

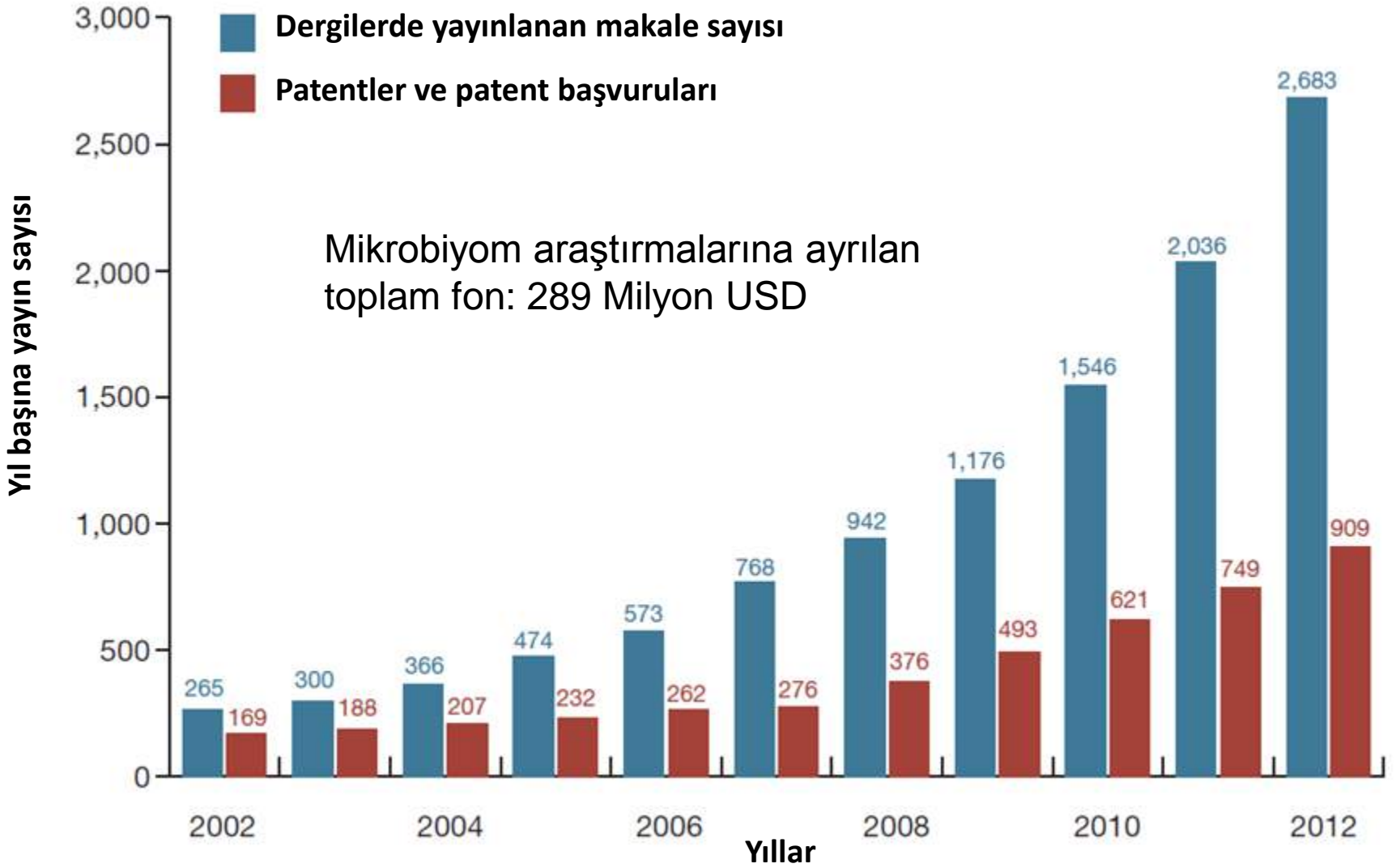


# Mikrobiyotaya Yakından Bakış ve İnsan Fizyolojisindeki Rolü

Osman Şadi YENEN

24 Nisan 2015

mycobiome *Roseburia intestinalis* beta diversity  
inflammaging meta-organism *B. thetaiotaomicron*  
Enzyme Commission eubiosis *Firmicutes* bioinformatics  
autobiont super-organism operational taxonomic units  
MetaHIT human microbiome project symbiont  
microbiota colonization resistance metabotypes  
virome whole genome shotgun sequencing  
supra-organism 16S rRNA contigs  
abundance metagenome  
Kyoto Encyclopedia of Genes and Genomes  
physiological inflammation Clusters of Orthologous Groups  
IMMUNOLOGICAL SCHIZOPHRENIA microbiome resilience  
demilitarization zone dysbiosis alpha diversity  
ENTEROTYPES *Faecalibacterium prausnitzii* Archaea  
Machine learning phylotypes *Bacteroidetes*  
amphibiosis pathobiont Gnotobiotics Exposome



***Microbiome, microbiota, gut flora, ya da gut microflora* anahtar sözcükleriyle saptanan yayınlar ve patentler ya da patent başvuruları (International Patent Documentation Center, INPADOC, verileri)**





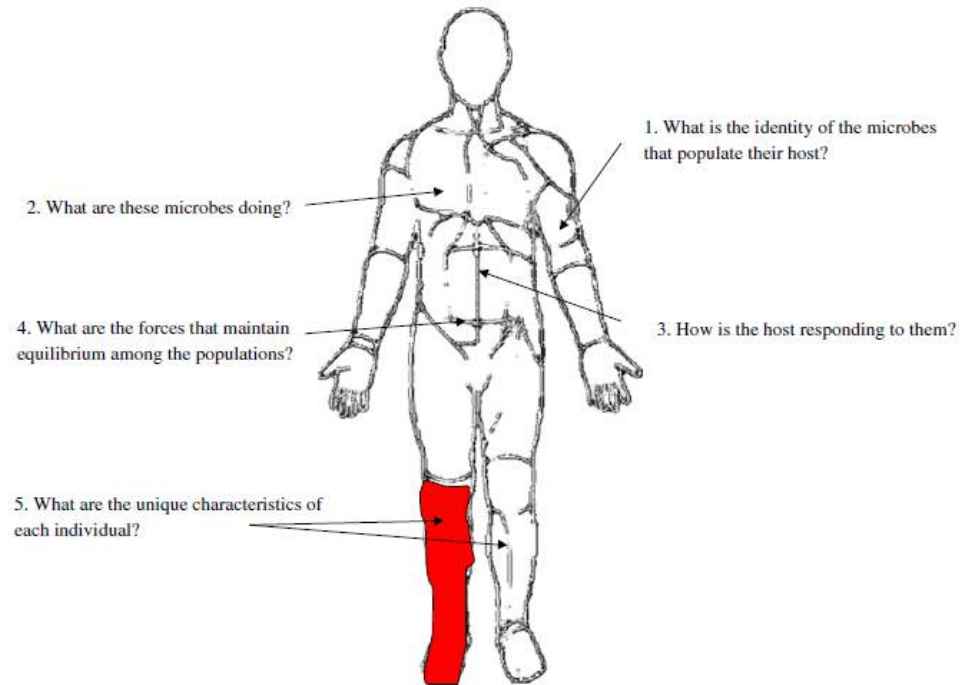
- **40 trilyon insan hücresi**
  - **22.000 insan geni**
  - **100 trilyon mikrop hücresi**
  - **9.8 milyon mikrop geni**
- 
- Evrendeki yıldızlar:  $\sim 10^{21}$
  - Vücudumuzdaki moleküller:  $\sim 10^{27}$
  - Vücudumuzdaki mikroplar:  $\sim 10^{14}$
  - Bağırsamımızdaki bakteriyofajlar:  $10^8-10^{10}$

EDITORIAL

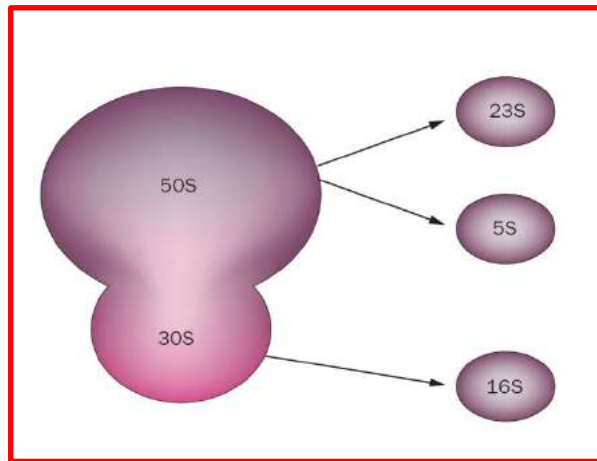
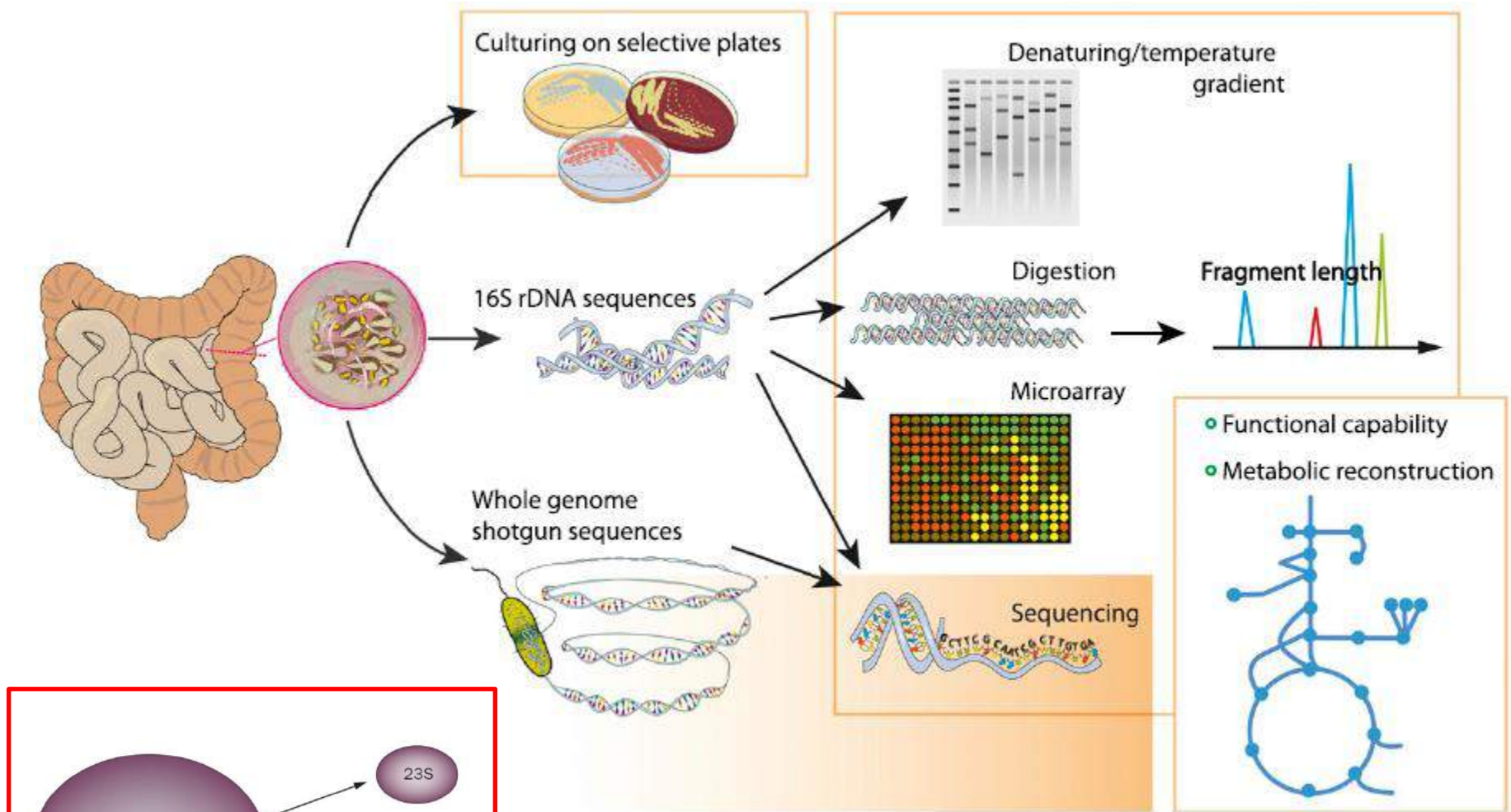
# ***Homo bacteriens* and a network of surprises**

