Microbiota & Diabetes

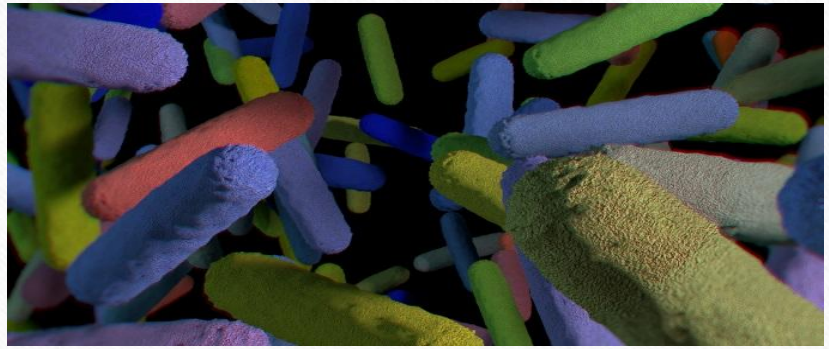
Abdulmoein Eid Al-Agha, FRCPCH
Professor of Pediatric Endocrinology, Head,
Pediatric Endocrinology & Diabetes section,
King Abdulaziz University Hospital, Saudi Arabia
www.aagha.kau.edu.sa

Objectives

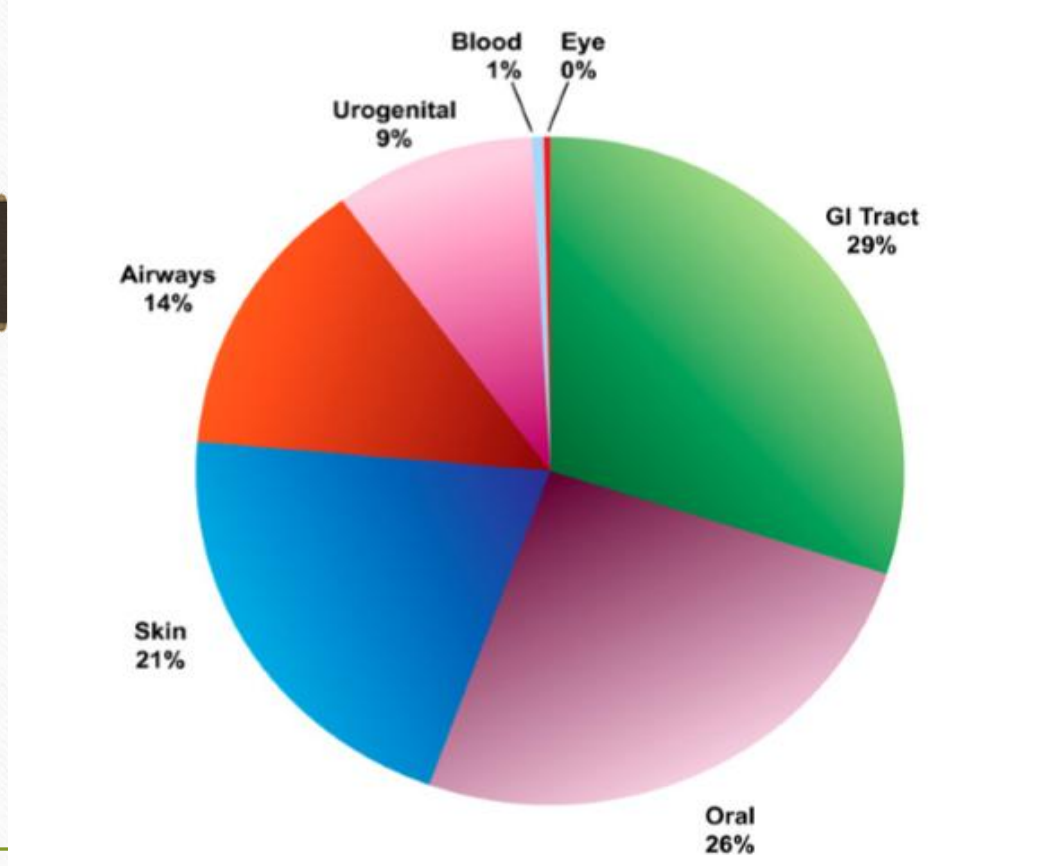
- Introduction into human microbiota (what are they?)
- What do we know on Gut microbiota?
- Environmental factors affecting Gut microbiota (from antenatal life till adulthood)
- Dysbiosis of the microbiota (change beneficial bacteria to abnormal dysregulated ones)
- High fat diet associated & obesity leads to microbiota dysbiosis which leads to type 2 DM & Metabolic syndrome
- Dysbiotic microbiota associations with various diseases including:
  - Obesity, insulin resistance, type 2 DM & type 1 DM

What is the "Microbiota"?

"the ecological community of commensal, symbiotic, & pathogenic microorganisms that share our body space"

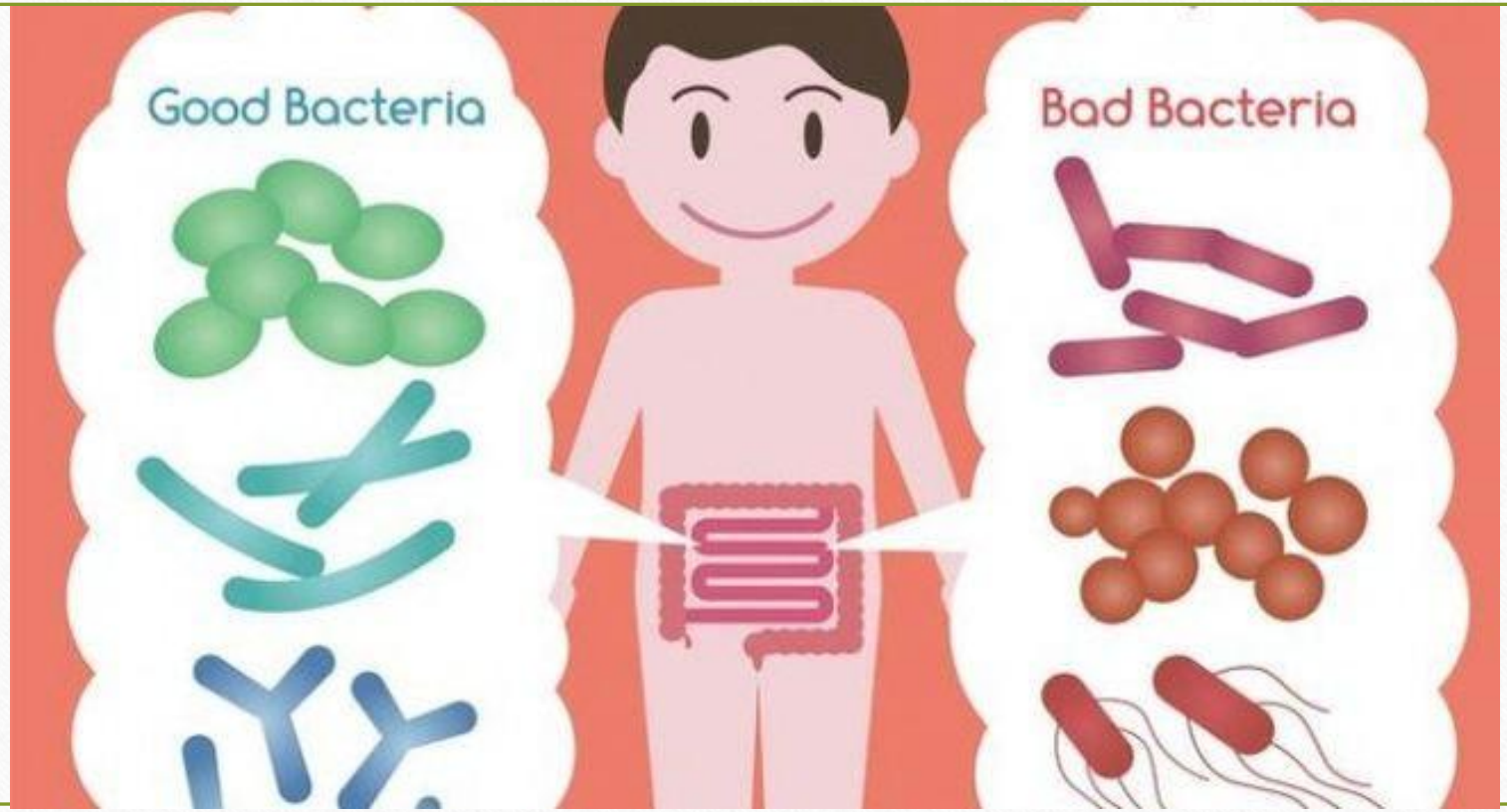


- gene sequencing on samples from 5 female body sites (gastrointestinal, mouth, vagina, skin, and nasal cavity) and 4 male body sites

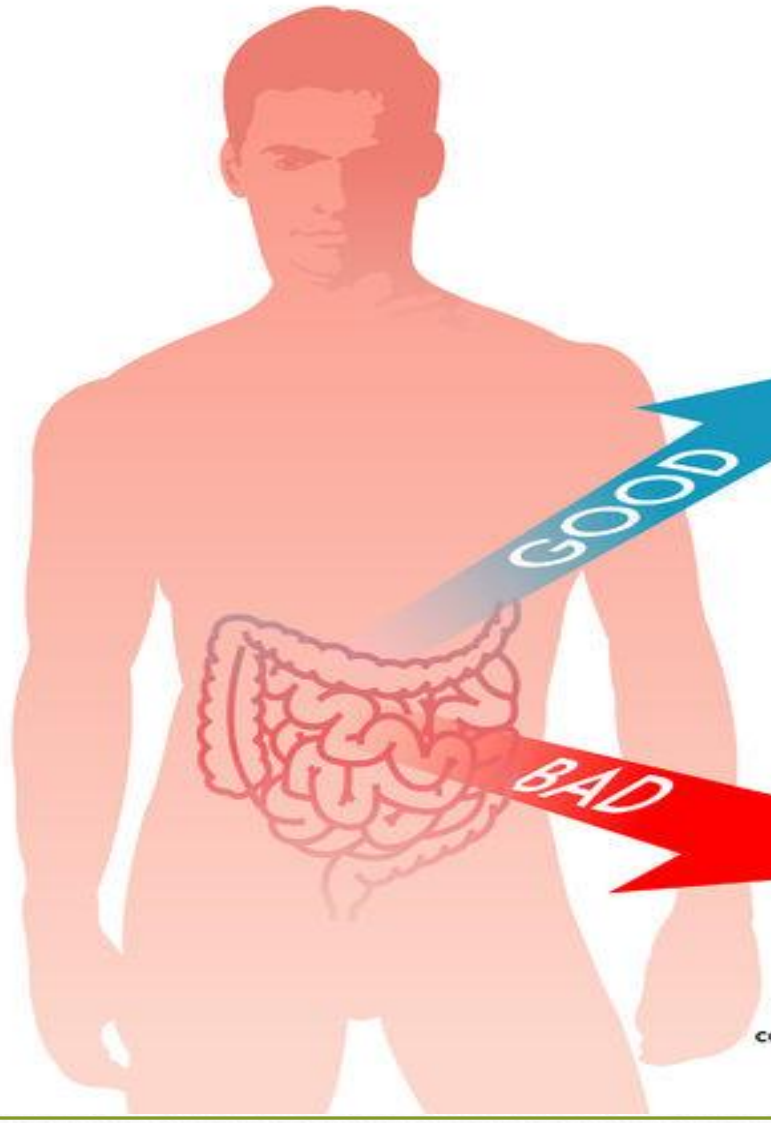


Bacterial Distribution by body site (Peterson, et al. 2009)

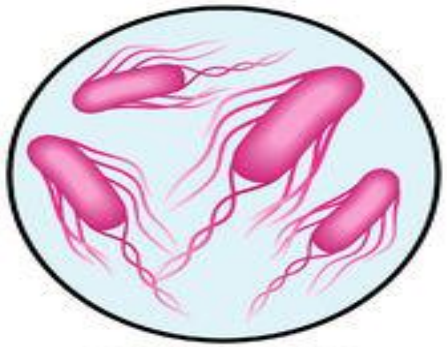
Symbiotic & Dysbiotic Microbiota



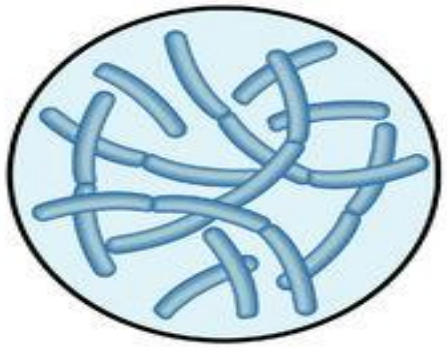
Good and Bad Bacterial Flora



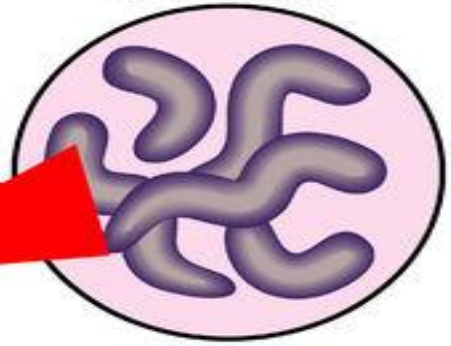
BIFIDOBACTERIA
The various strains help to regulate levels of other bacteria in the gut, modulate immune responses to invading pathogens, prevent tumour formation and produce vitamins.



