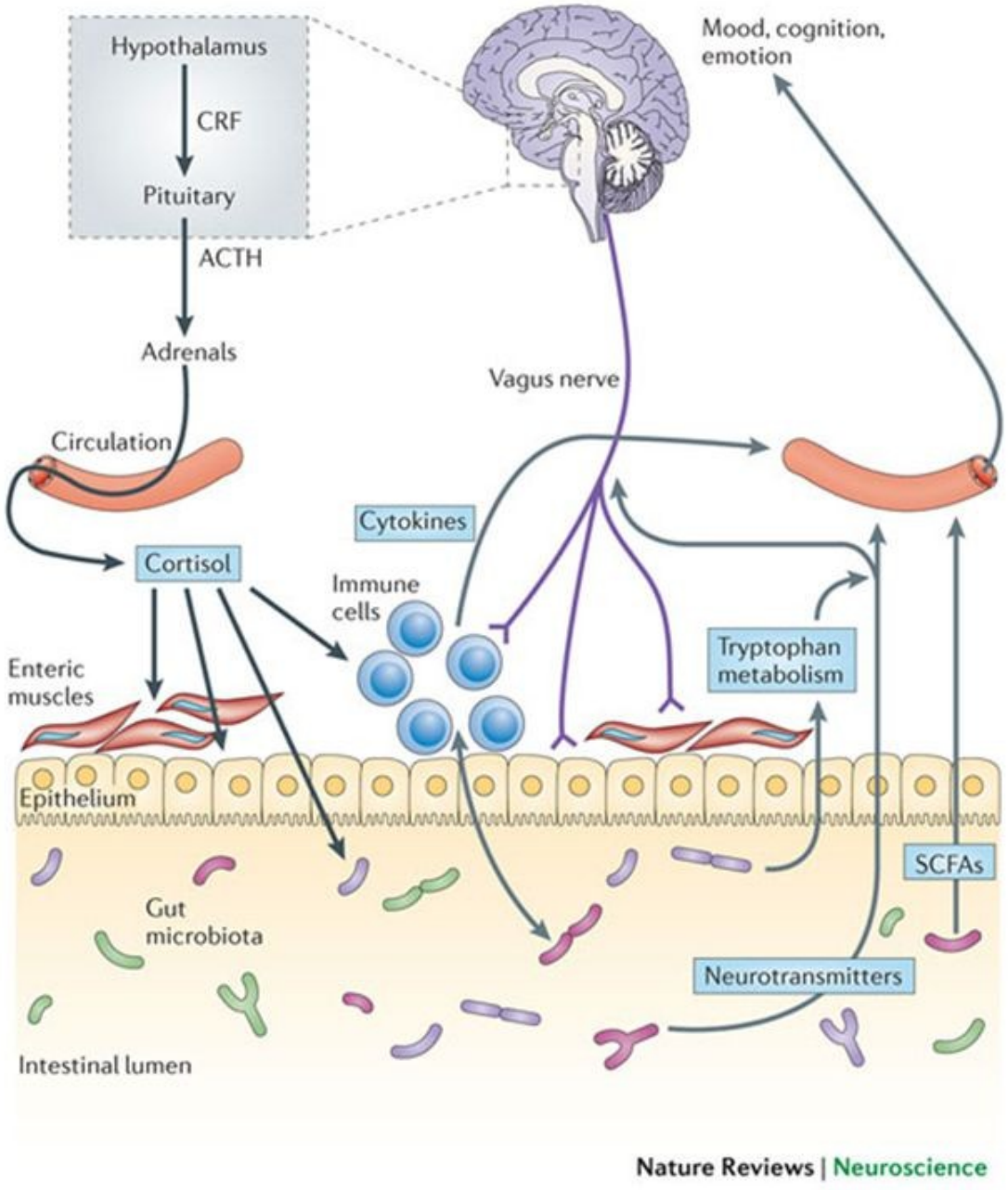
Mikroflóra a obezita



Regulation of fatty acid uptake by suppression of fasting-induced adipose factor (Fiaf)….. is a protein secreted by adipose tissues, liver and intestine that inhibits the activity of Lipoprotein Lipase (LPL), a key enzyme in the hydrolysis of the release of fatty acids for transport into cells.