B. HENDERSON and M. WILSON

**‘Unutulmuş organ’  
‘Son insan organı’  
‘Metabolik organ’**

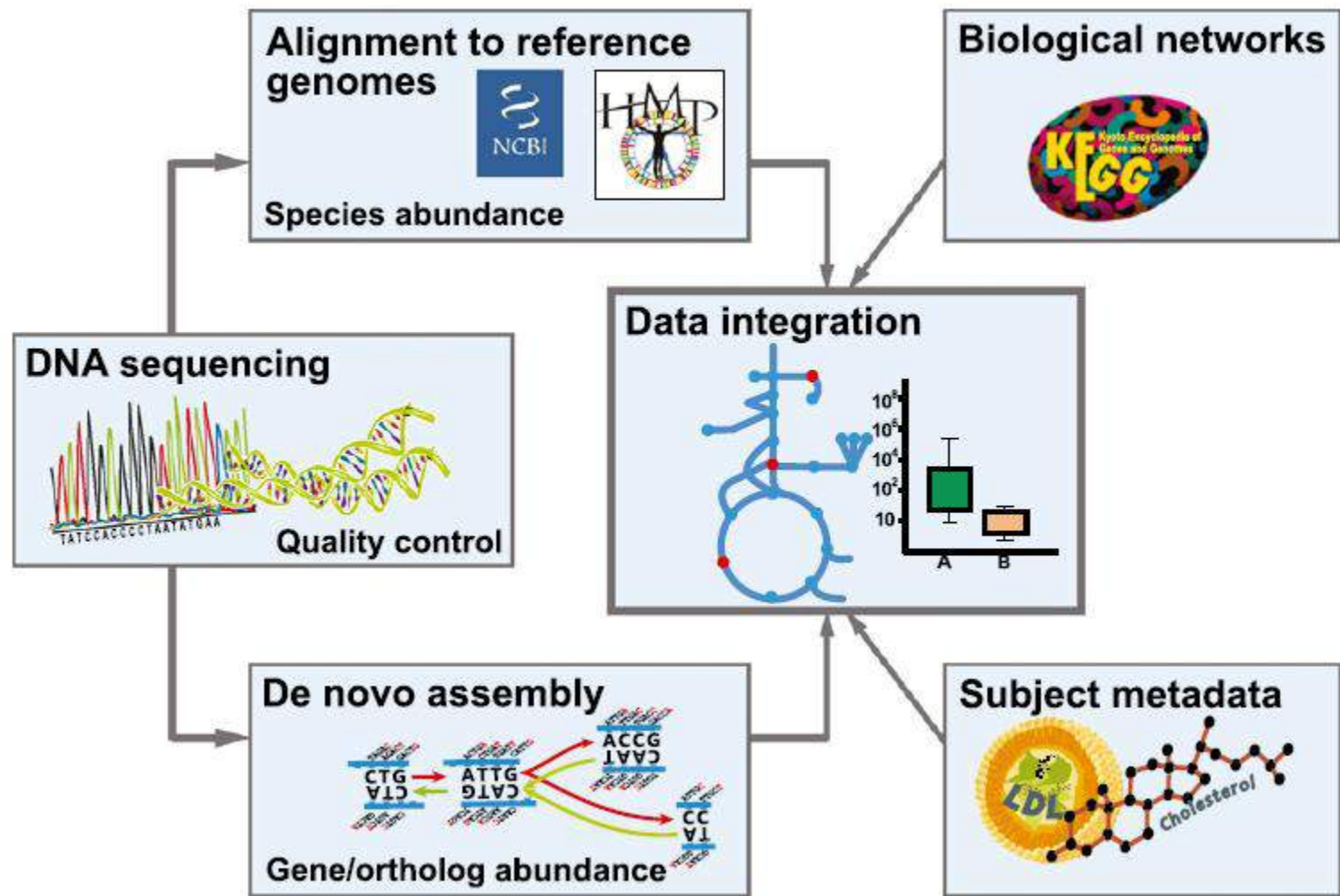


*(Blaser MJ: 2010)*



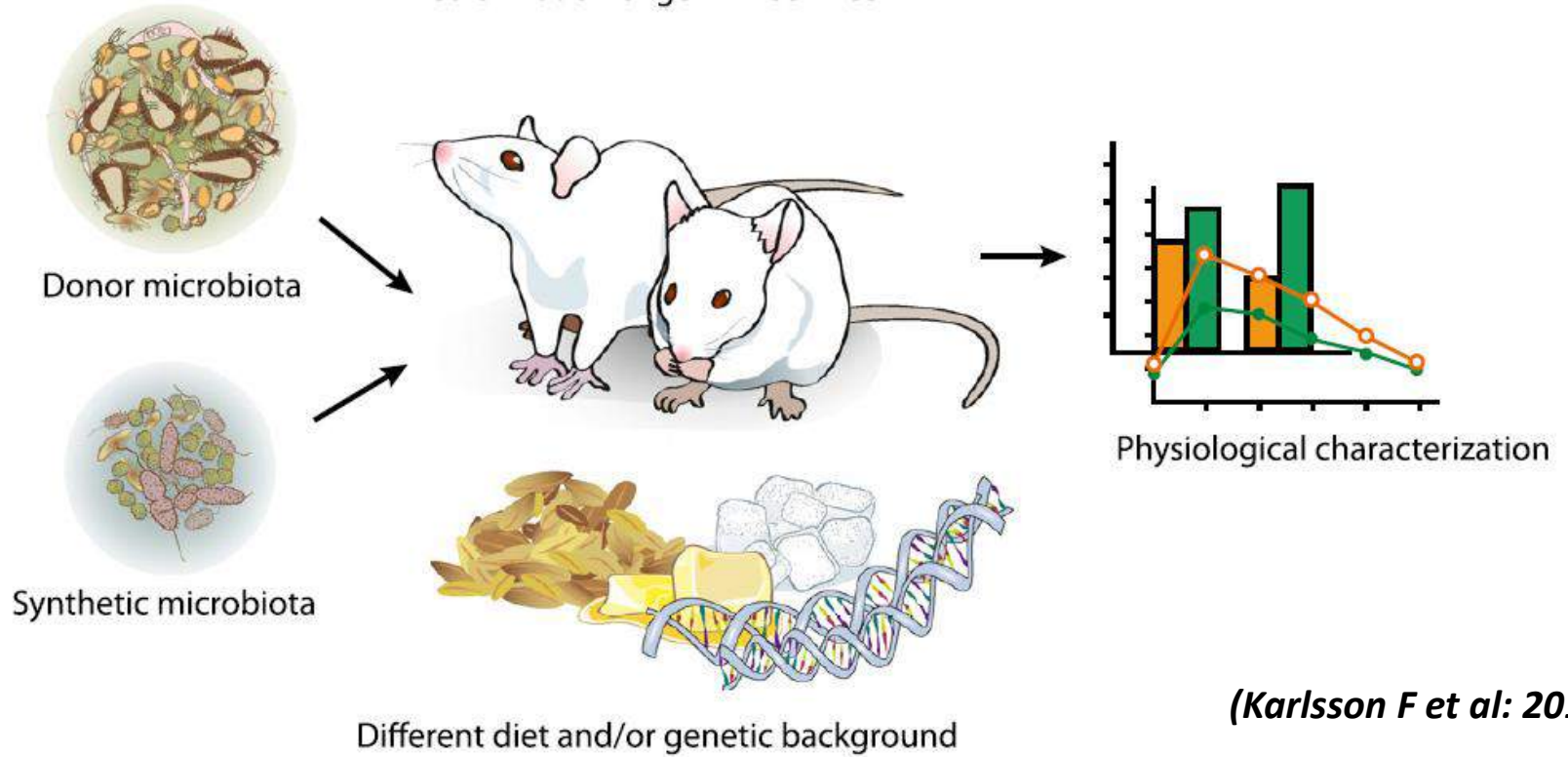
## Methods for studying the microbiota



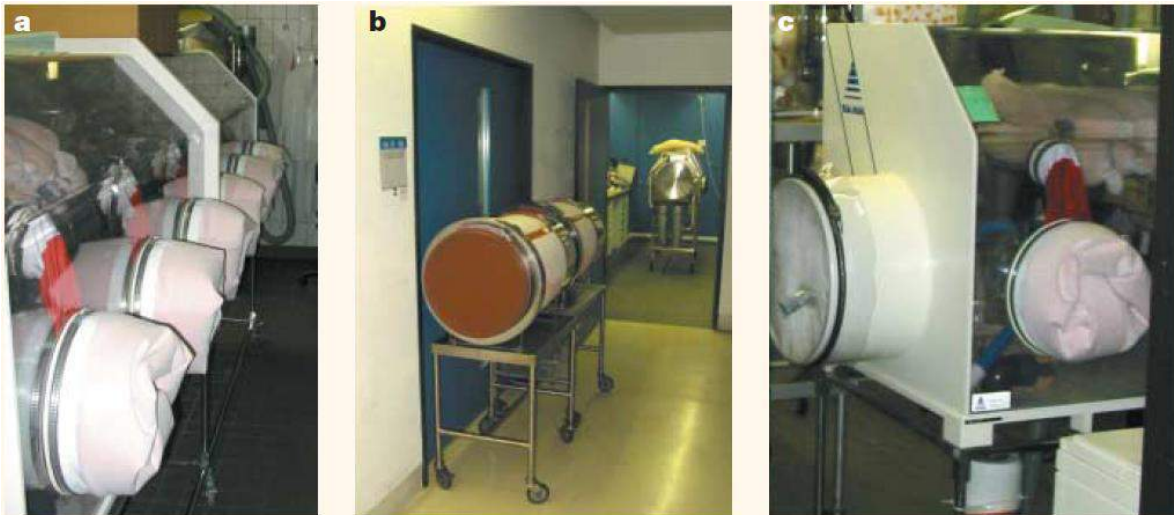


Bioinformatic pipeline for analysis of whole metagenome shotgun sequences