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.

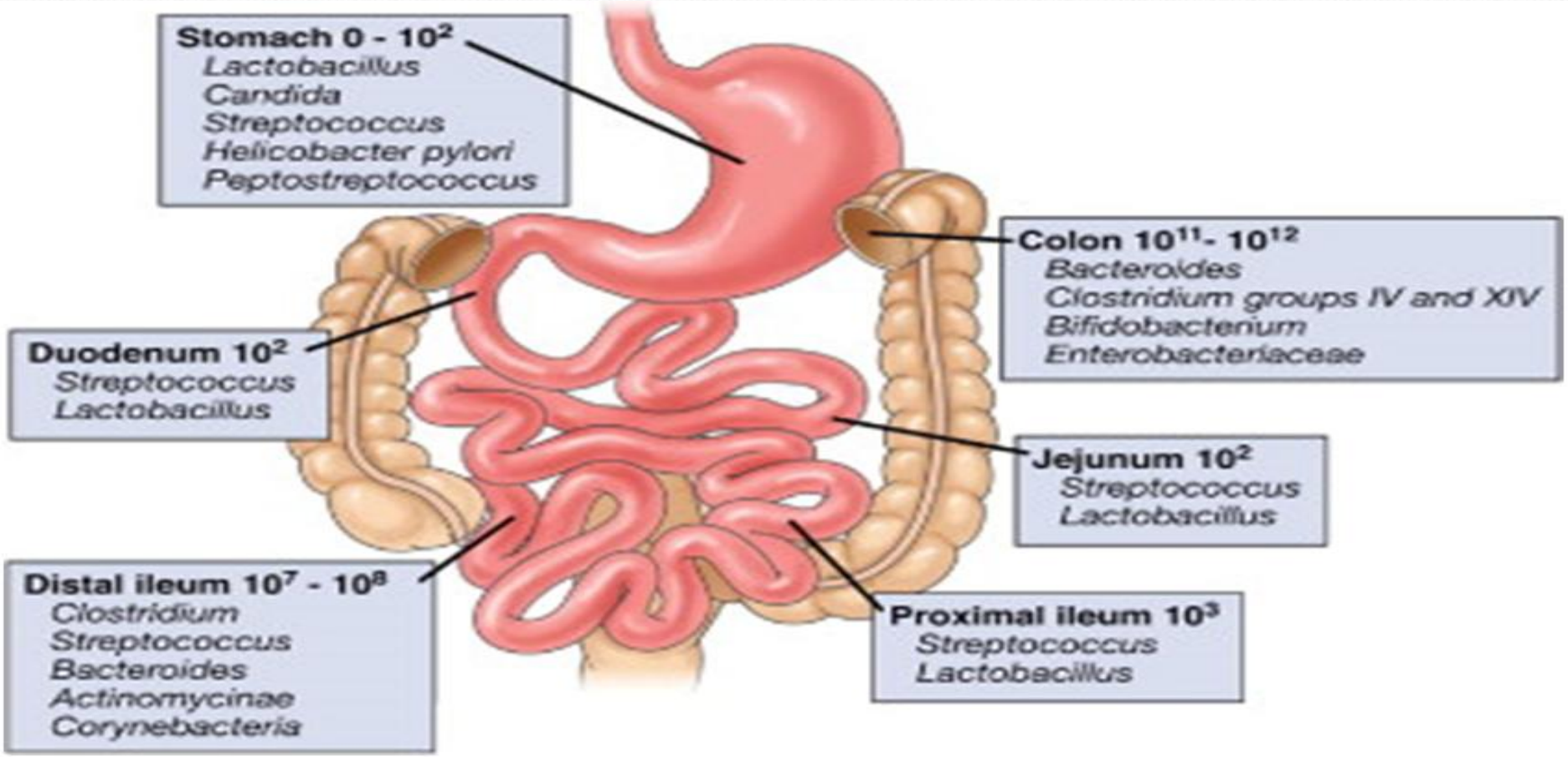
- What do we know about the gut Microbiota in health/ Disease states?

Gut Microbiota

Gut Microbiota

- Trillions of micro-organisms inhabit the distal gut, where they together weigh about 1.5 kg
- Regarded as a microbial organ that carries out key functions that the human host is incapable to perform by itself
- More than 90% of the prevalent bacterial species can be grouped into the two bacterial Phyla Firmicutes (Gram-positive) & Bacteroidetes (Gram-negative)

Composition & luminal concentrations of dominant microbial species in various regions of the gastrointestinal tract

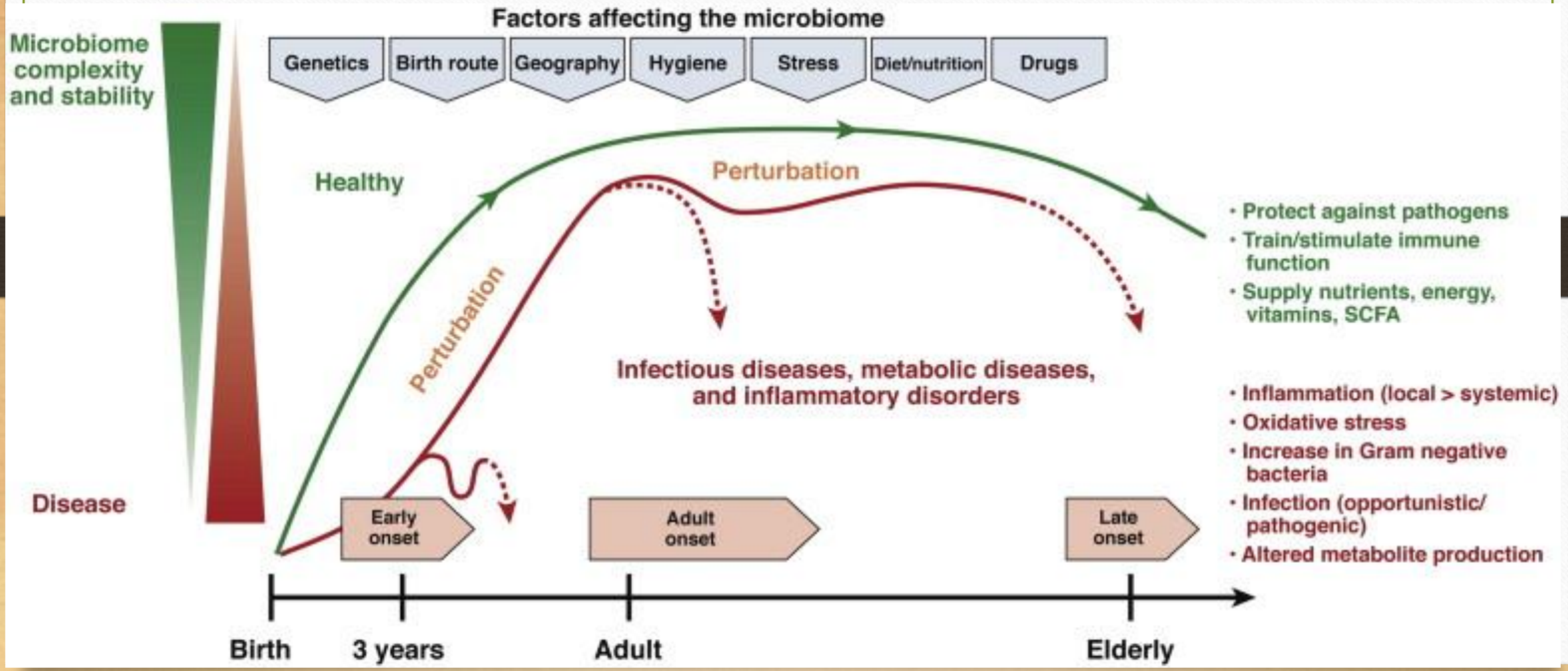


Gastroenterology 2008 134(2)