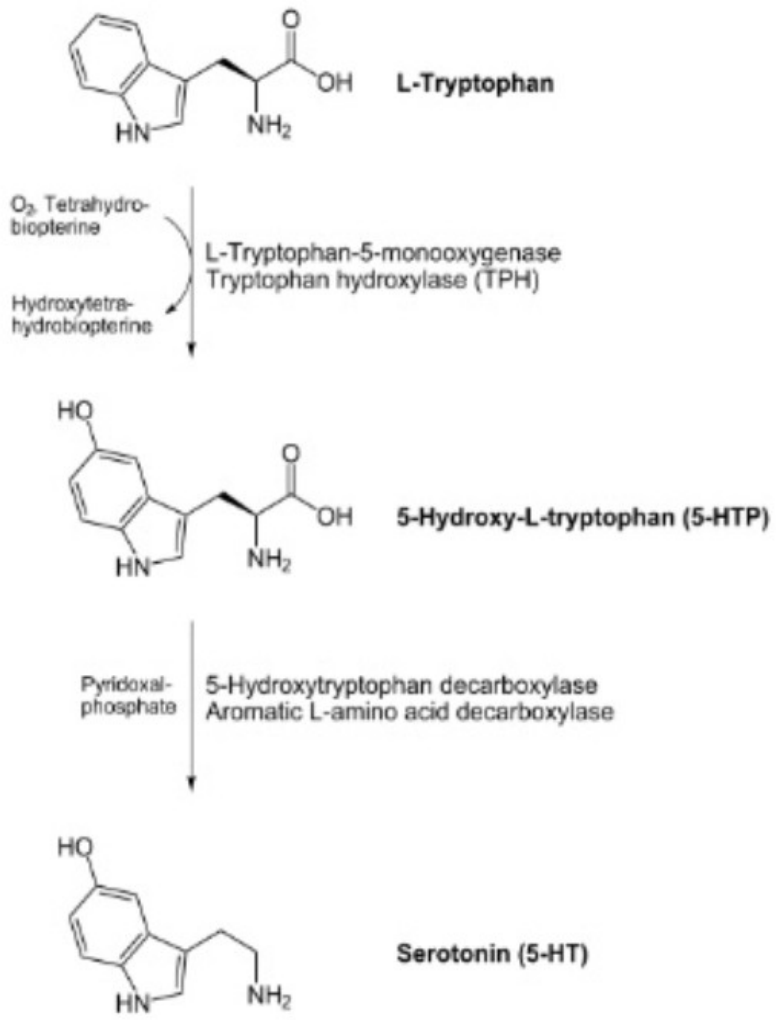
Mikroflóra a vliv mozek

Pathways involved in bidirectional communication between the gut microbiota and the brain.