# Colonization of germ-free mice



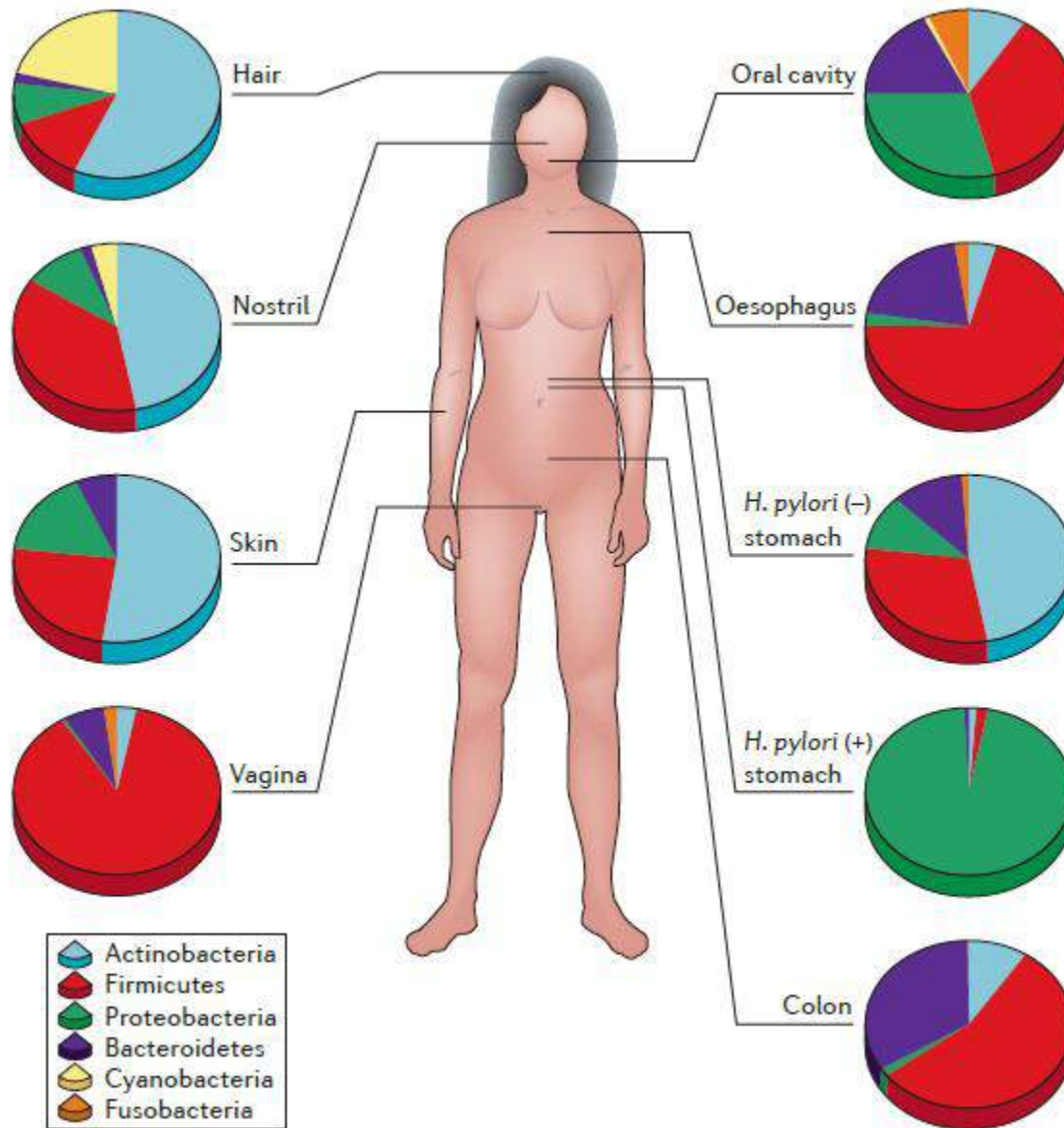
*(Karlsson F et al: 2013)*



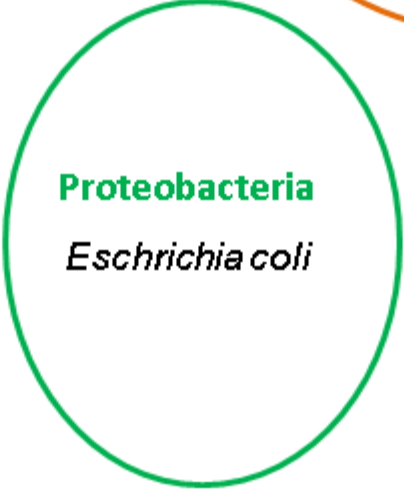
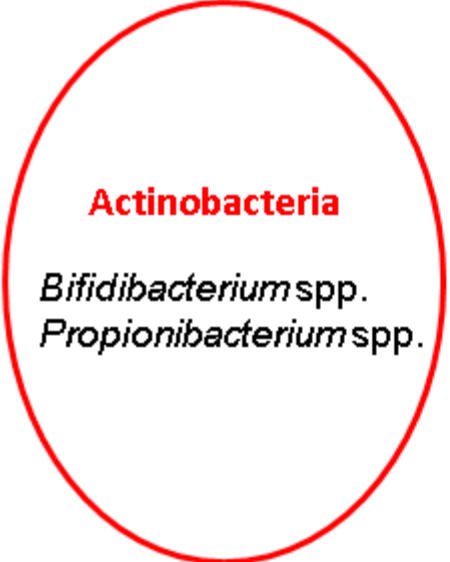
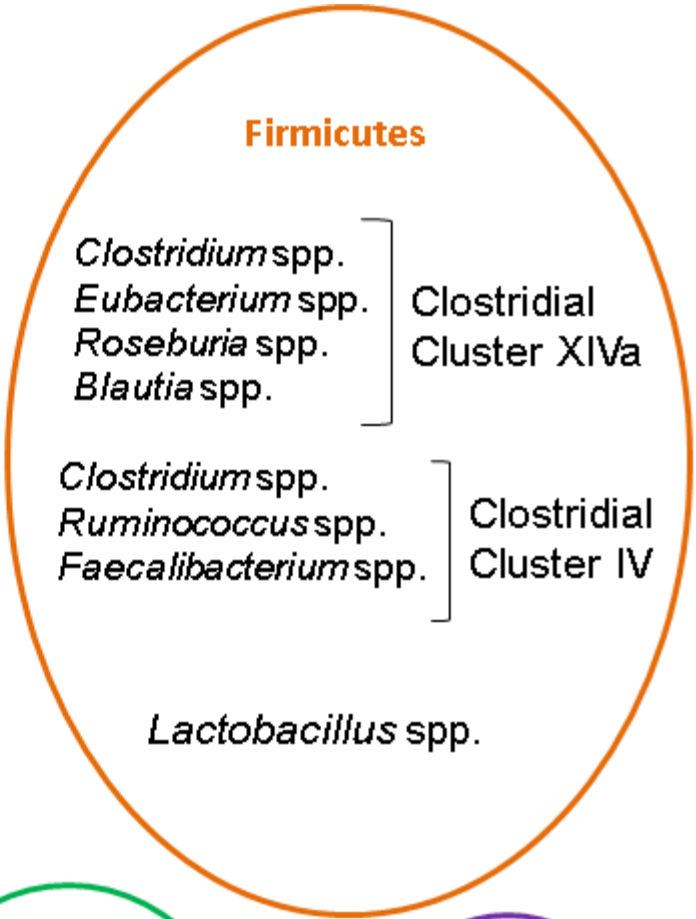
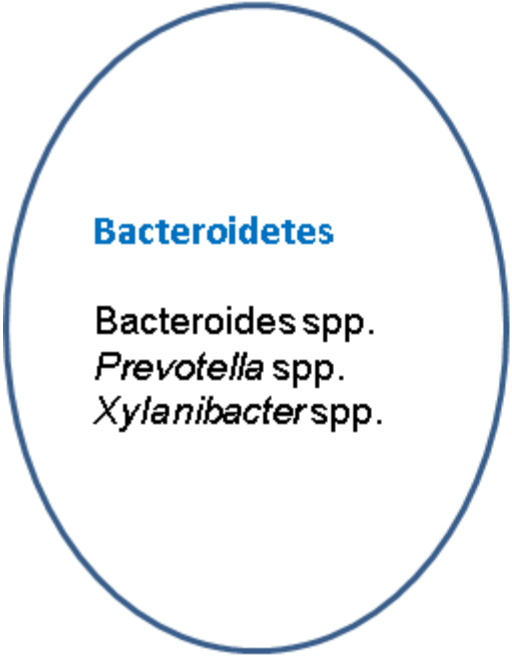
**Keeping germ-free mice in an isolator**