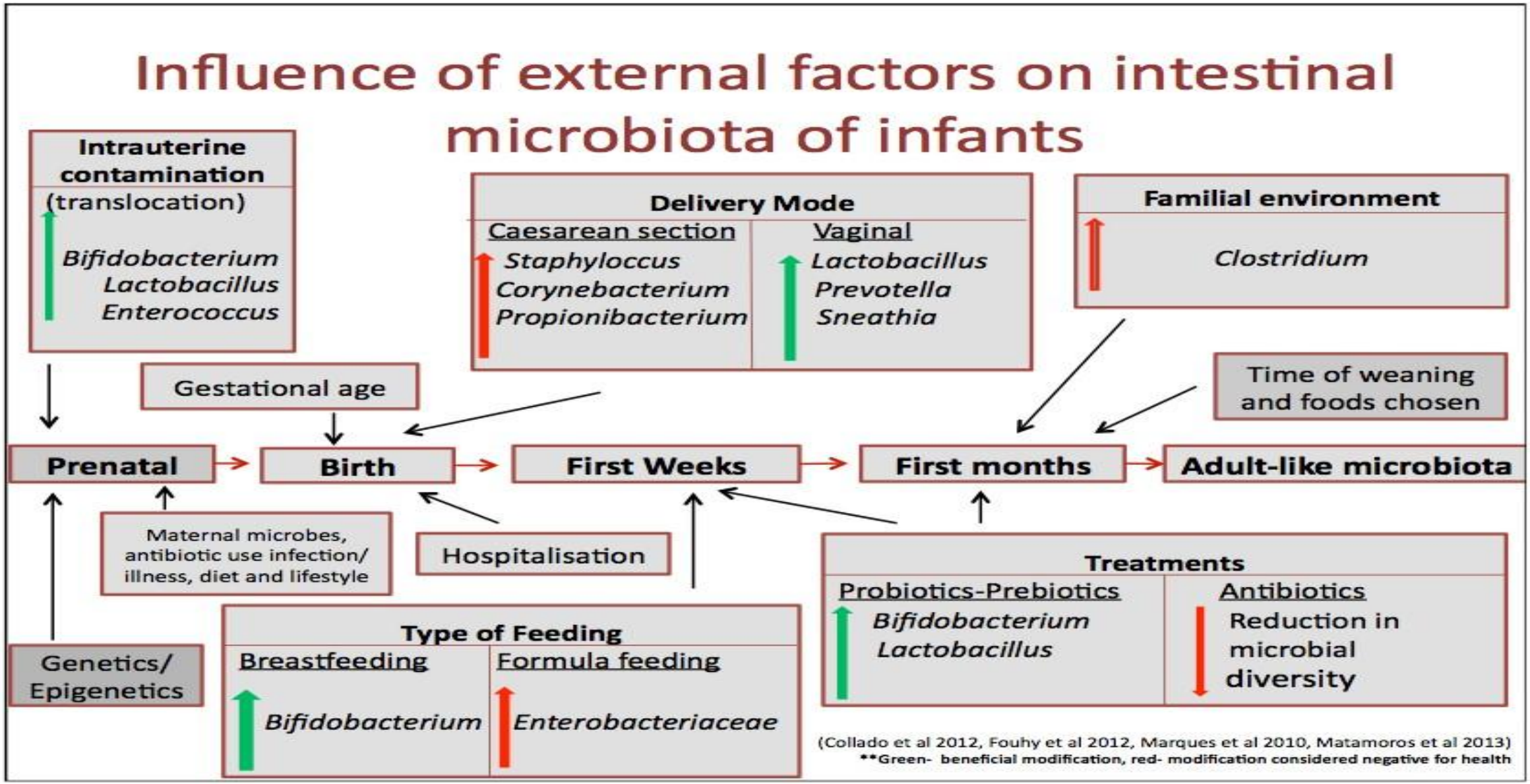
Beneficial Effects of Gut Microbiota

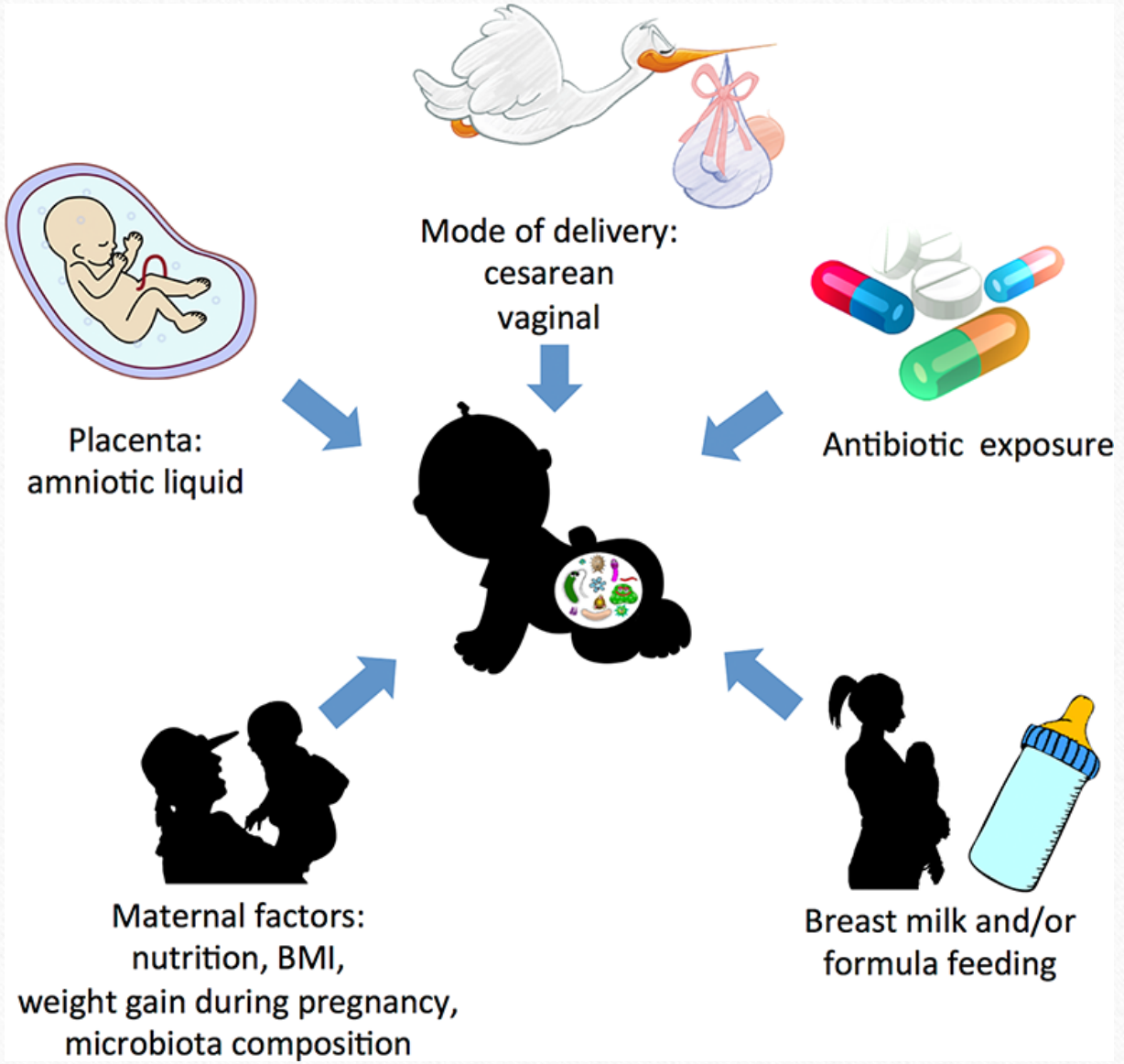
- Protects against pathogens
- Helps maturate and constantly educate the immune system
- Plays a role for regulation of intestinal hormone secretions & for gastrointestinal nerve activity
- Members of gut microbiota synthesize vitamin K , folate & vitamin B12
- Produce short-chain fatty acids (SCFAs) by fermentation of otherwise non-digestible carbohydrates

Factors affecting Gut Microbiome



Influence of external factors on intestinal microbiota of infants

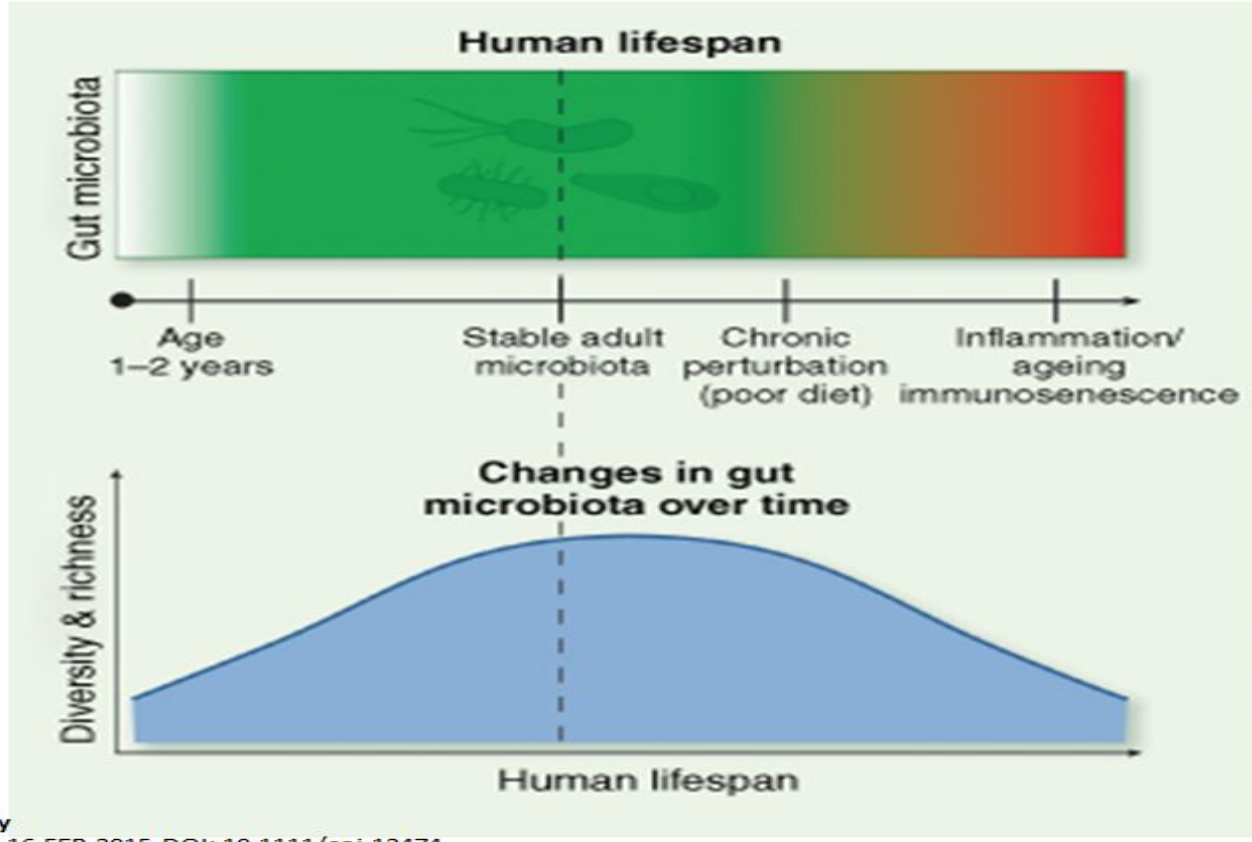



Mode of delivery:
cesarean
vaginal
Placenta:
amniotic liquid
Antibiotic exposure
Maternal factors:
nutrition, BMI,
weight gain during pregnancy,
microbiota composition
Breast milk and/or
formula feeding