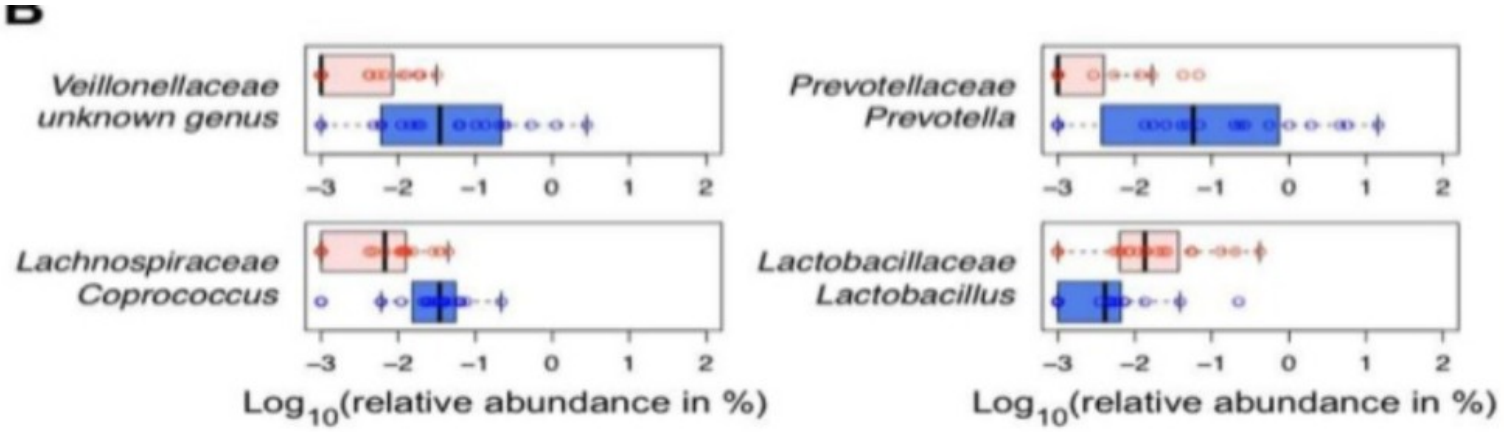


John F. Cryan & Timothy G. Dinan
Nature Reviews Neuroscience **13**, 701-712 (October 2012)