*(Macpherson AJ, Harris NL: 2004)*



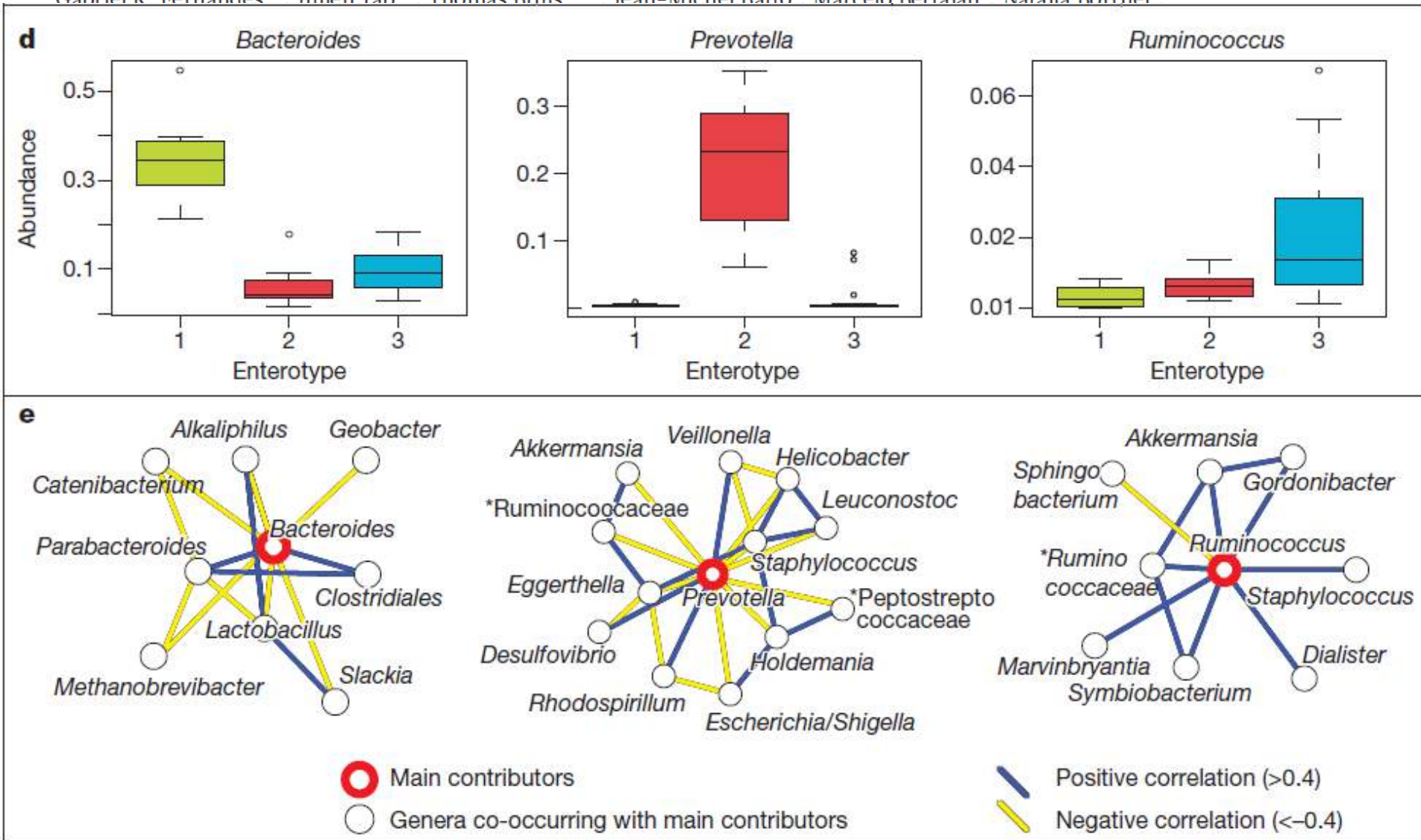


**Compositional differences in the microbiome by anatomical site**



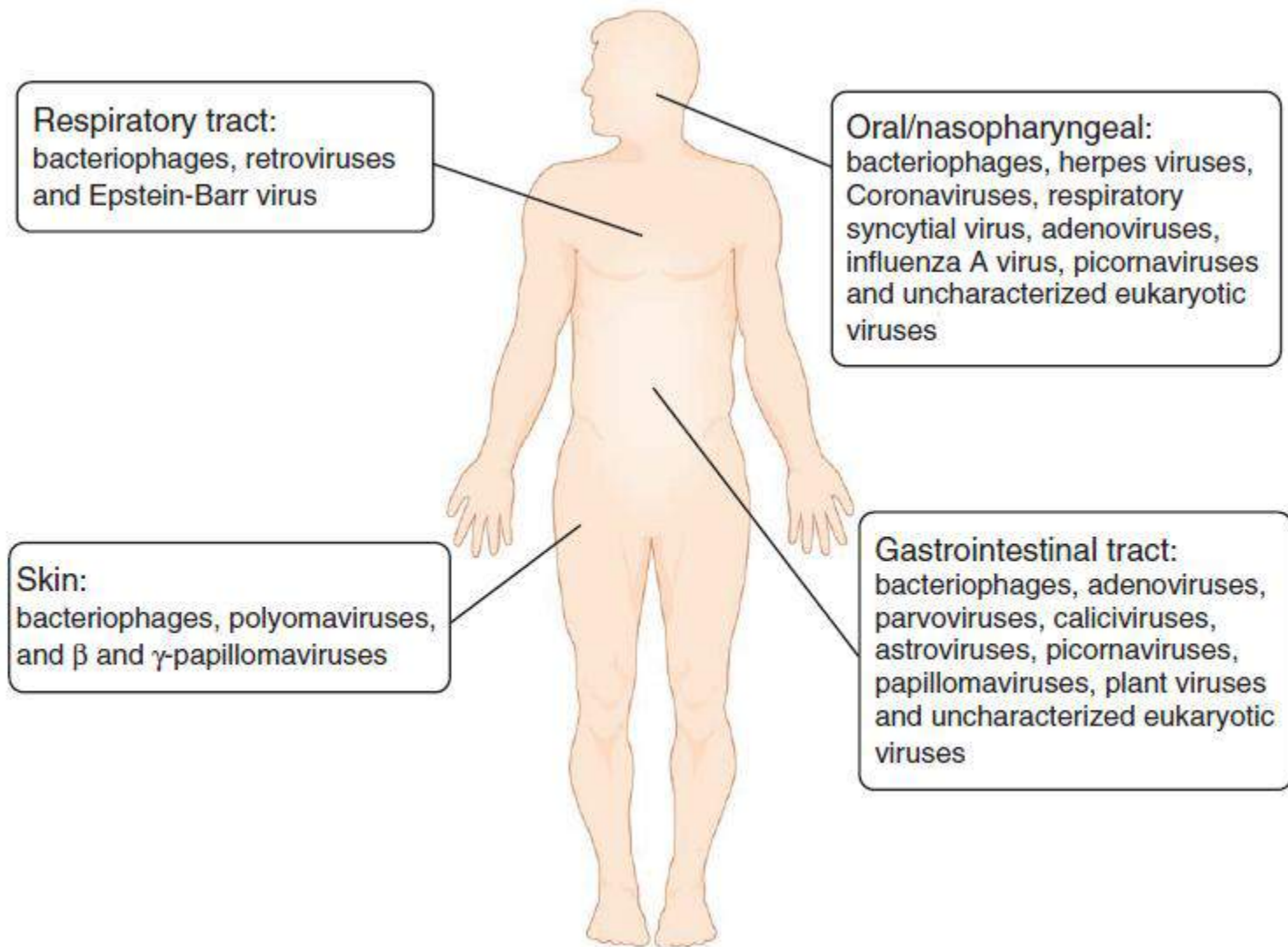
# Enterotypes of the human gut microbiome

Manimozhiyan Arumugam<sup>1\*</sup>, Jeroen Raes<sup>1,2\*</sup>, Eric Pelletier<sup>3,4,5</sup>, Denis Le Paslier<sup>3,4,5</sup>, Takuji Yamada<sup>1</sup>, Daniel R. Mende<sup>1</sup>, Gabriel R. Fernandes<sup>1,6</sup>, Julien Tan<sup>1,7</sup>, Thomas Bruis<sup>3,4,5</sup>, Jean-Michel Ratto<sup>7</sup>, Marcelo Bertalan<sup>8</sup>, Natalia Borrue1<sup>9</sup>



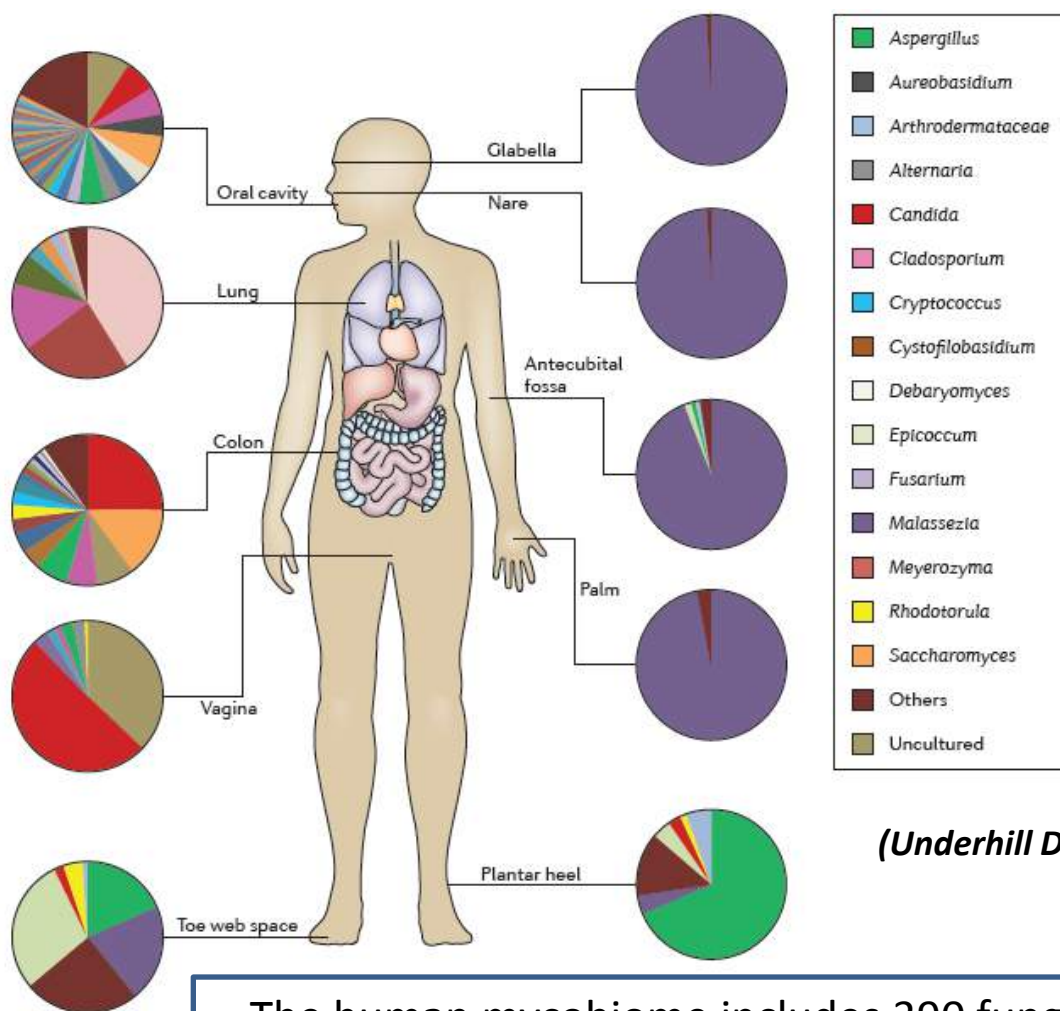
(Nature 2011; 473: 174-180)





## Anatomical locations of resident viruses in humans

# The human mycobiota



(Underhill DM, Iliev ID: 2014)

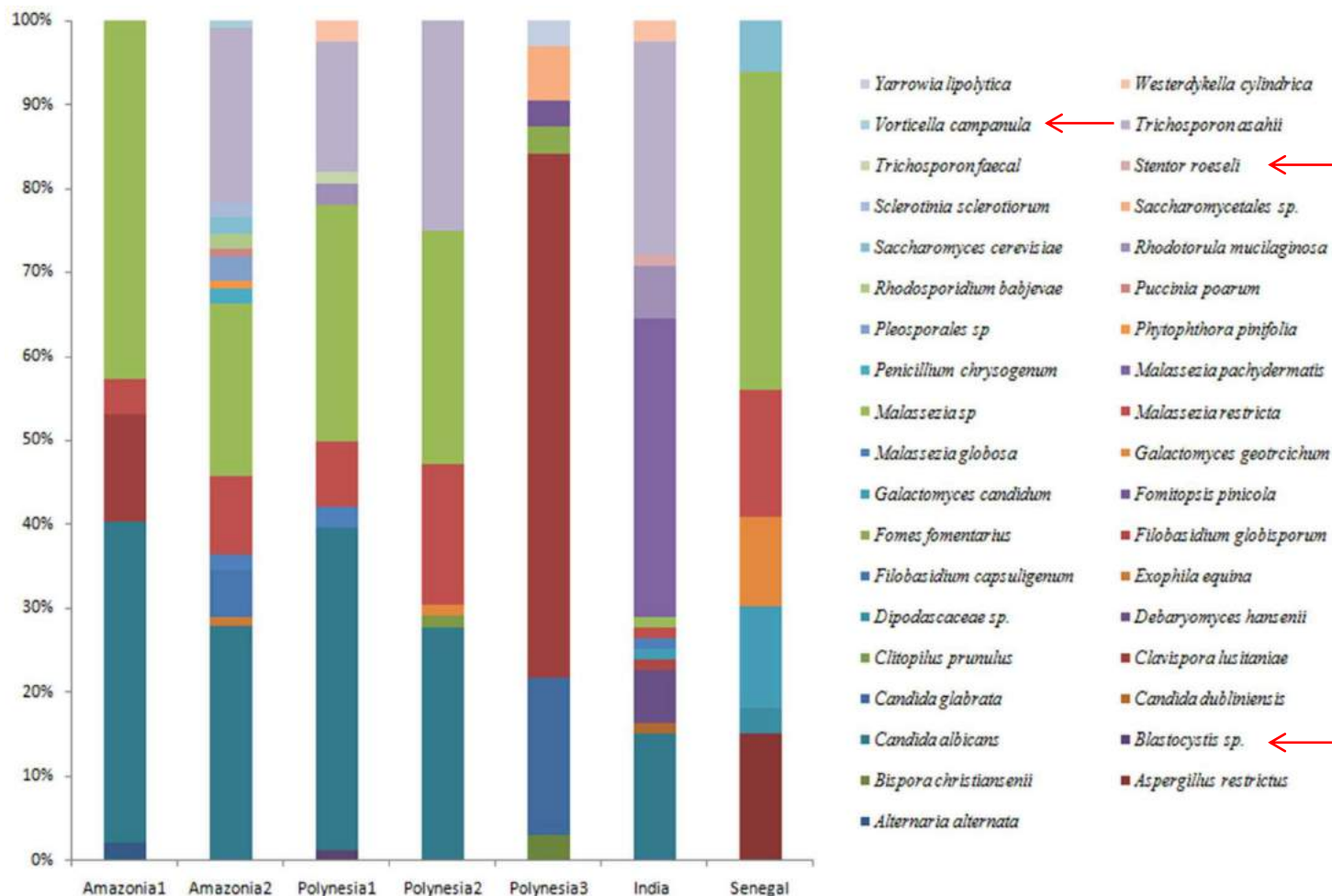
The human mycobiome includes 390 fungal species detected on the skin, in the vagina, in the oral cavity, and in the digestive tract that includes 335 species and 158 genera. Among these, **221 species are found only in the digestive tract, 88 only in the oral cavity, and 26 in both.** These species belong to 126 genera of yeast and filamentous fungi, of the Ascomycota, Basidiomycota, and Zygomycota phyla.

(Gouba N, Drancourt M: 2015)