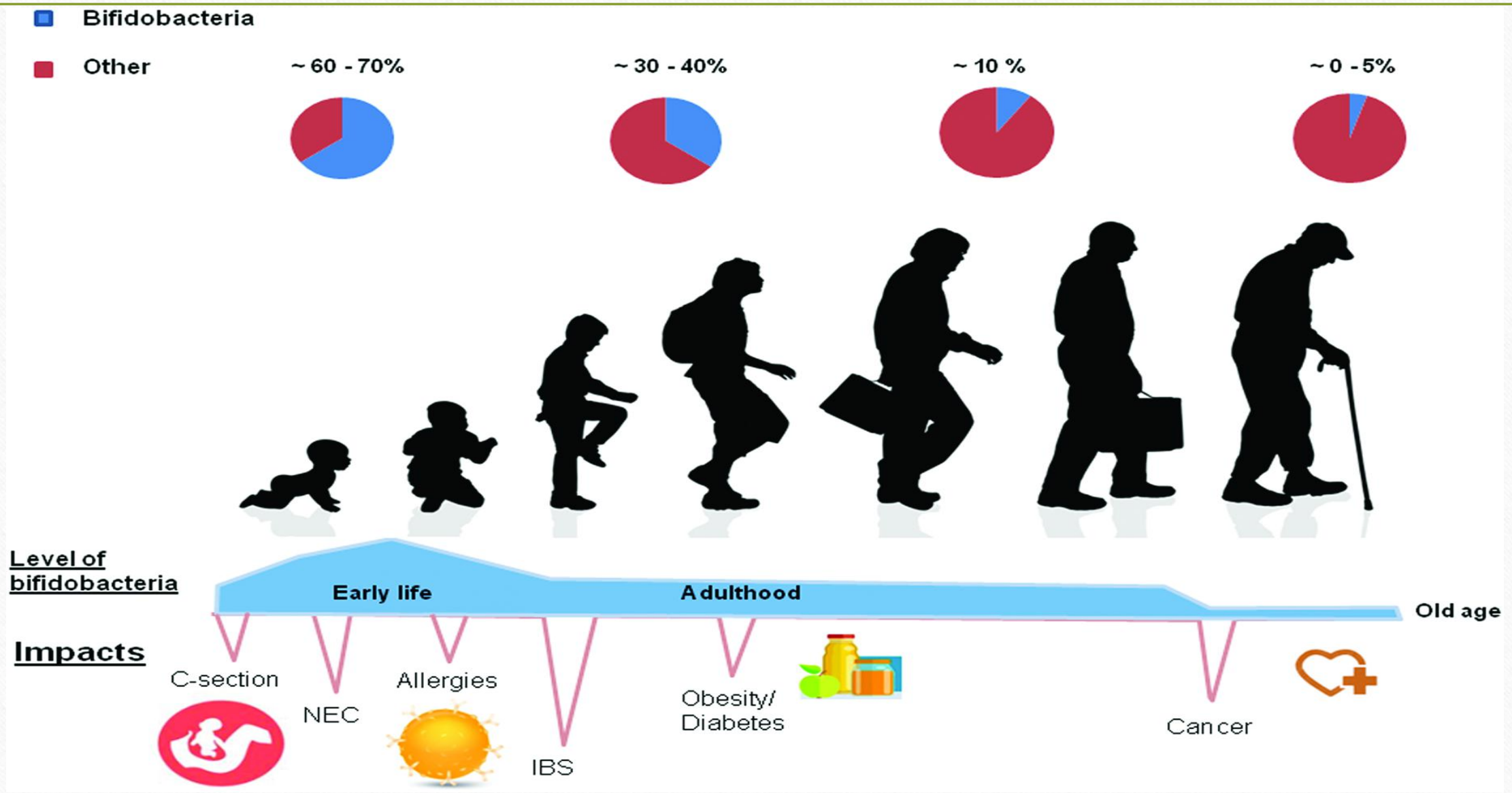
Breast -vs- formula

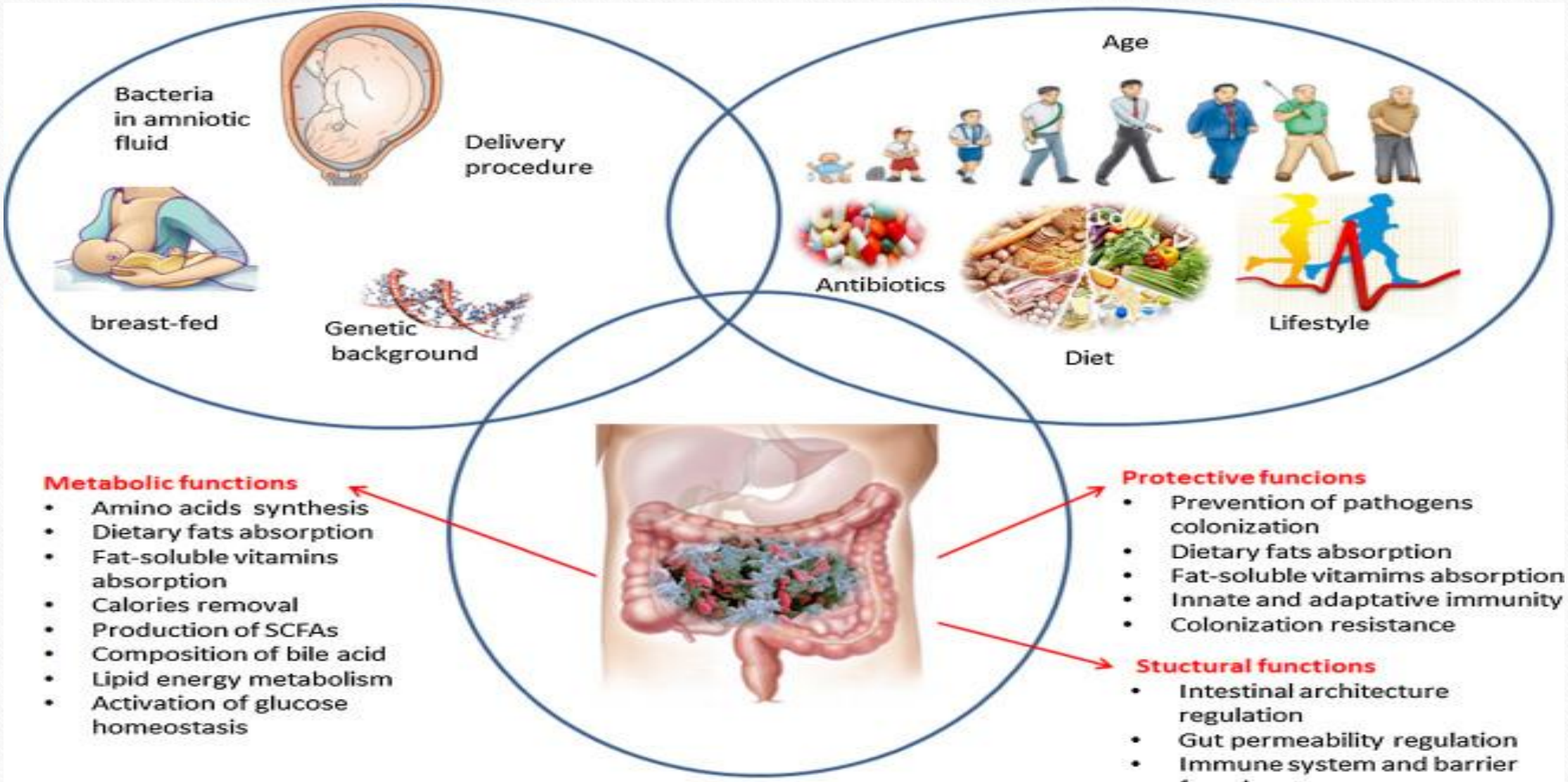
Breast Fed	Formula Fed
Bifidobacteria	Bifidobacteria
Enterobacteria	Escherichia Coli
	Clostridium difficle
	Bacteriodes
	Prevotella
	Lactobacillus
	Enterobacteriaceae

The gut Microbiota during the human lifespan



Clinical & Experimental Immunology
Volume 179, Issue 3, pages 363-377, 16 FEB 2015 DOI: 10.1111/cei.12474
http://onlinelibrary.wiley.com/doi/10.1111/cei.12474/full#cei12474-fig-0001


Bifidobacteria
Other
~ 60 - 70%
~ 30 - 40%
~ 10 %
~ 0 - 5%
Level of bifidobacteria
Early life
Adulthood
Old age
Impacts
C-section
NEC
Allergies
IBS
Obesity/ Diabetes
Cancer



Metabolic functions

- Amino acids synthesis
- Dietary fats absorption
- Fat-soluble vitamins absorption
- Calories removal
- Production of SCFAs
- Composition of bile acid
- Lipid energy metabolism
- Activation of glucose homeostasis

Protective funcions

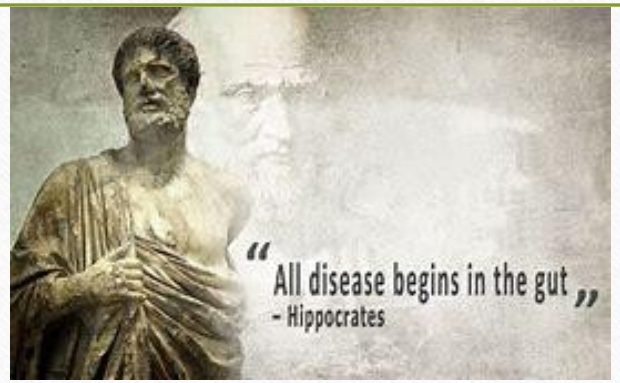
- Prevention of pathogens colonization
- Dietary fats absorption
- Fat-soluble vitamims absorption
- Innate and adaptative immunity
- Colonization resistance

Stuctural functions

- Intestinal architecture regulation
- Gut permeability regulation
- Immune system and barrier function

“Dysbiosis”= dysregulated (abnormal) Microbiota

“Father of Medicine”



Hippocrates 'famous statement that “all disease begins in the gut” recognized the essential role played by the gut & diet in many of the vital homoeostatic functions of the human body

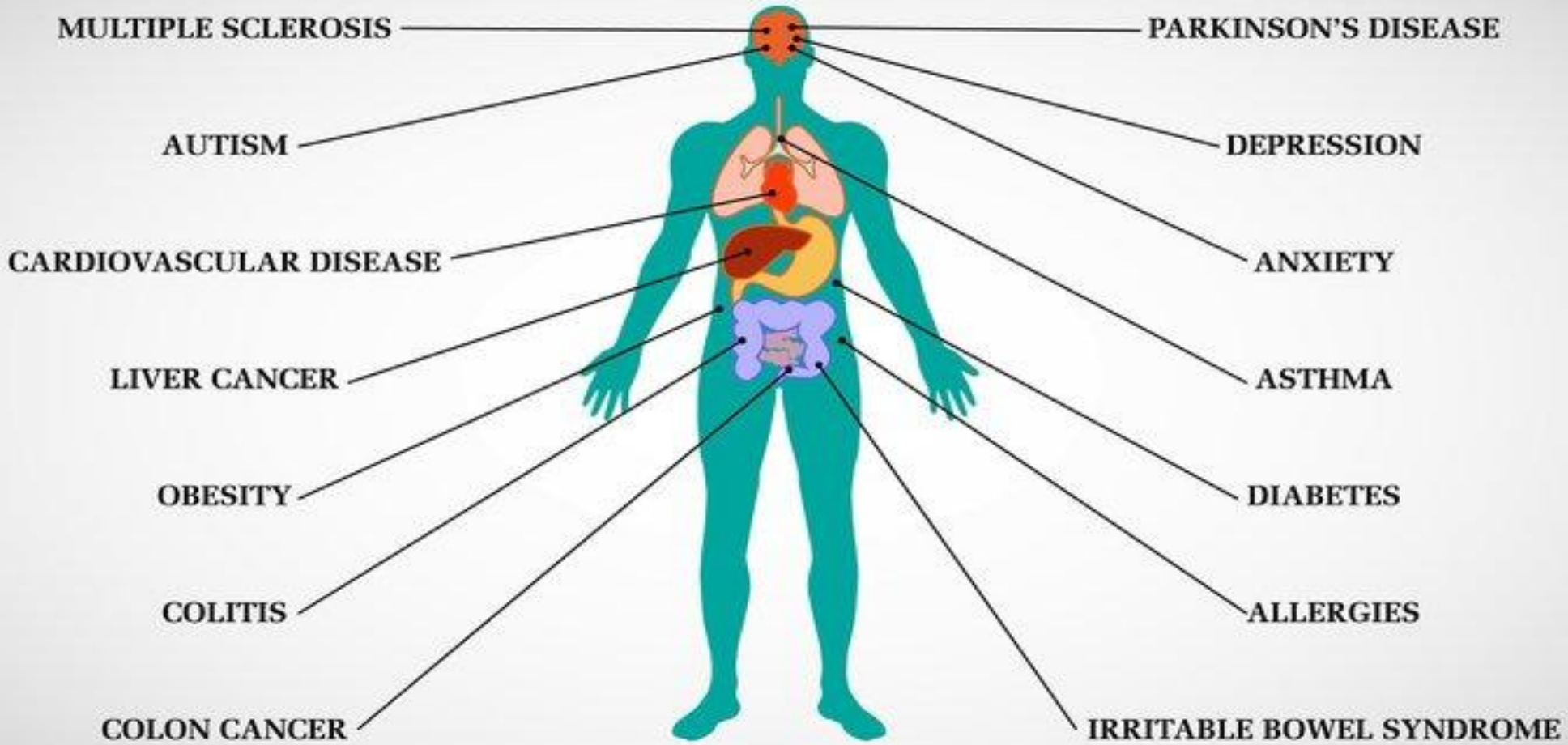
Gut Microbiota

A healthy gut is the sign of healthy life

Saurav Das
Department of Agricultural Biotechnology

Alterations in gut Microbiota have been linked with:

Metabolic diseases
IBD
CDI
Celiac disease
Allergies
Autism
Obesity& Type 2 DM
Malignancy
Type I DM
NASH
Depression


MULTIPLE SCLEROSIS
AUTISM
CARDIOVASCULAR DISEASE
LIVER CANCER
OBESITY
COLITIS
COLON CANCER
PARKINSON'S DISEASE
DEPRESSION
ANXIETY
ASTHMA
DIABETES
ALLERGIES
IRRITABLE BOWEL SYNDROME