Mikroflóra a vliv mozek



Mikroflóra a autismus

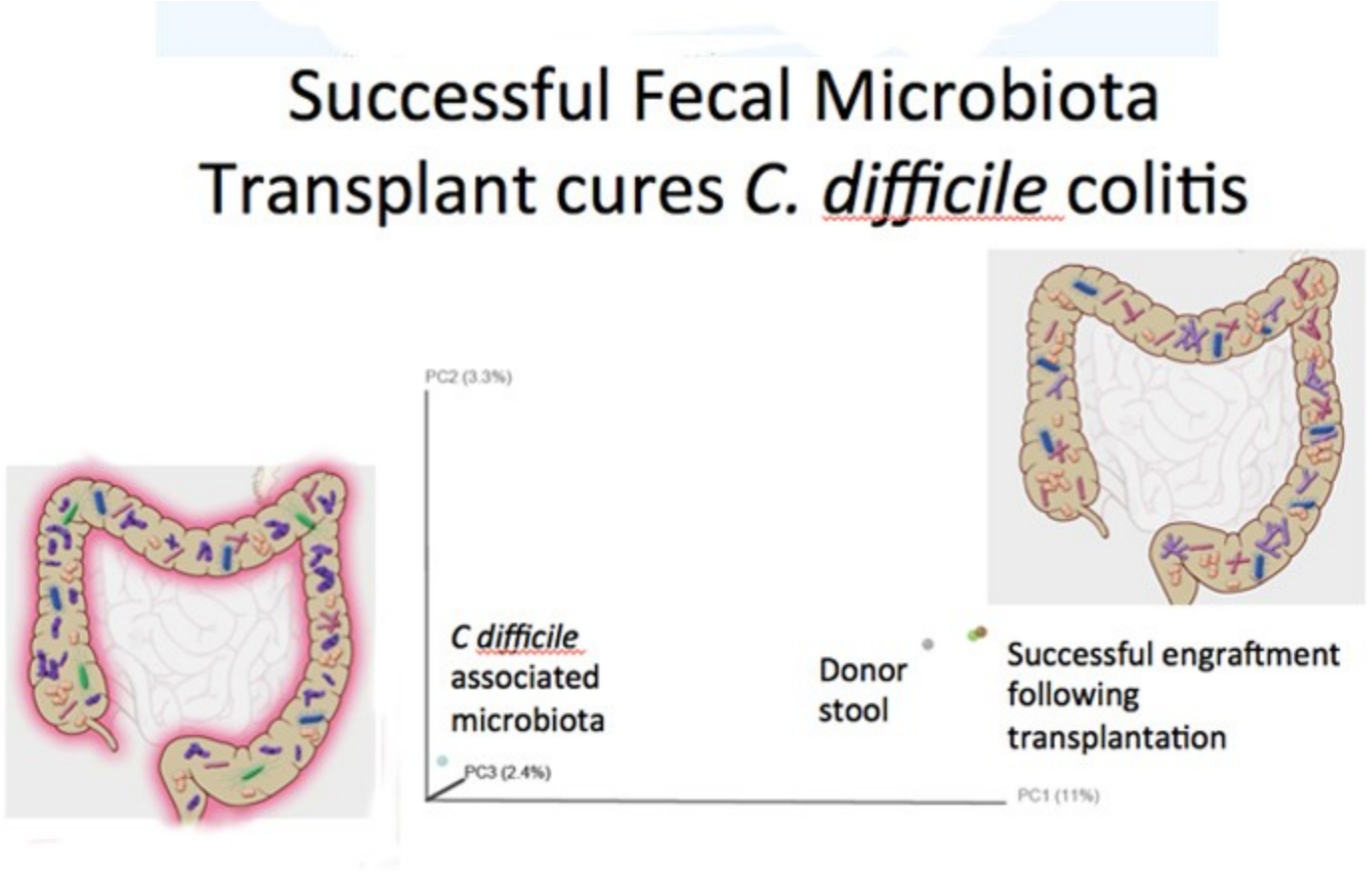


Dr. Dae-Wook Kang, Arizona State University

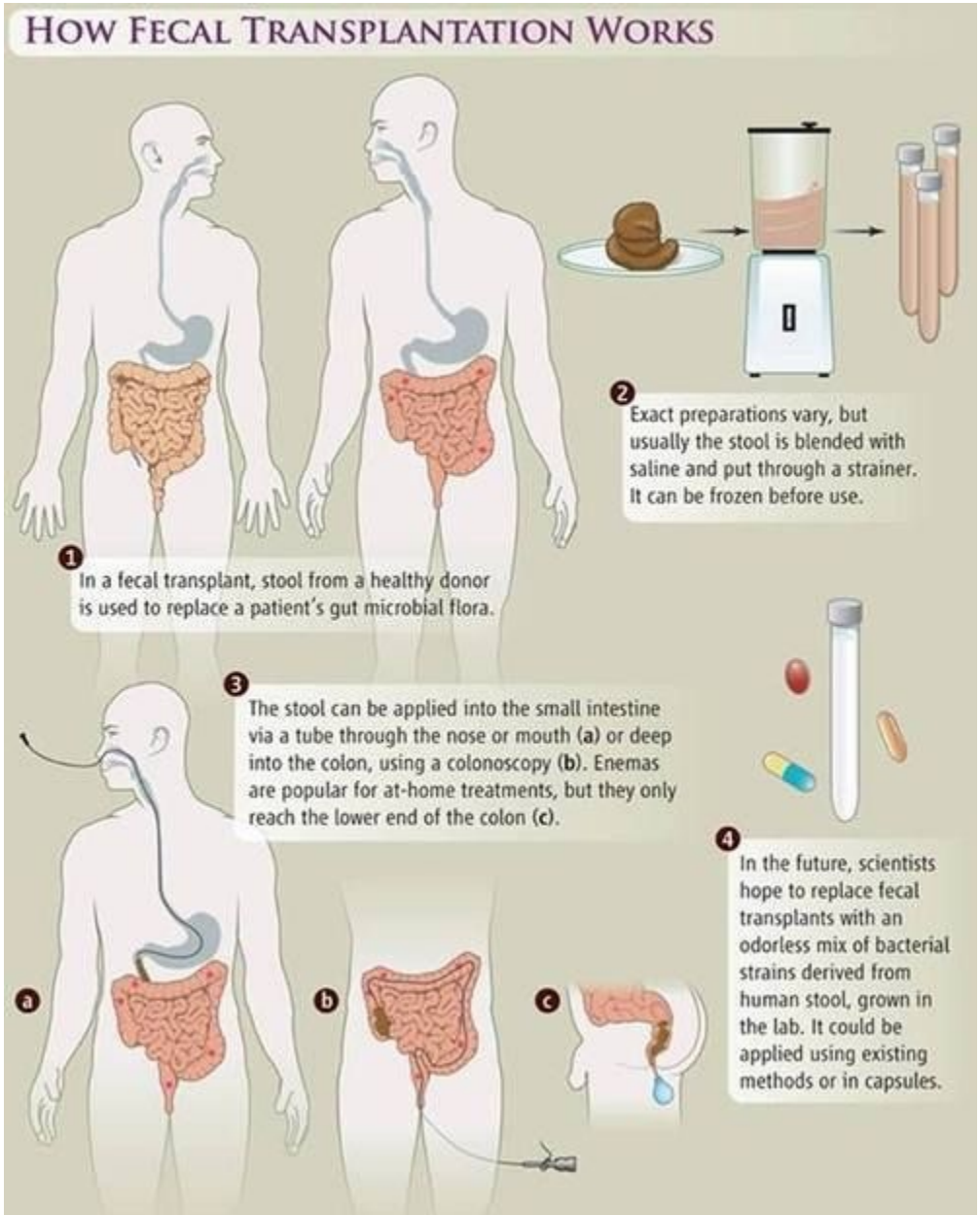
Autistic Children significantly have fewer types of gut bacteria and significantly lower amounts of three critical bacteria prevotella, coprococcus and veillonellaceae. These three bacterial groups represent important strains of carbohydrate degrading and fermenting microbes. So, In may cases the autistic children have IBD symptoms and they have found that when they tried to manage the IBD with application of probiotics the child seems to recover a fewer percent.