# Eukaryote Culturomics of the Gut Reveals New Species

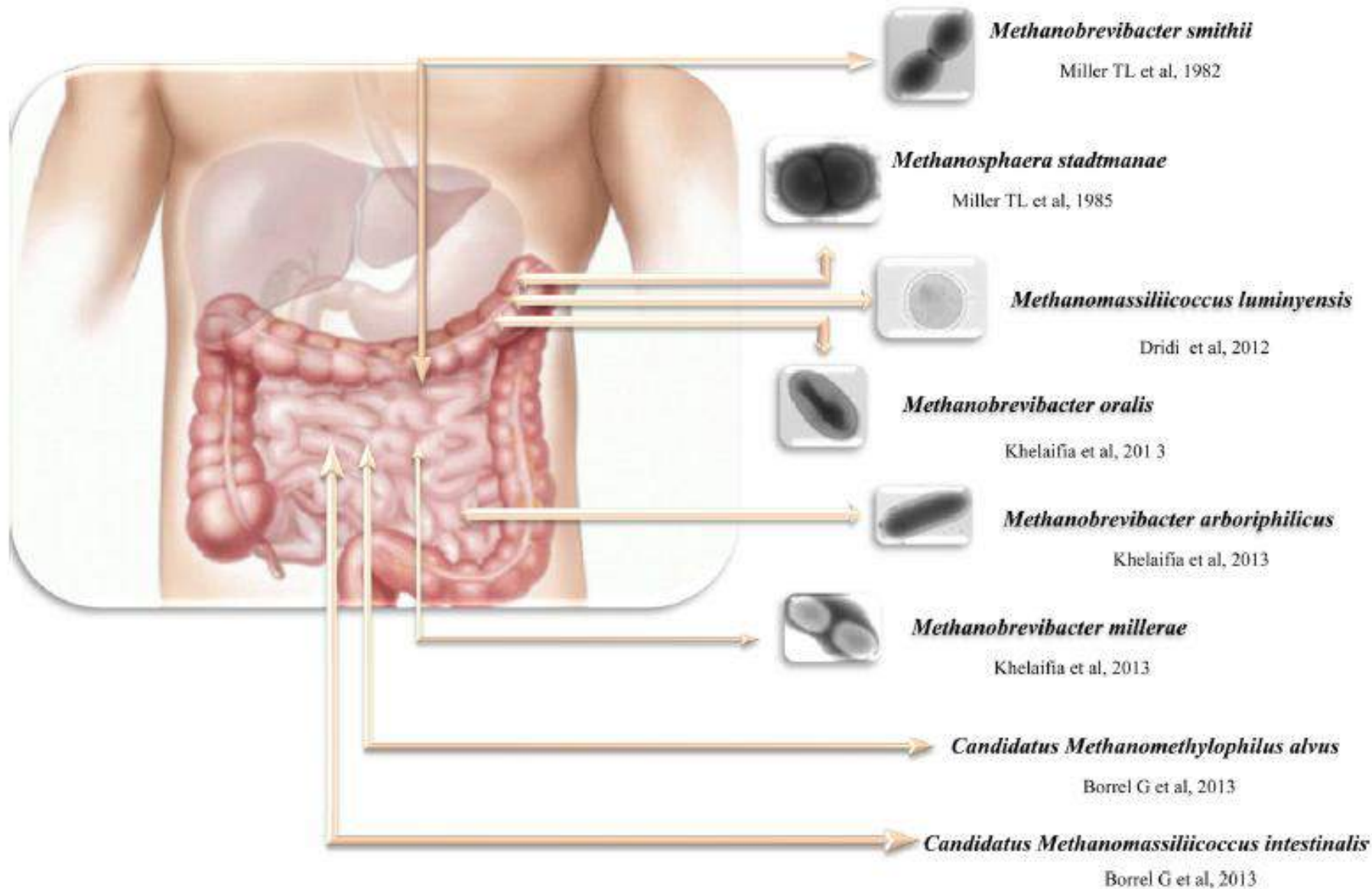
Nina Gouba, Didier Raoult, Michel Drancourt\*

A total of 41 microeukaryotes including 38 different fungal species and three protists were detected.



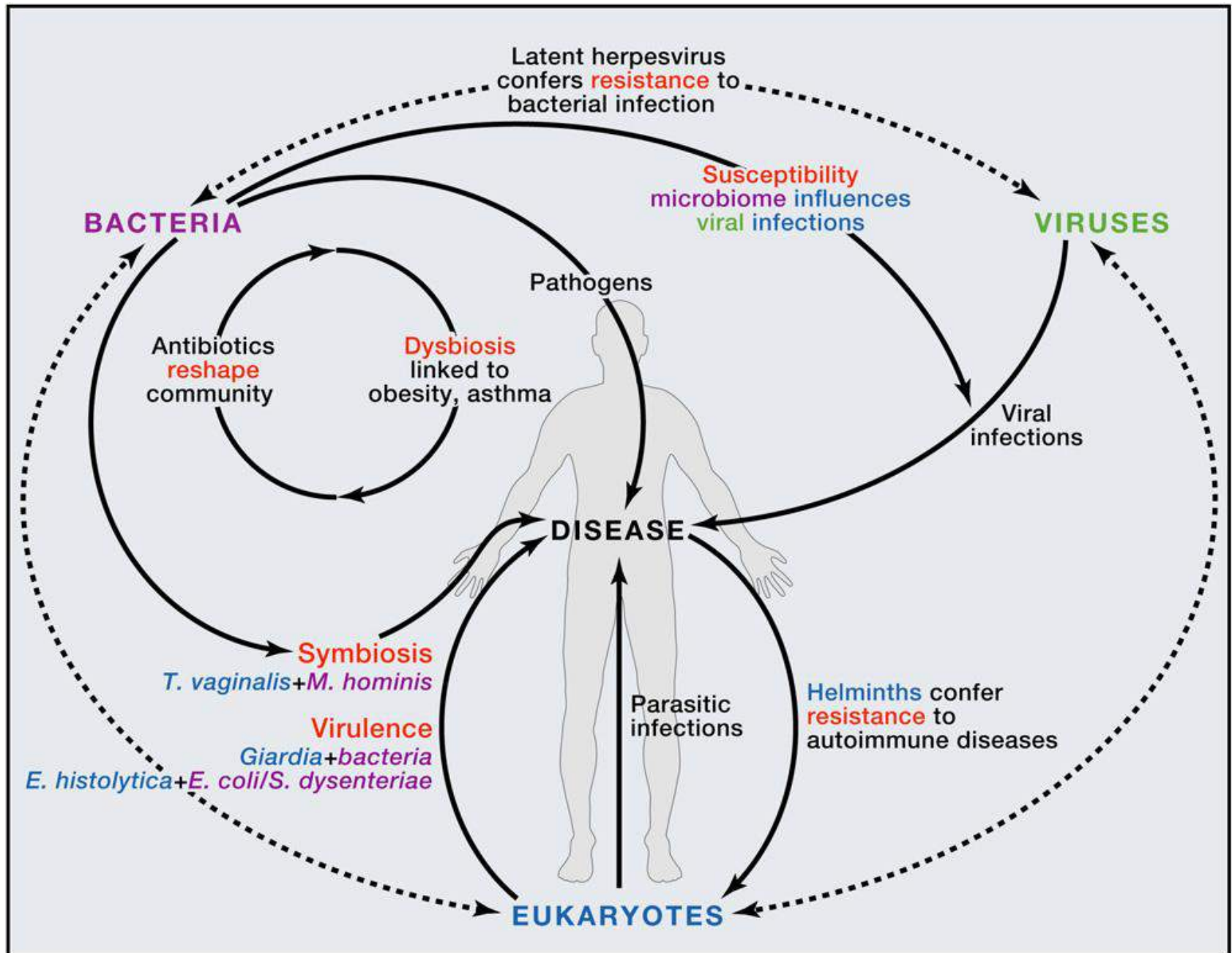
(Gouba N et al: 2014)





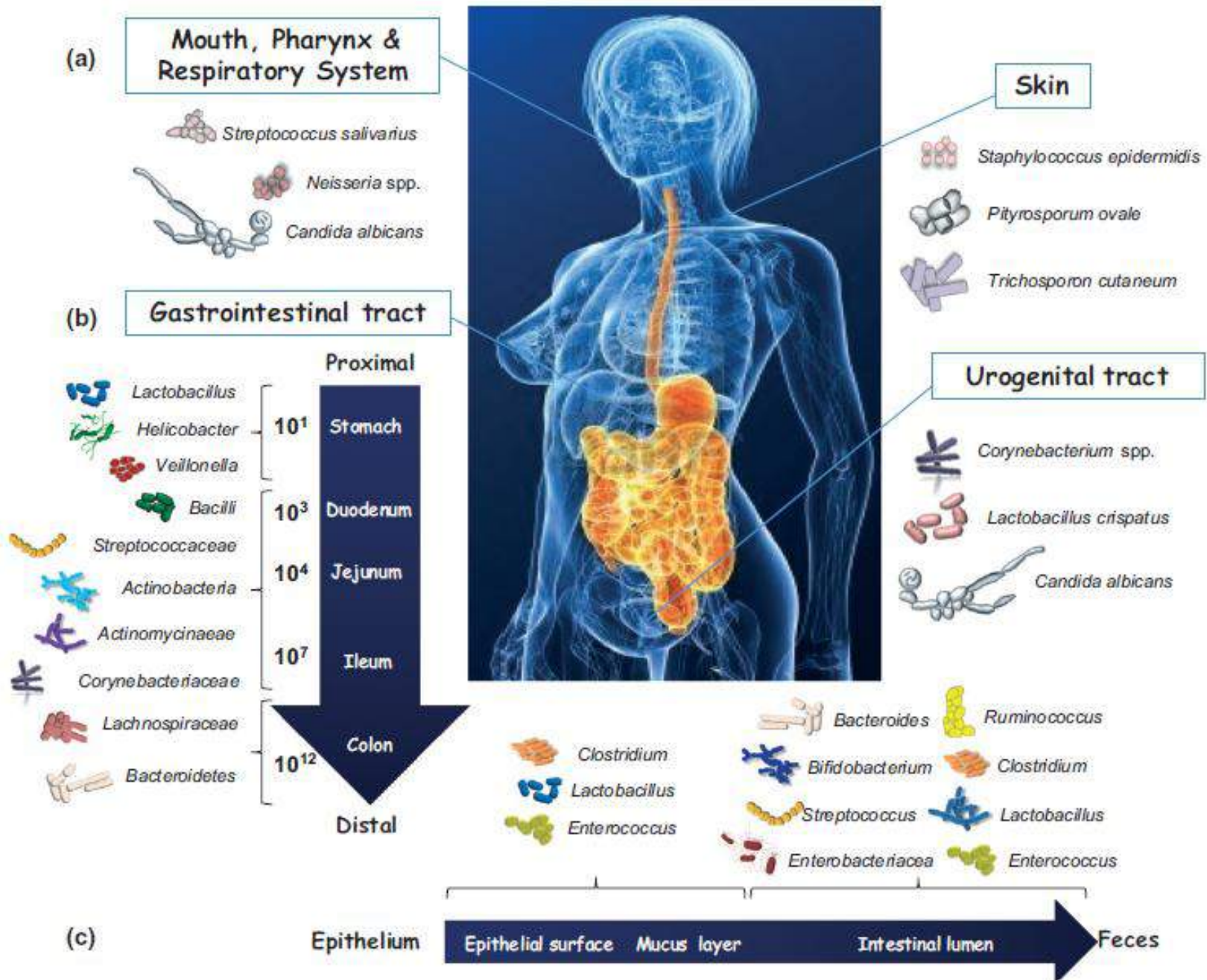
## Archaeal species detected in or cultured from the human gut

(Lagier J-C et al: 2015)

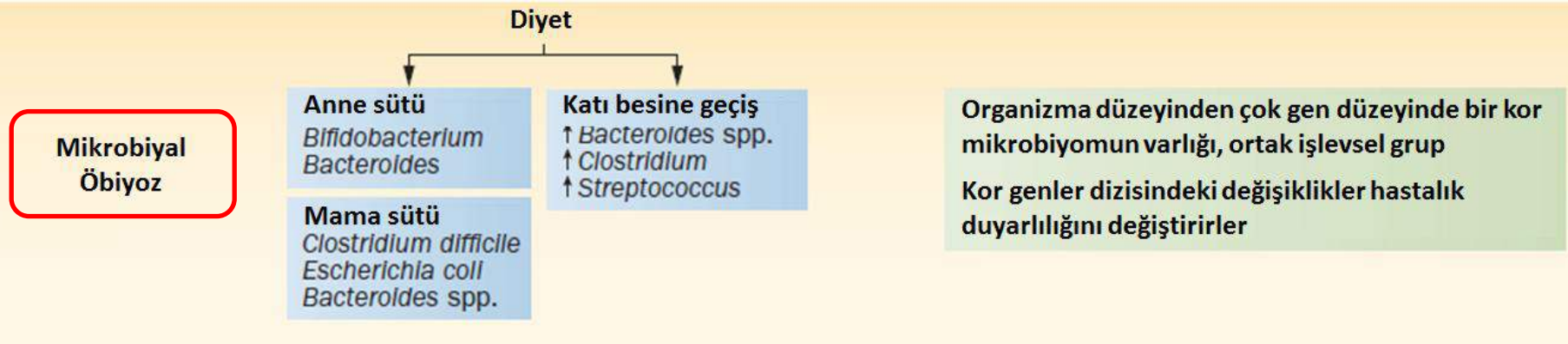
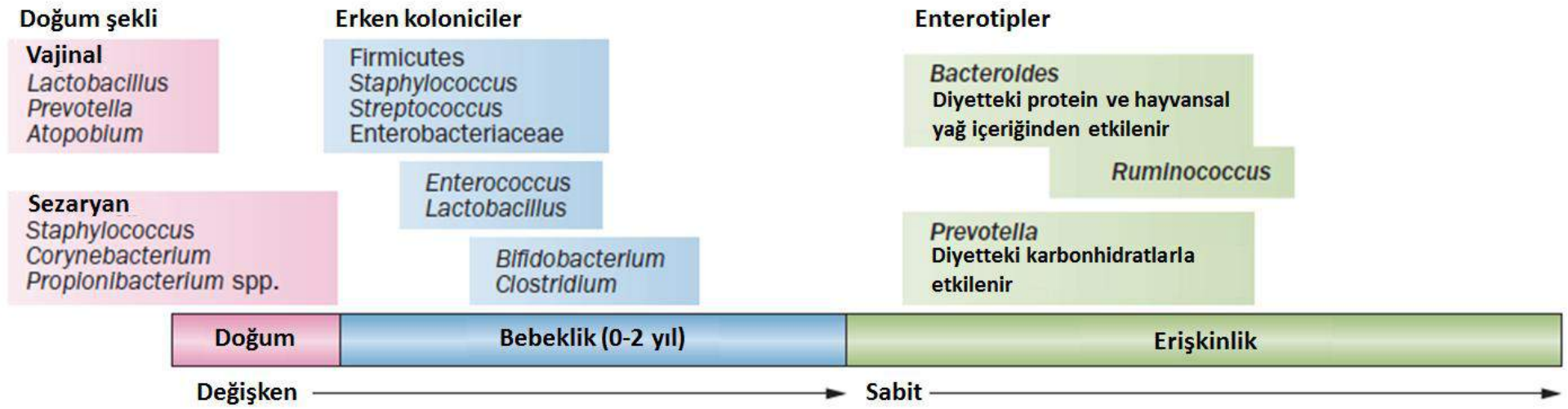