Impact of diet on gut Microbiota

- A healthy gut microbiome is characterized by the presence of microbes that enhance metabolism, & are resilient to infection and inflammation and resistant to autoimmunity and cancer
- Studies examining the influence of nutrients (such as dietary fibers and fats) and dietary habits (vegetarians or vegans) in different populations have allowed stratification of the human population based on three principal bacteria and their micro biome's genetic abundance

Gut Microbiota dysbiosis & Type 2 DM

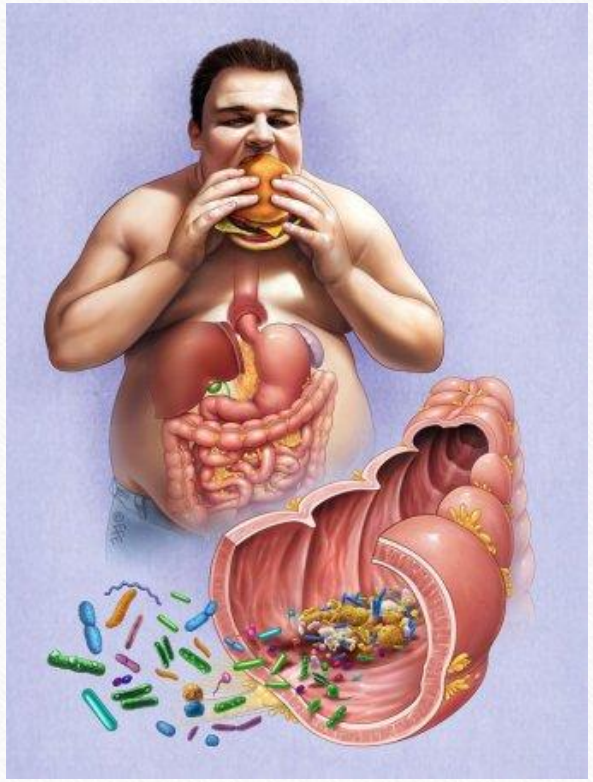
Risk factors for type 2 diabetes, including:

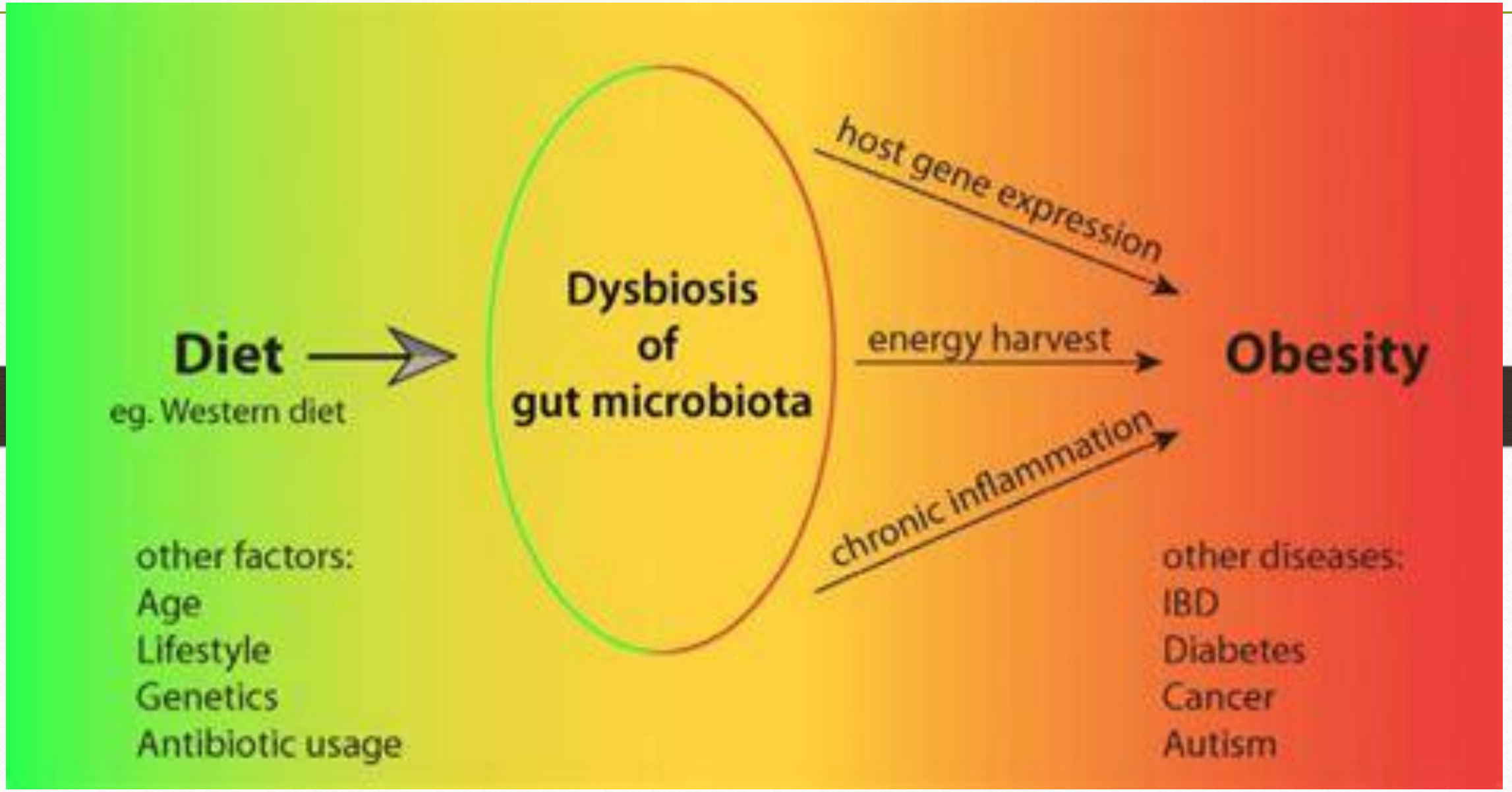
- Genetic predisposition
- Poor physical activity
- Fetal programming
- Obesity
- Altered configuration of the Microbiota has emerged as a new candidate that may be linked to obesity & type 2 diabetes

Microbiota Dysbiosis associated with Type 2 Diabetes

- Alterations in the gut microbiota have been linked to the increasing prevalence of metabolic disorders including obesity, insulin resistance & type 2 diabetes
- Accumulating evidence over the past decade has linked the development of metabolic syndrome related to diabetes to variations in gut microbiota
- Remarkably, decreased synthesis of short-chain fatty acids, have been significantly associated with the predisposition to diabetes and related disorders

High Fat Diet & Gut Microbiota dysbiosis



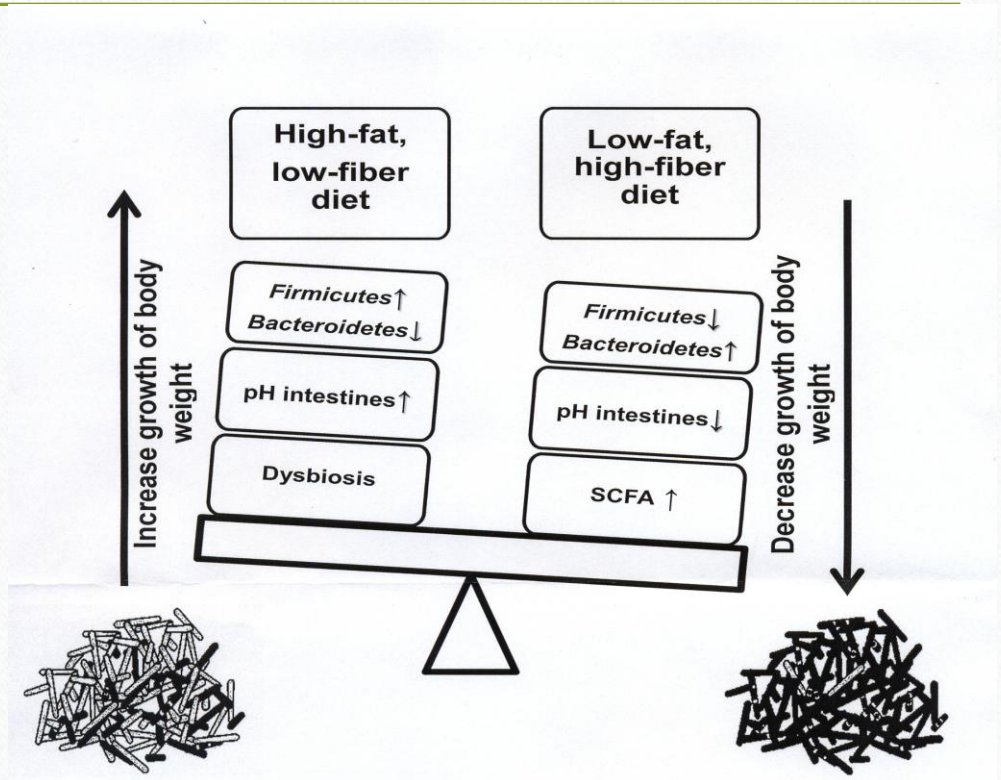

Diet
eg. Western diet
Dysbiosis
of
gut microbiota
host gene expression
energy harvest
chronic inflammation
Obesity
other factors:
Age
Lifestyle
Genetics
Antibiotic usage
other diseases:
IBD
Diabetes
Cancer
Autism