Dae-Wook Kang, PLOS One, July , 2013

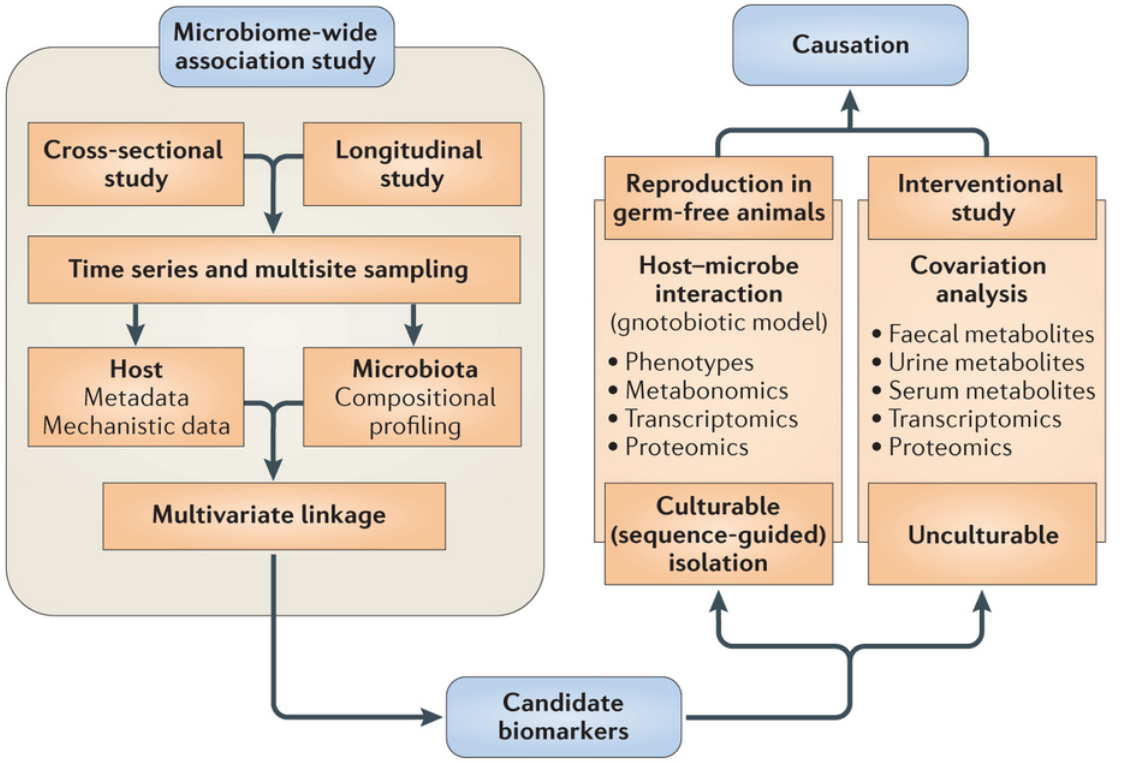
Transplantace střevní mikroflóry



Transplantace střevní mikroflóry



Výzkum mikroflóry



Nature Reviews | Microbiology

In order to screen all the potential key gut microbial phylotypes that might be associated with the aetiology or development of a specific chronic disease, a microbiome-wide association study should first be carried out. Either cross-sectional or longitudinal experiments can be involved, accompanied by time series and multisite sampling to obtain measurements of both host phenotypes and the compositional and functional profiles of the gut microbiota. Multivariate statistical tools, such as principal component analysis, redundancy analysis and partial least squares models, can be used to identify candidate key members of the gut microbiota as putative causative agents. Sequence-guided isolation should then be carried out to obtain a pure culture of the key bacteria, followed by reproduction of the disease in gnotobiotic animals associated with the key bacterium and/or a defined consortium of relevant bacteria, to generate a gnotobiotic model of the disease. For those diseases for which it is difficult to obtain a pure culture of the candidate key bacteria, large-scale interventional studies can be carried out to assess whether a reduction in the levels of candidate sequences leads to an improvement in the disease phenotypes. A multi-omics covariation analysis might be used to examine the correlating patterns of changes for the candidate key players and faecal, urinary, serum and/or plasma metabolites, or even whole transcriptomic or proteomic pathways; any such correlations might be indicative of a mechanistic connection between the putative cause and the disease.