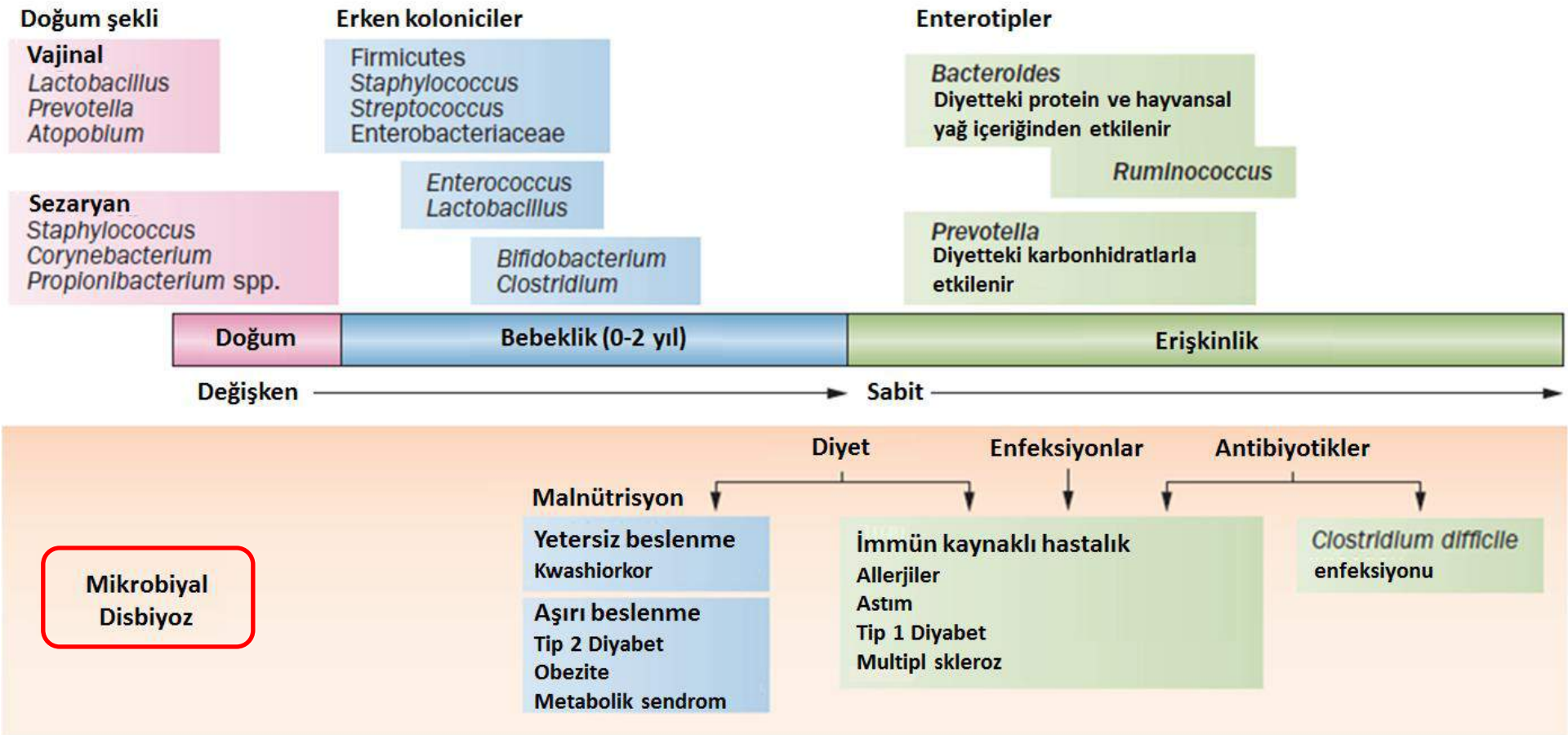
Effect of Interactions of Bacteria, Viruses, and Eukaryotes in Health and Disease

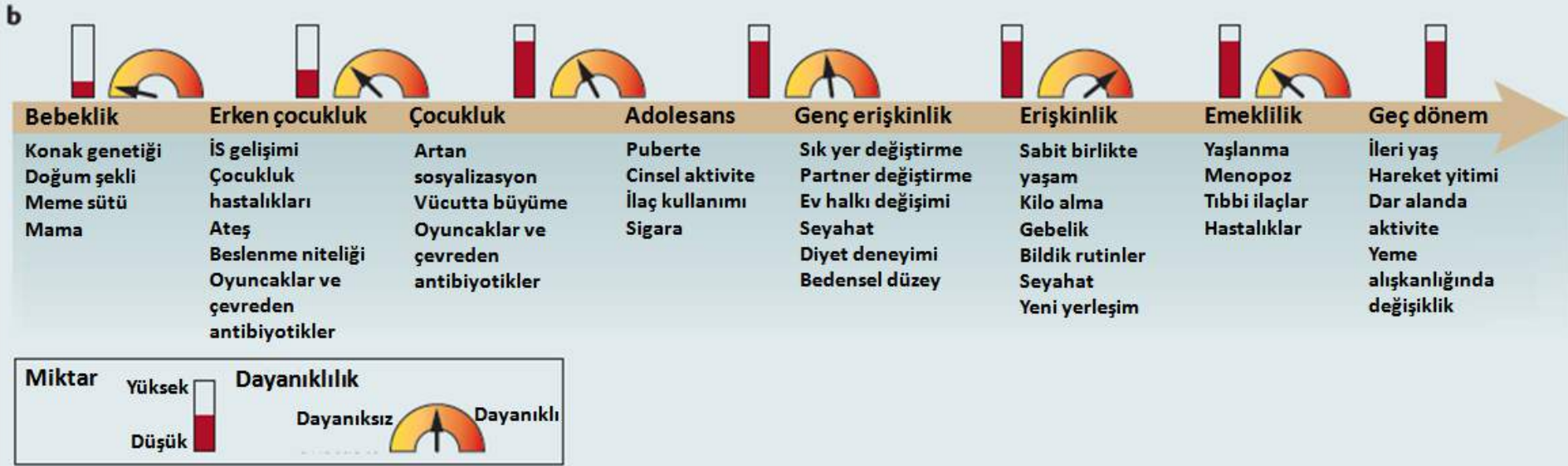
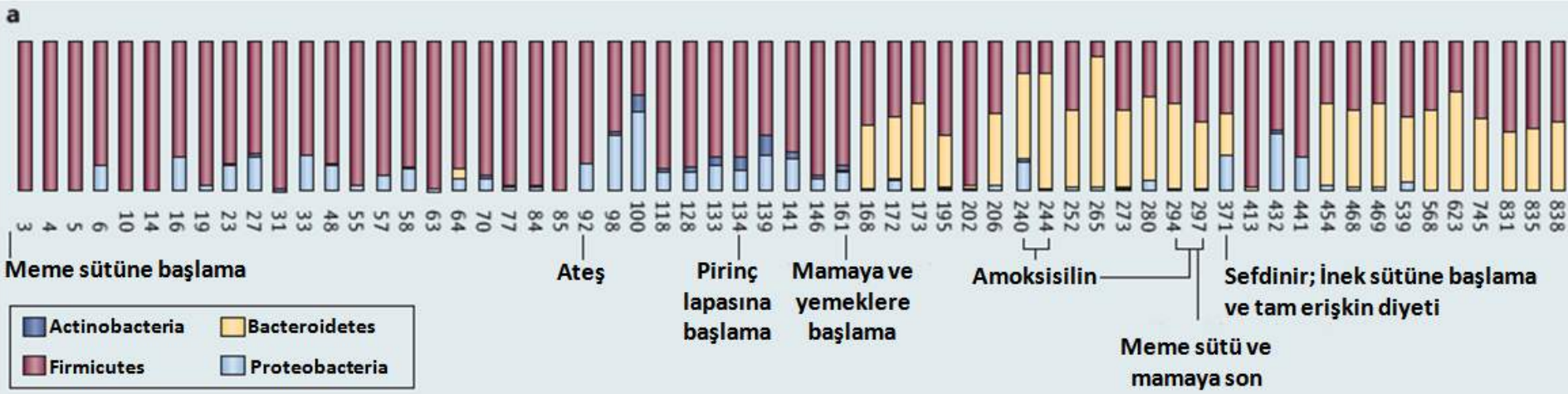
(Clemente JC et al: 2012)







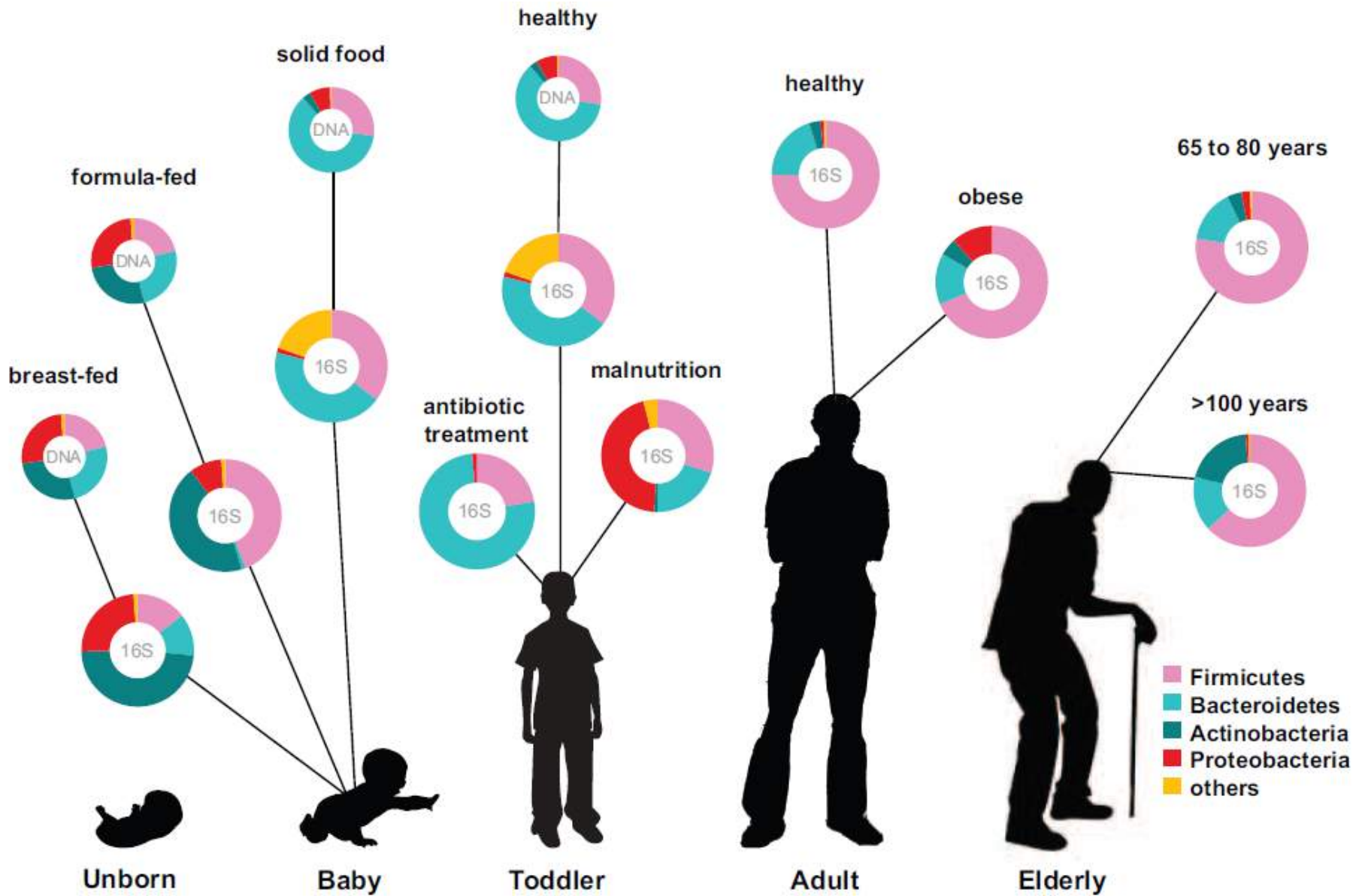




**Mikrobiyotanın gelişimi ve dayanıklılığı ile barsak mikrobiyomunu yaşam boyu etkileyen çevresel faktörler (Batı ülkeleri bireyleri)**