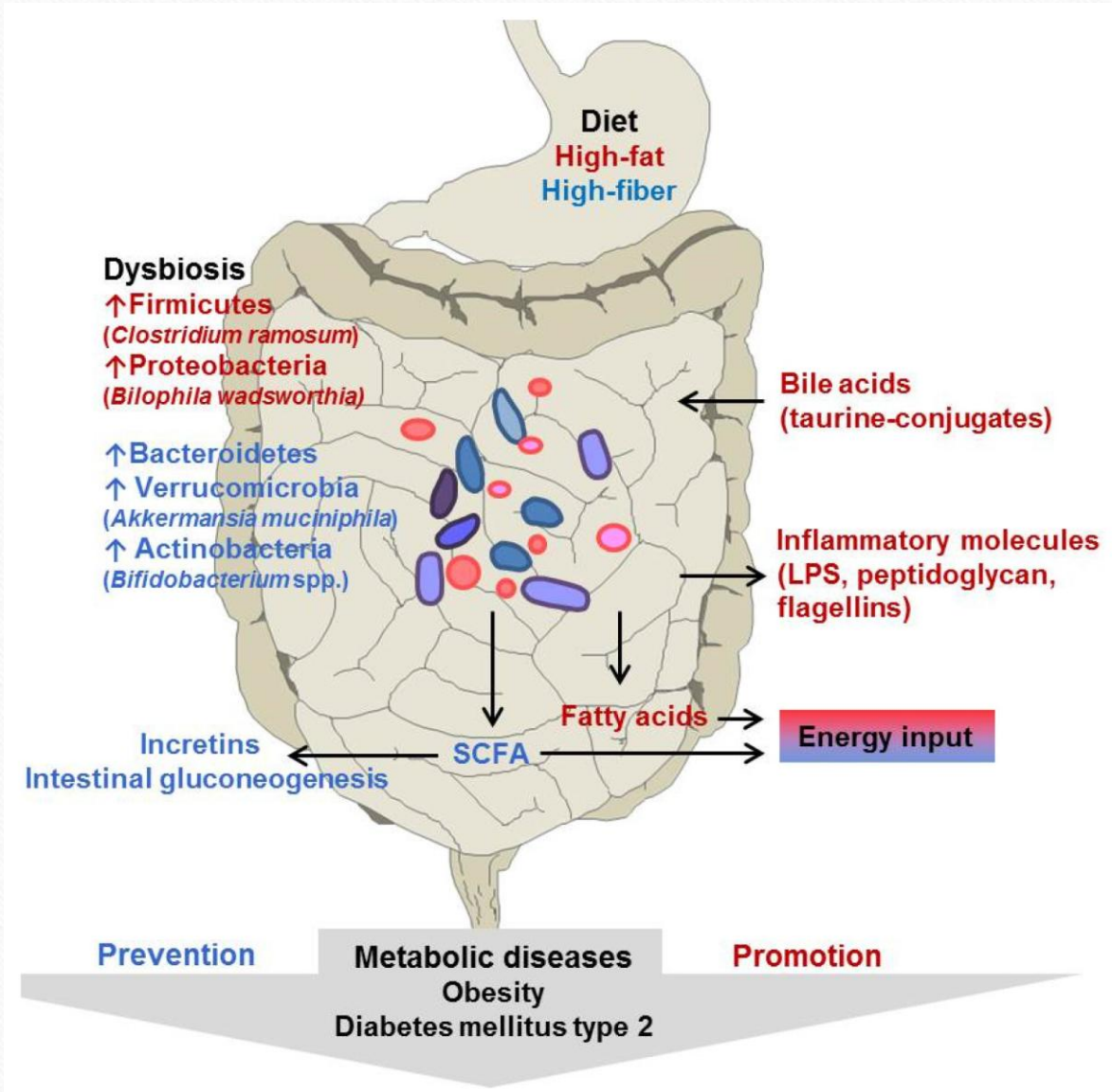
Metabolic Endotoxemia Phenomenon

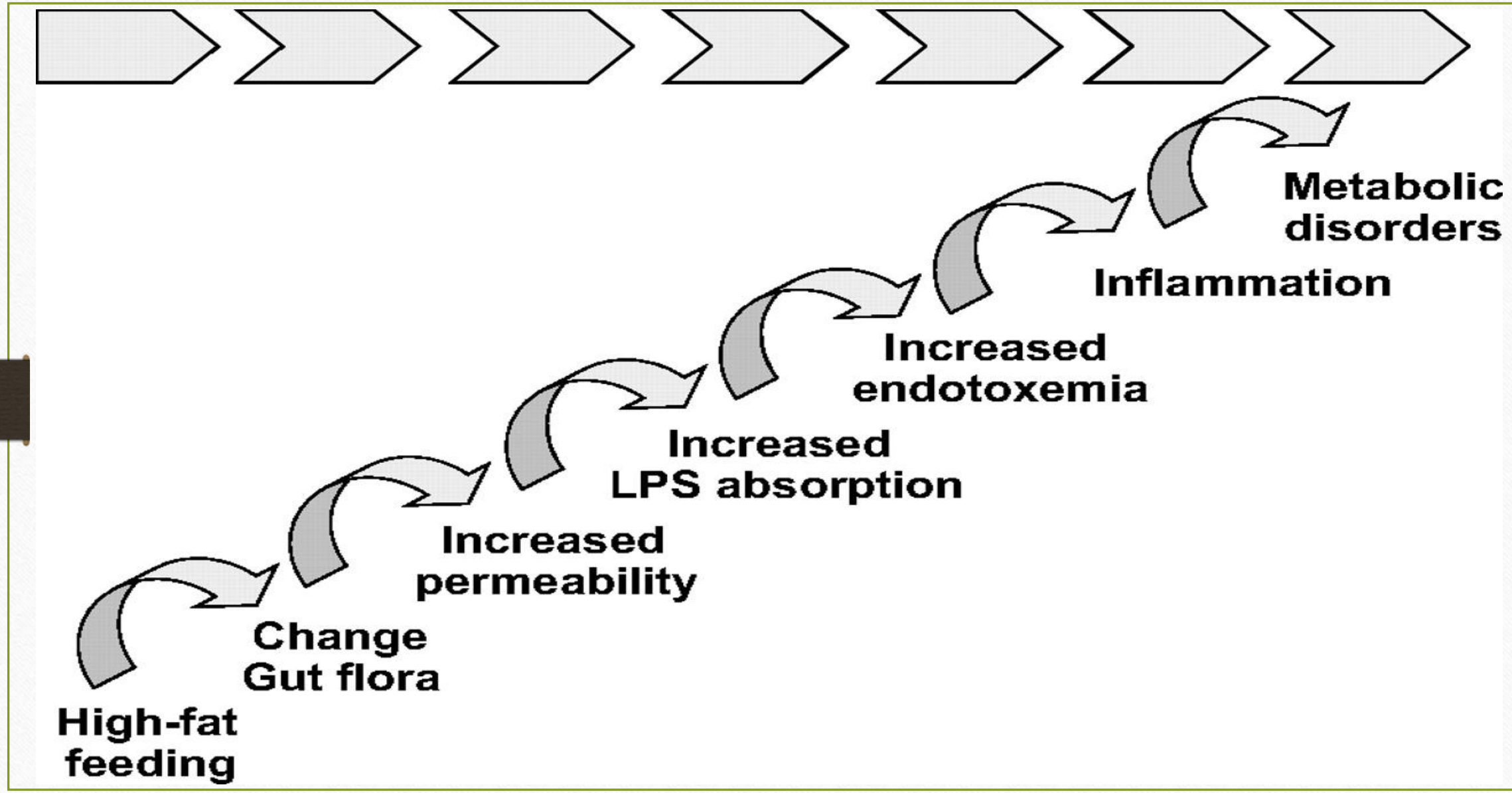
- High-fat diet (HFD) is known to translocate microbiota into a lipopolysaccharide (LPS)-enriched intestinal microbiota with a consequently elevated plasma concentration of LPS, which characterizes a state of metabolic Endotoxemia

  - Cani P, Bibiloni R, Knauf C, Waget A, Neyrinck A, Delzenne N, et al. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. Diabetes (2008) 57:1470–81.10.2337/db07-1403

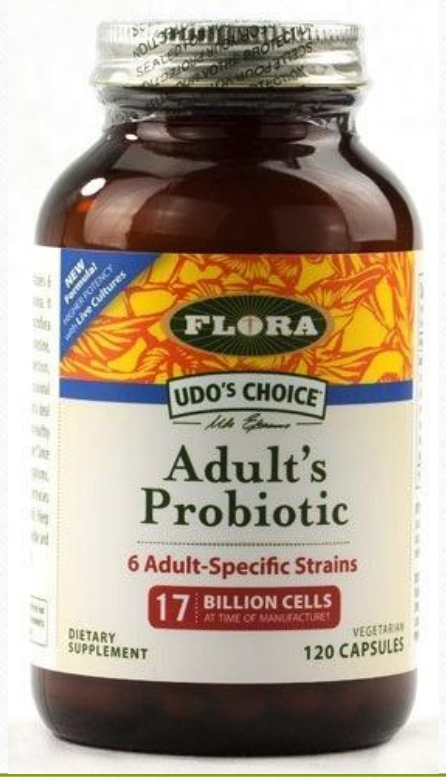
High Fiber diet will increase proportion and function of gut Microbiota