Výzkum mikroflóry

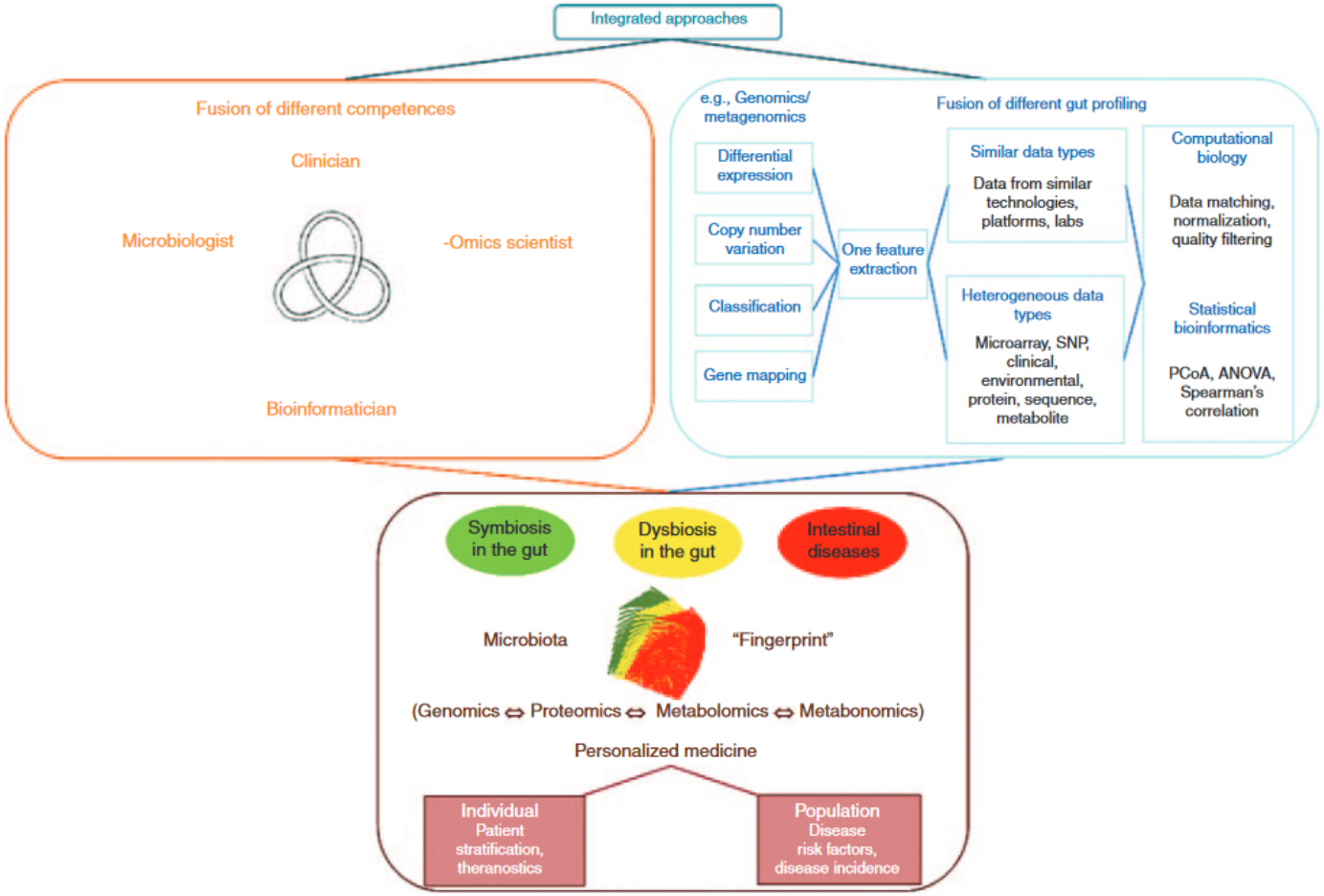


Figure 2. The "knot -omics" strategies and clinical needs: the key to disentangle gut microbiota–related diseases through the symbiosis–dysbiosis route. Chaotropic bacterial factors contribute to the onset of gut symbiosis imbalance, generating entropy, triggering inflammation, and inducing, in some cases, disease status. The different levels of complexity can be unveiled by new "-omics" approaches. Such approaches need heterogeneous multidisciplinary competences, integration of different types and levels of data, and production of specialized and dedicated operational pipelines. The result of such integrated approaches provides "-omics" charts to "fingerprint" gut microbiota in different case controls, hence defining individual- and population-based gut microbiota profiling. PCoA, principal coordinate analysis; SNP, single-nucleotide polymorphism.

Výzkum mikroflóry

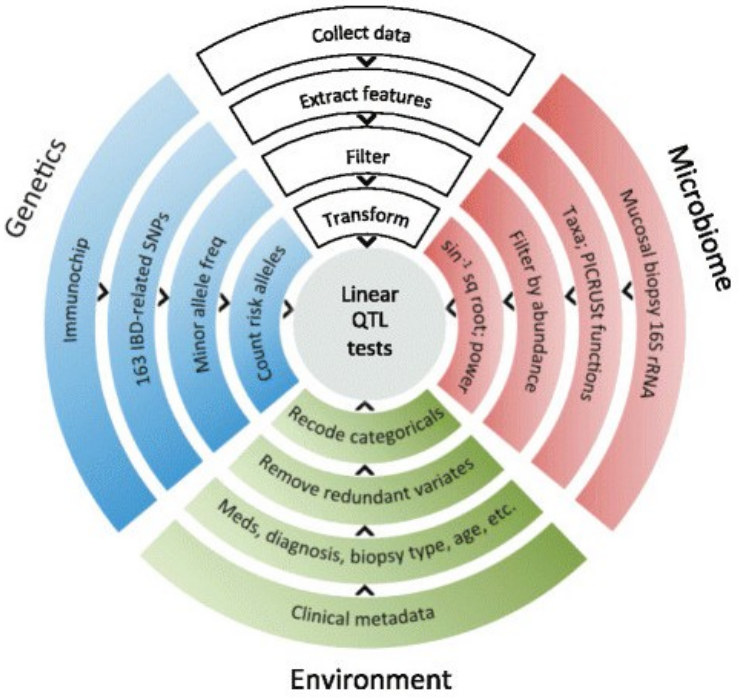


Figure 1

Schematic of multiomics genotype-microbiome association testing methodology. Host genome-microbiome association testing involves potentially thousands or millions of genetic polymorphisms and hundreds or thousands of bacterial taxa and genes. Full feature-by-feature association testing is likely to be underpowered in all but the largest cohorts or meta-analyses; therefore, our methodology includes careful feature selection from both data types. Raw genetic polymorphisms were derived from Immunochip data and filtered by known IBD associations from a large-cohort GWAS study [1]. Microbiome sequences were binned by lineage at all taxonomic levels. After data normalization and filtering (see Methods), a simple linear test was performed for association between minor allele count and bacterial taxon relative abundance while controlling for clinical covariates. QTL, quantitative trait loci.