(Spor A et al: 2011)



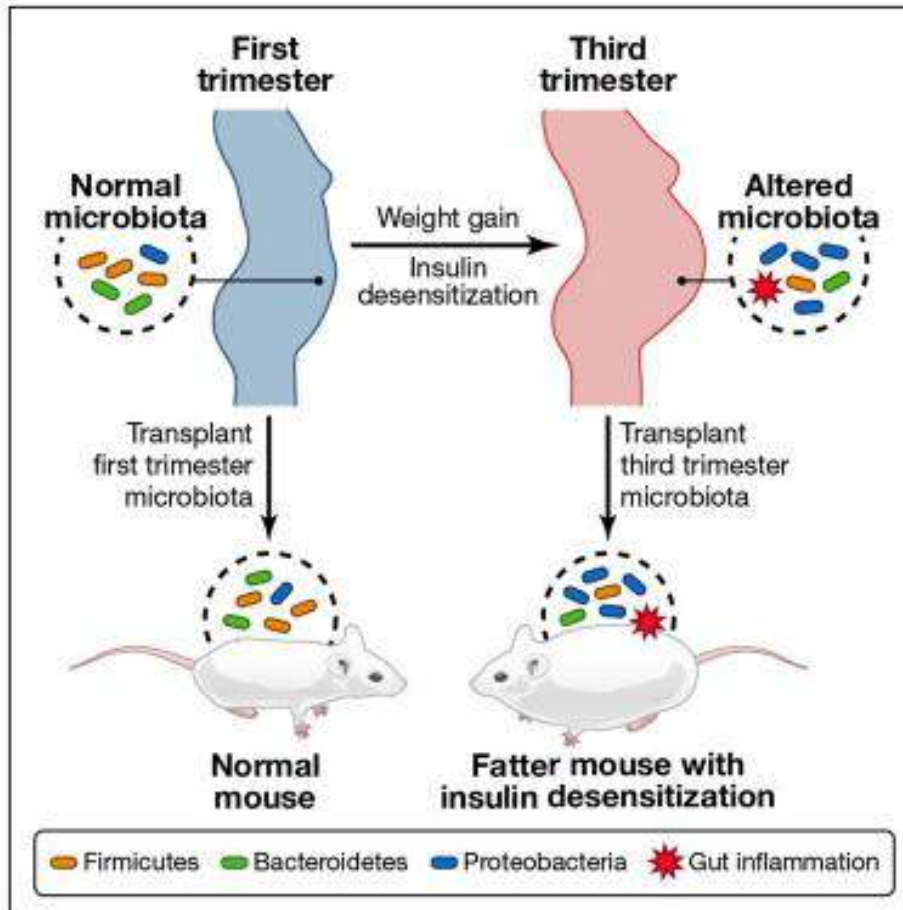


**Human microbiota: onset and shaping through life stages and perturbations**

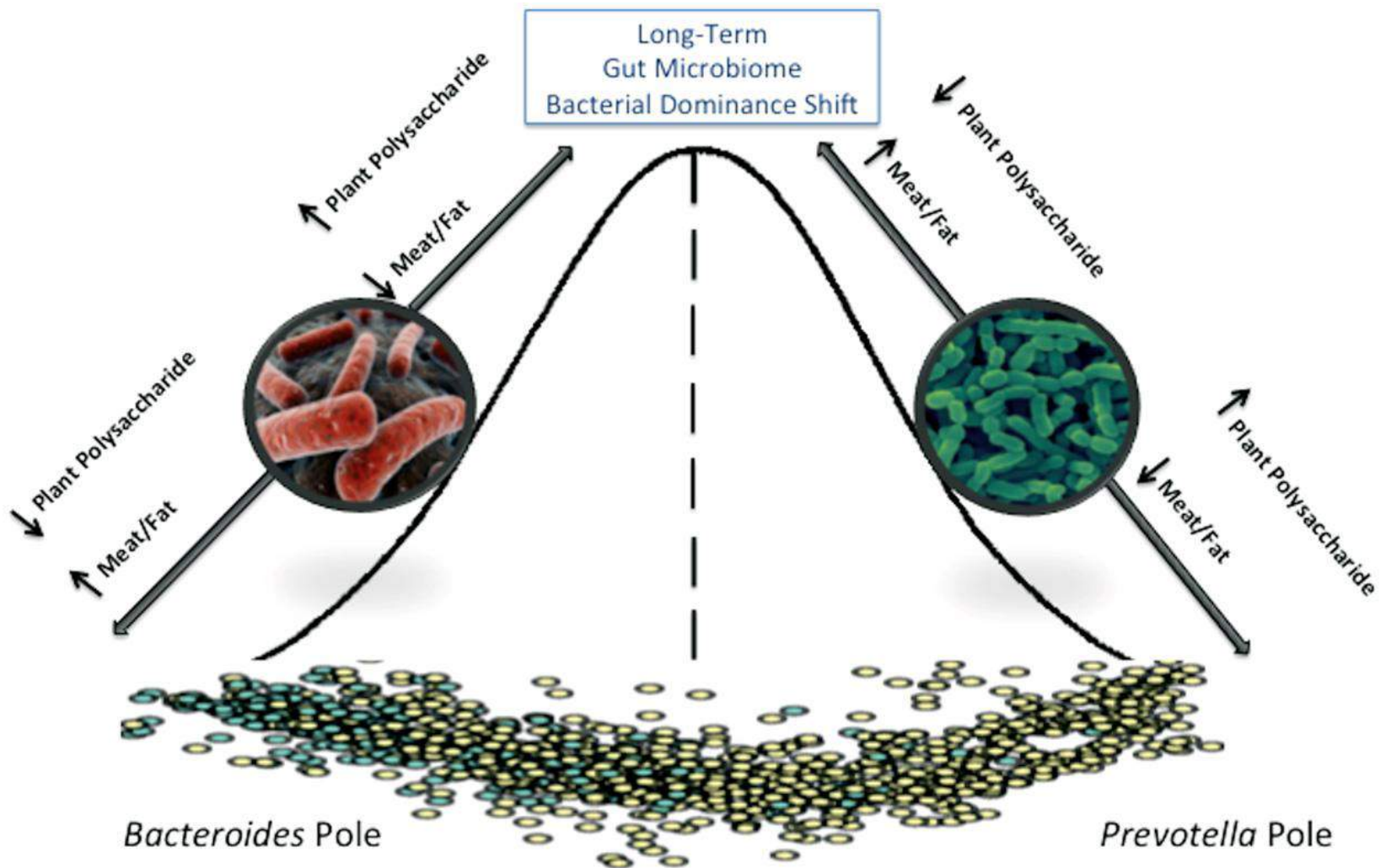
*(Ottman N et al: 2012)*

# Host Remodeling of the Gut Microbiome and Metabolic Changes during Pregnancy

Omry Koren,<sup>1</sup> Julia K. Goodrich,<sup>1</sup> Tyler C. Cullender,<sup>1</sup> Aymé Spor,<sup>1,11</sup> Kirsi Laitinen,<sup>3,4</sup> Helene Kling Bäckhed,<sup>6,7</sup> Antonio Gonzalez,<sup>8</sup> Jeffrey J. Werner,<sup>2,12</sup> Largus T. Angenent,<sup>2</sup> Rob Knight,<sup>9,10</sup> Fredrik Bäckhed,<sup>6,7</sup> Erika Isolauri,<sup>5</sup> Seppo Salminen,<sup>4</sup> and Ruth E. Ley<sup>1,\*</sup>



- The composition of the gut microbiota changes dramatically during pregnancy
- Third trimester stool is associated with greater inflammation and energy content
- Third trimester microbiota induce pregnancy-like metabolism in germ-free mice
- Gut microbiota impacts metabolism in pregnancy similarly to metabolic syndrome



**The adult gut microbiome is characterized as existing in a steady state that requires a major disturbance to permanently alter that state**

Short-term diet interventions may transiently alter the gut microbiome community structure, but long-term diet changes are required to shift to a new steady-state.