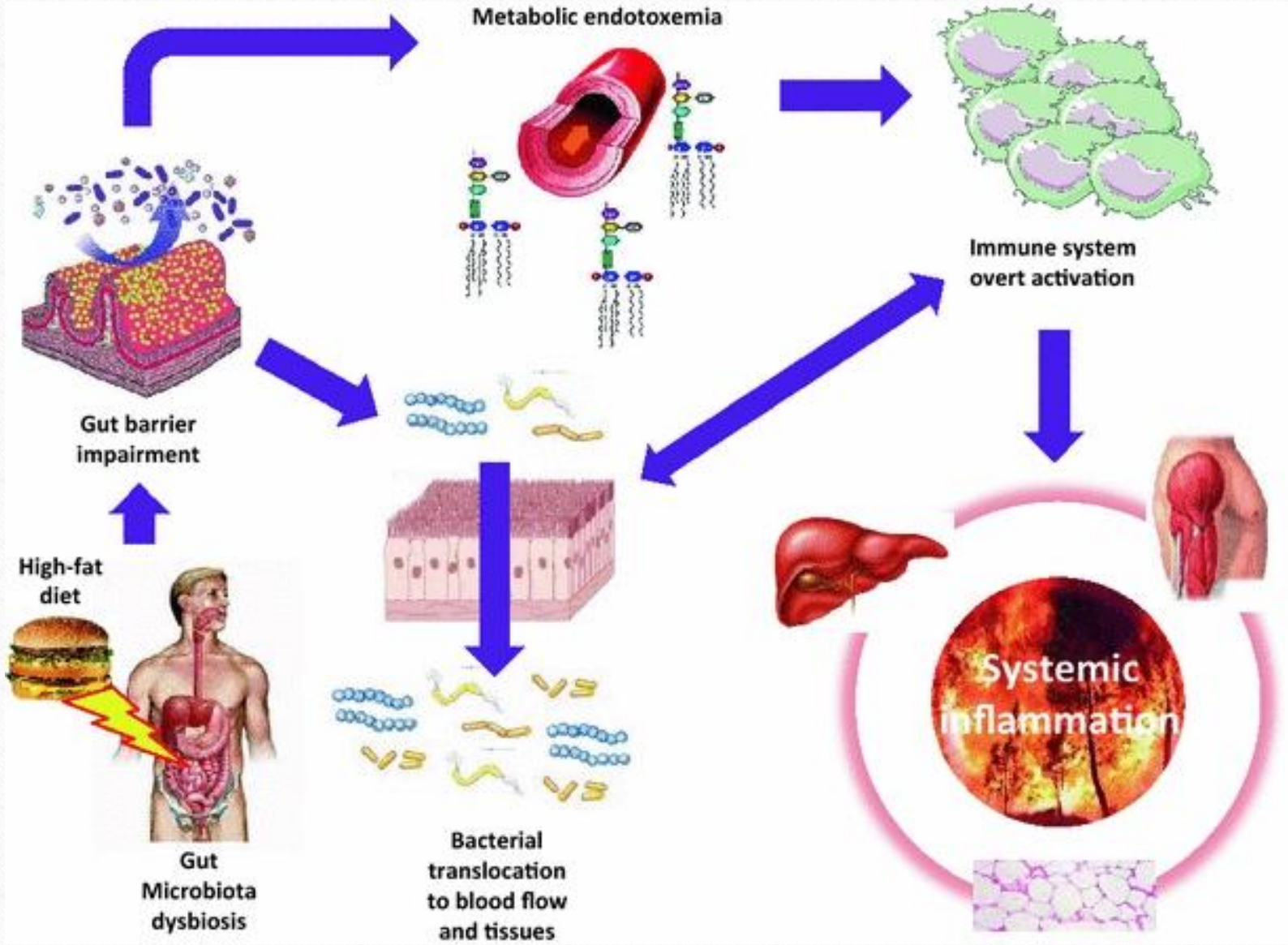


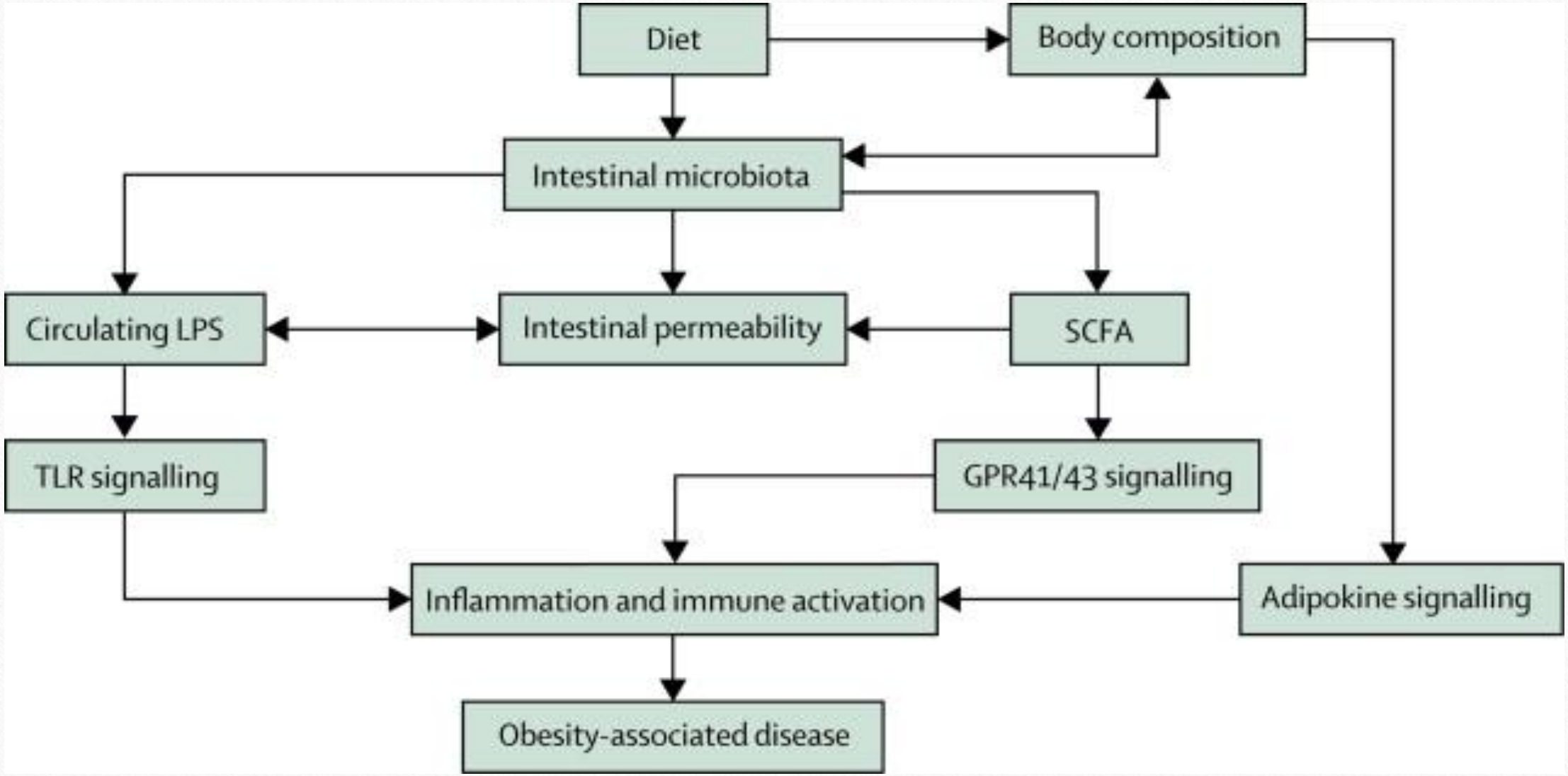

Diet
High-fat
High-fiber
Dysbiosis
↑Firmicutes
(Clostridium ramosum)
↑Proteobacteria
(Bilophila wadsworthia)
↑Bacteroidetes
↑ Verrucomicrobia
(Akkermansia muciniphila)
↑ Actinobacteria
(Bifidobacterium spp.)
Bile acids
(taurine-conjugates)
Inflammatory molecules
(LPS, peptidoglycan,
flagellins)
Fatty acids
Energy input
Incretins
Intestinal gluconeogenesis
SCFA
Prevention
Metabolic diseases
Obesity
Diabetes mellitus type 2
Promotion


High-fat feeding
Change Gut flora
Increased permeability
Increased LPS absorption
Increased endotoxemia
Inflammation
Metabolic disorders

Pre/Probiotics as for healthy intestinal microbiota

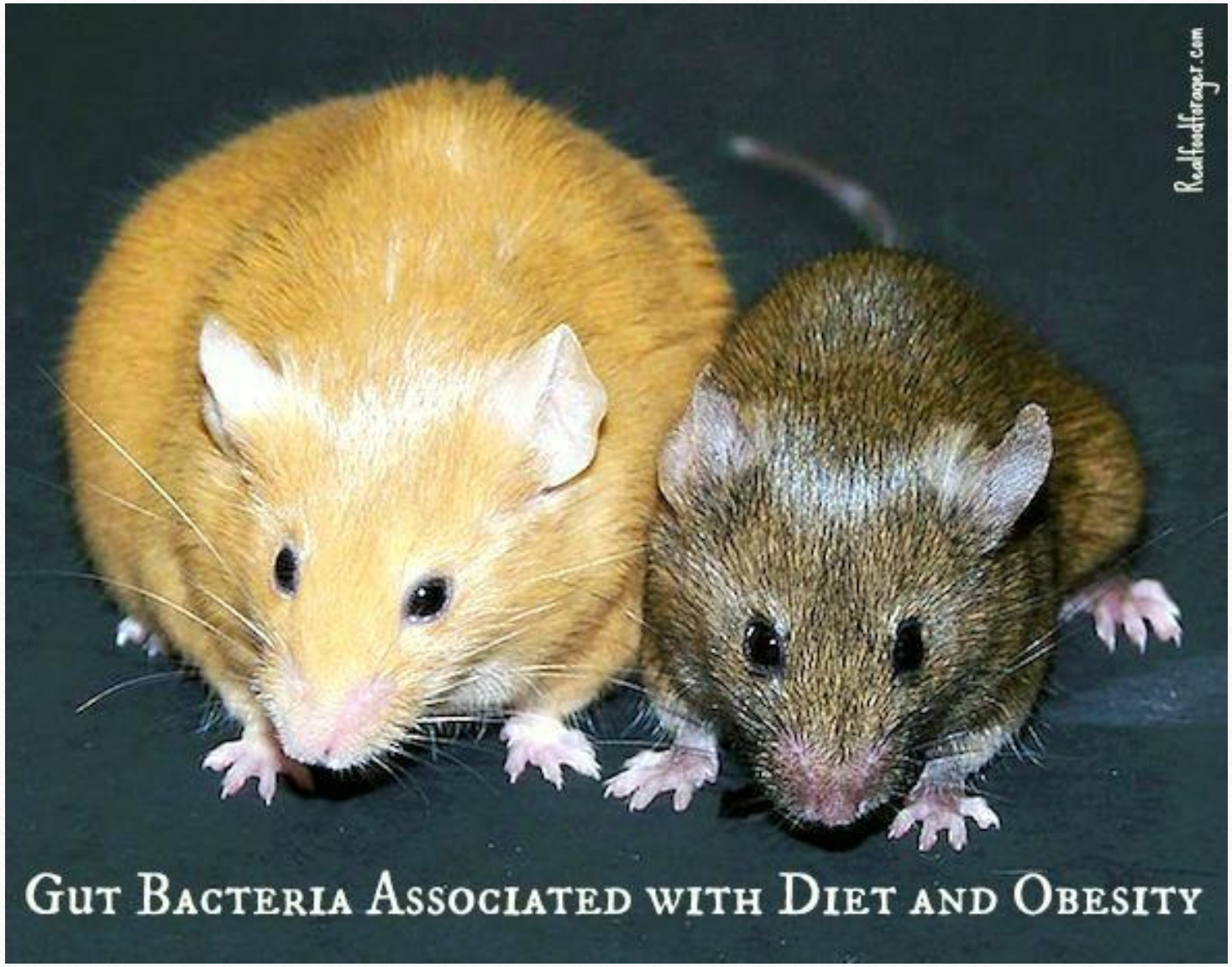


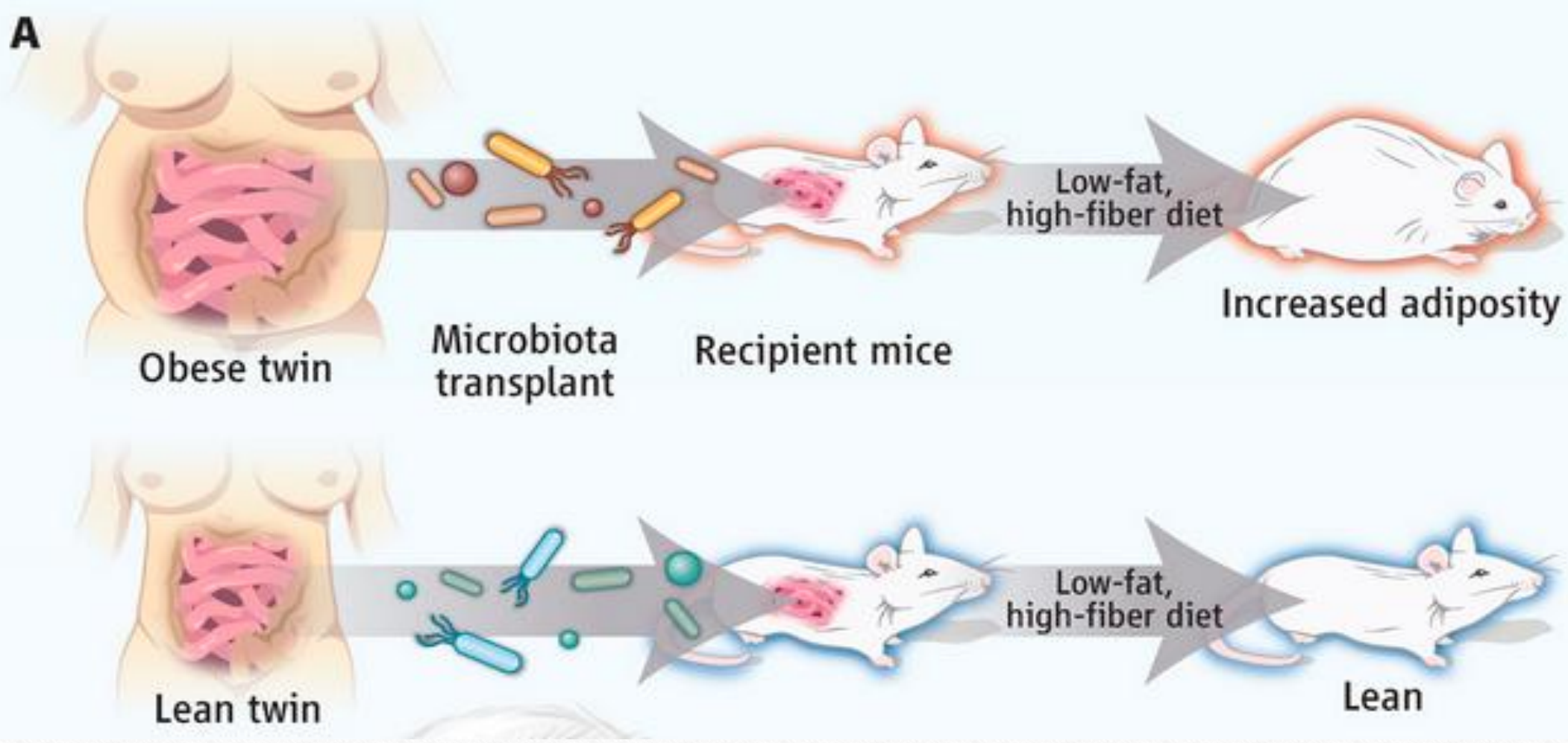

Metabolic endotoxemia
Immune system
overt activation
Gut barrier
impairment
High-fat
diet
Gut
Microbiota
dysbiosis
Bacterial
translocation
to blood flow
and tissues
Systemic
inflammation


Diet
Body composition
Intestinal microbiota
Circulating LPS
Intestinal permeability
SCFA
TLR signalling
GPR41/43 signalling
Inflammation and immune activation
Adipokine signalling
Obesity-associated disease

High Fat Diet & Type 2 Diabetes

- HFD has also been shown to cause a loss of intestinal T helper (Th) 17 cells putatively through an altered gut microbiota that interfere with the induction of Th17 cells by the antigen-presenting cells, resulting in diminished intestinal defense and integrity
- Moreover, it has been demonstrated that immunization with the HFD-associated ileum microbial extracts reversed partially gut microbiota Dysbiosis and prevented hyperglycemia and insulin resistance in response to HFD likely by enhancing the proliferation of intestinal CD4 T cells
- This underlines the potential of vaccination for preventing and managing T2DM


Realfoodforager.com
Gut Bacteria Associated with Diet and Obesity


A
Obese twin
Microbiota transplant
Recipient mice
Low-fat, high-fiber diet
Increased adiposity
Lean twin
Low-fat, high-fiber diet
Lean

Evidence connecting microbiota to the obesity and TDM2

- ✓ "MT from obese humans increased fat deposits in lean recipients" (Ridaura et al., 2013).
- "Obesity and IR in mice could be significantly reduced by diminishing the gut microbiota with BS antibiotics" (Cani et al., 2008).
- ✓ "MT from healthy donors improved insulin resistance in the first six weeks in diabetic human volunteers" (Vrieze et al., 2012).
- "A whole-grains diet,reduces endotoxin producers and enrich beneficial bifidobacteria in the gut of obese adult human volunteers, leading to significant alleviation of inflammation, adiposity and IR. (Xiao et al., 2014, Fei and Zhao, 2013).

Conclusion "Dysbiosis of gut Microbiota & obesity with type 2 DM"

- As the dysbiosis of gut microbiota is increasingly appreciated as a mechanism accounting for metabolic diseases, the growing understanding of microbiota-driven immune and metabolic responses has begun to reveal potential interventional targets, sustaining the development of new therapeutic strategies by dietary and/or pharmacological means

Conclusion "Dysbiosis of gut Microbiota & obesity with type 2 DM"

- Dietary intervention (e.g., prebiotics, probiotics, and postbiotics) and fecal microbiota transplantation that tackle microbiota Dysbiosis
- Manipulation of the key players in the intestinal integrity and function, bacterial recognition and translocation, tissue inflammation, and host nutrient-sensing mechanisms by using :
  - recent reports about vaccination and genetic modulation of the gut microbial metabolites further add to our knowledge of the therapeutics of metabolic diseases

The "Perfect Storm" for Type 1 Diabetes
The Complex Interplay Between Intestinal Microbiota, Gut Permeability, and Mucosal Immunity

Dysbiosis of gut Microbiota & type 1 diabetes

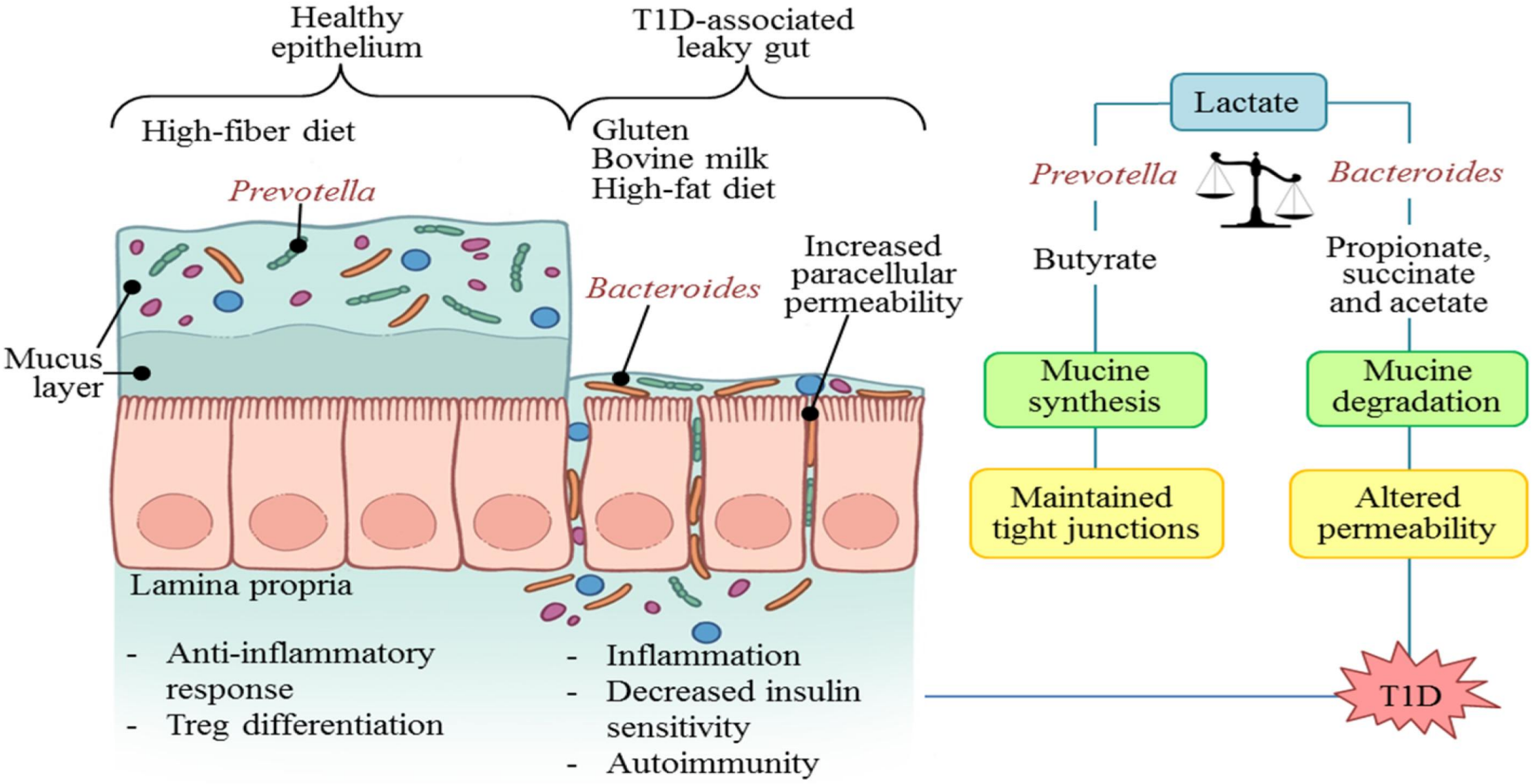
- Recent data showed the critical role of the gastrointestinal microbiota in the protection or the triggering of type 1 diabetes
- In both models, the target pancreatic insulin producing beta cells are attacked and destroyed by activated immune cells, leading to type-1 diabetes.
- In human, the incidence of type 1 diabetes has increased during the past several decades in developed countries where environmental conditions have dramatically changed

Dysbiosis of gut Microbiota & type 1 diabetes

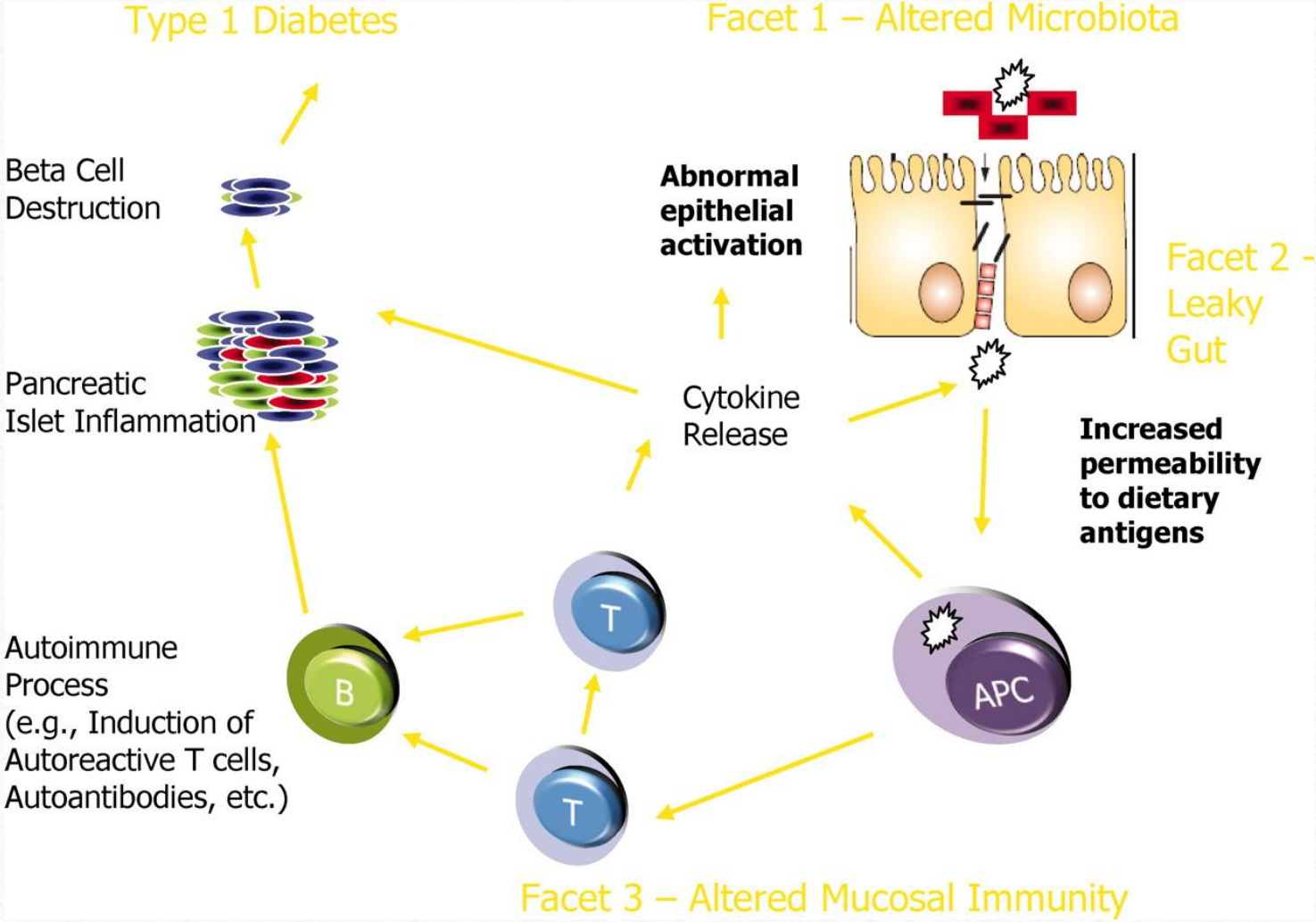
- Increased intestinal permeability has been observed in animal models of type 1 diabetes as well as in humans with or at increased-risk for the disease
- An altered mucosal immune system has been associated with the disease and is likely a major contributor resulting in the autoimmunity that underlies type 1 diabetes

Dysbiosis of gut Microbiota & type 1 diabetes

- This hypothesis suggests that bacterial antigens would be presented by the innate immune system to the T lymphocytes very early in life supporting the notion that immunostimulation can benefit the maturation of the postnatal immune system
- Consequently, in case of misrecognition of the bacterial antigen, the adaptive immune system will be exacerbating its aggressiveness against the pancreatic cells and destroy them
- Consequently, the recognition of bacterial determinants from intestinal Microbiota would be a triggering factor of autoimmune disease
- The Toll-like receptors (TLRs) are innate pattern-recognition receptors involved in host defense that control over commensal bacteria and maintain tissue integrity
- The corresponding signaling molecule is MyD88 adaptor, therefore mice lacking this molecular mechanisms were protected against insulitis


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
Lactate
Prevotella
Bacteroides
Butyrate
Propionate, succinate and acetate
Mucine synthesis
Mucine degradation
Maintained tight junctions
Altered permeability
T1D

Hypothetical model of the contribution of various gut components to the pathogenesis of type 1 diabetes.



Outi Vaarala et al. Diabetes 2008;57:2555-2562

American Diabetes Association.

Conclusion

- Clearly, much work remains in terms of understanding the role of the gut in type 1 & type 2 diabetes development.
- Despite numerous studies showing health benefits of probiotics, the enthusiasm for their application as well as other means to alter the intestinal microbial ecosystem in the prevention of diabetes needs to be tempered due to the current lack of knowledge of the normal developing intestinal microbiota, in addition to questions as to how it affects the developing immune system

Conclusion /Future understanding

- Future studies using newly developed techniques to evaluate intestinal Microbiota, coupled with the rapidly emerging fields of proteomics and metabolomics, are certainly needed
- Finally, the role of gut as modulator of –cell autoimmunity, and/or as the place for initiation of –cell autoimmunity, should provide new understanding of the changing incidence of type 1 diabetes at different times and in different populations

Thank You