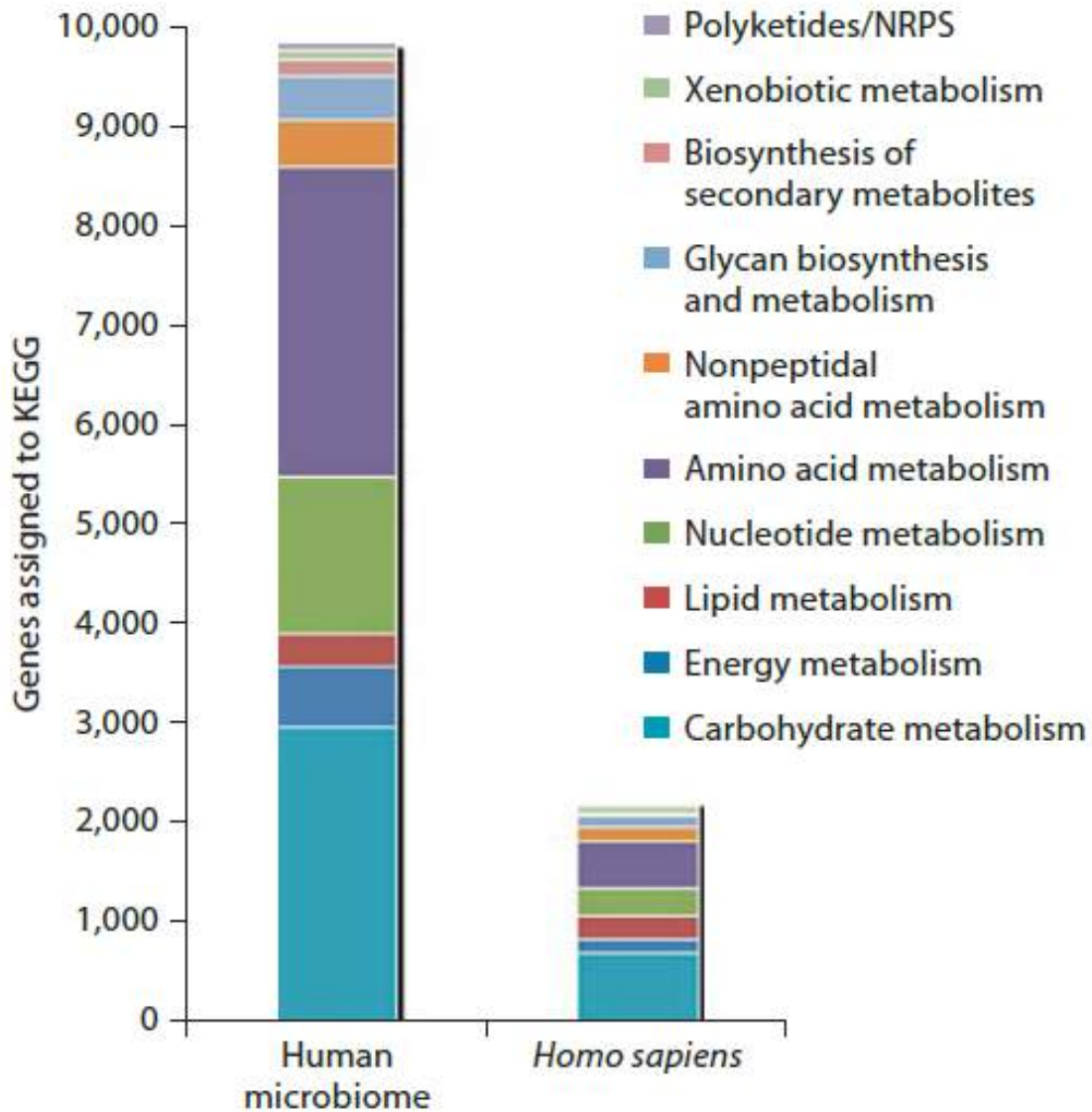
*(Voreades N et al: 2014)*



# An integrated catalog of reference genes in the human gut microbiome

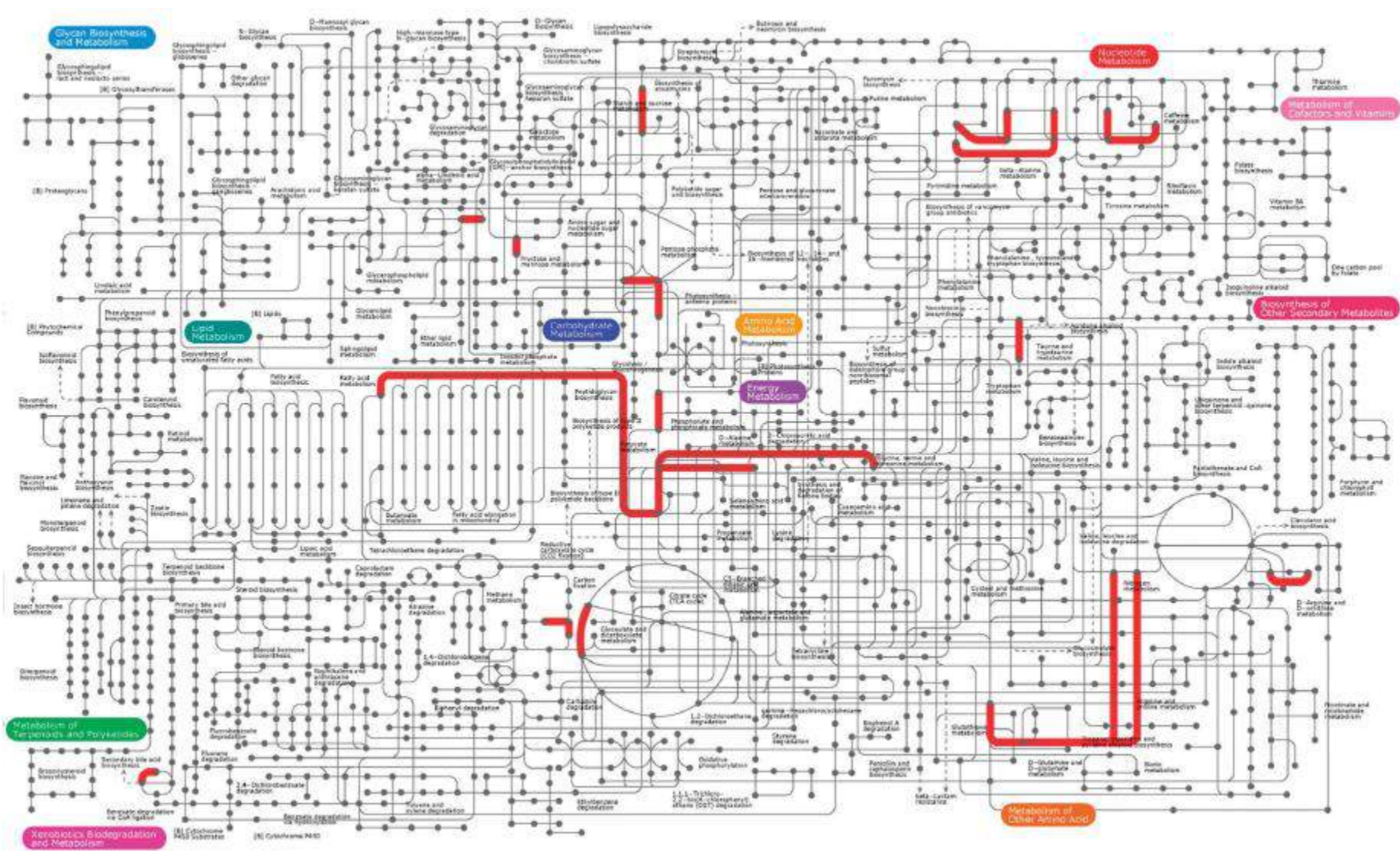
Junhua Li<sup>1-3,19</sup>, Huijue Jia<sup>1,19</sup>, Xianghang Cai<sup>1,19</sup>, Huanzi Zhong<sup>1,19</sup>, Qiang Feng<sup>1,4,19</sup>, Shinichi Sunagawa<sup>5</sup>, Manimozhiyan Arumugam<sup>1,5,6</sup>, Jens Roat Kultima<sup>5</sup>, Edi Prifti<sup>7</sup>, Trine Nielsen<sup>6</sup>, Agnieszka Sierakowska Juncker<sup>8</sup>, Chaysavanh Manichanh<sup>9</sup>, Bing Chen<sup>1</sup>, Wenwei Zhang<sup>1</sup>, Florence Levenez<sup>7</sup>, Juan Wang<sup>1</sup>, Xun Xu<sup>1</sup>, Liang Xiao<sup>1</sup>, Suisha Liang<sup>1</sup>, Dongya Zhang<sup>1</sup>, Zhaoxi Zhang<sup>1</sup>, Weineng Chen<sup>1</sup>, Hailong Zhao<sup>1</sup>, Jumana Yousuf Al-Aama<sup>10,11</sup>, Sherif Edris<sup>11,12</sup>, Huanming Yang<sup>1,11,13</sup>, Jian Wang<sup>1,13</sup>, Torben Hansen<sup>6</sup>, Henrik Bjorn Nielsen<sup>8</sup>, Soren Brunak<sup>8</sup>, Karsten Kristiansen<sup>4</sup>, Francisco Guarner<sup>9</sup>, Oluf Pedersen<sup>6</sup>, Joel Doré<sup>7,14</sup>, S Dusko Ehrlich<sup>7,15</sup>, MetaHIT Consortium<sup>16</sup>, Peer Bork<sup>5,17</sup> & Jun Wang<sup>1,4,6,11,18</sup>

Gene catalog	Reference	Sample size	Number of ORFs	Complete ORFs (%)	Total length (bp)	Average length (bp)	N50 (bp)	N90 (bp)	Max length	Min length
European	Current study	760	8,096,991	56.18	6,039,847,368	746	1,023	381	88,086	102
	MetaHIT 2010 study	124	3,299,822	46.26	2,323,171,095	704	909	378	23,034	102
American	Current study	139	2,681,342	55.45	1,996,356,219	745	1,005	387	40,011	102
	HMP 2012 study*	139	4,581,984	NA	2,571,088,392	561	765	285	26,109	102
Chinese	Current study**	368	3,547,396	60.05	2,750,208,618	775	1,053	405	88,230	102
3CGC	Current study	1,267	9,750,788	56.34	7,298,407,194	748	1,029	384	88,230	102
SPGC	Current study	NA	659,492	99.77	612,211,588	928	1,221	513	24,615	100
IGC	Current study	1,267***	9,879,896	57.74	7,436,156,055	753	1,035	384	88,230	100



**Comparison of the number of KEGG (Kyoto Encyclopedia of Genes and Genomes) genes involved in metabolic pathways within all the assembled data of the human genomes and the human intestinal metagenome. KEGG genes are organized in functional categories according to their belonging to different pathways of cellular metabolism.**





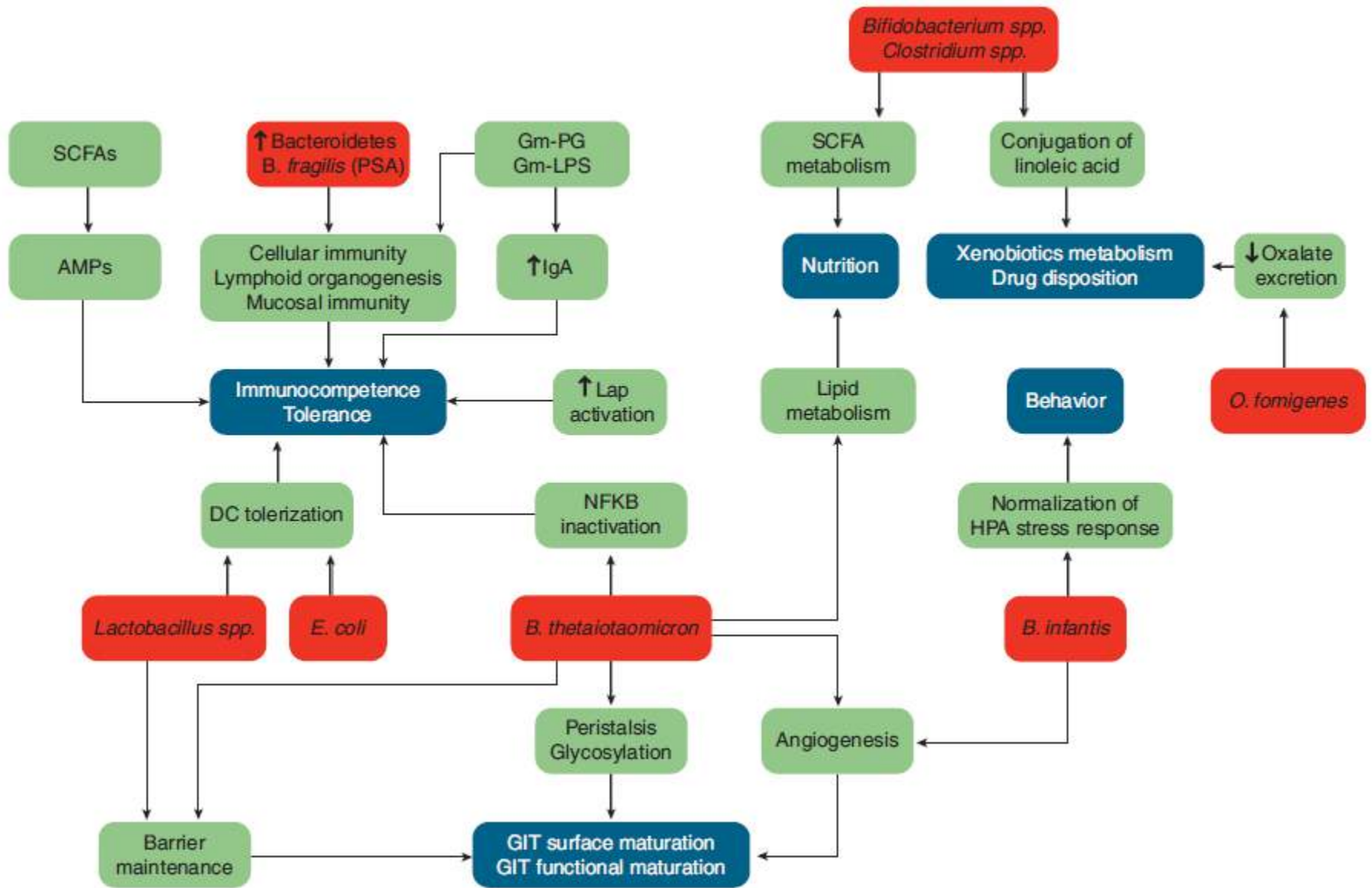
Visualization of the most common (present in >70% of the samples) metabolic reactions (59 reactions) of the group of healthy individuals. Glycolysis, pyruvate metabolism, fatty acid metabolism, amino acid and nitrogen metabolism were the most conserved parts of the metabolic network.

(Jacobsen UP et al: 2013)

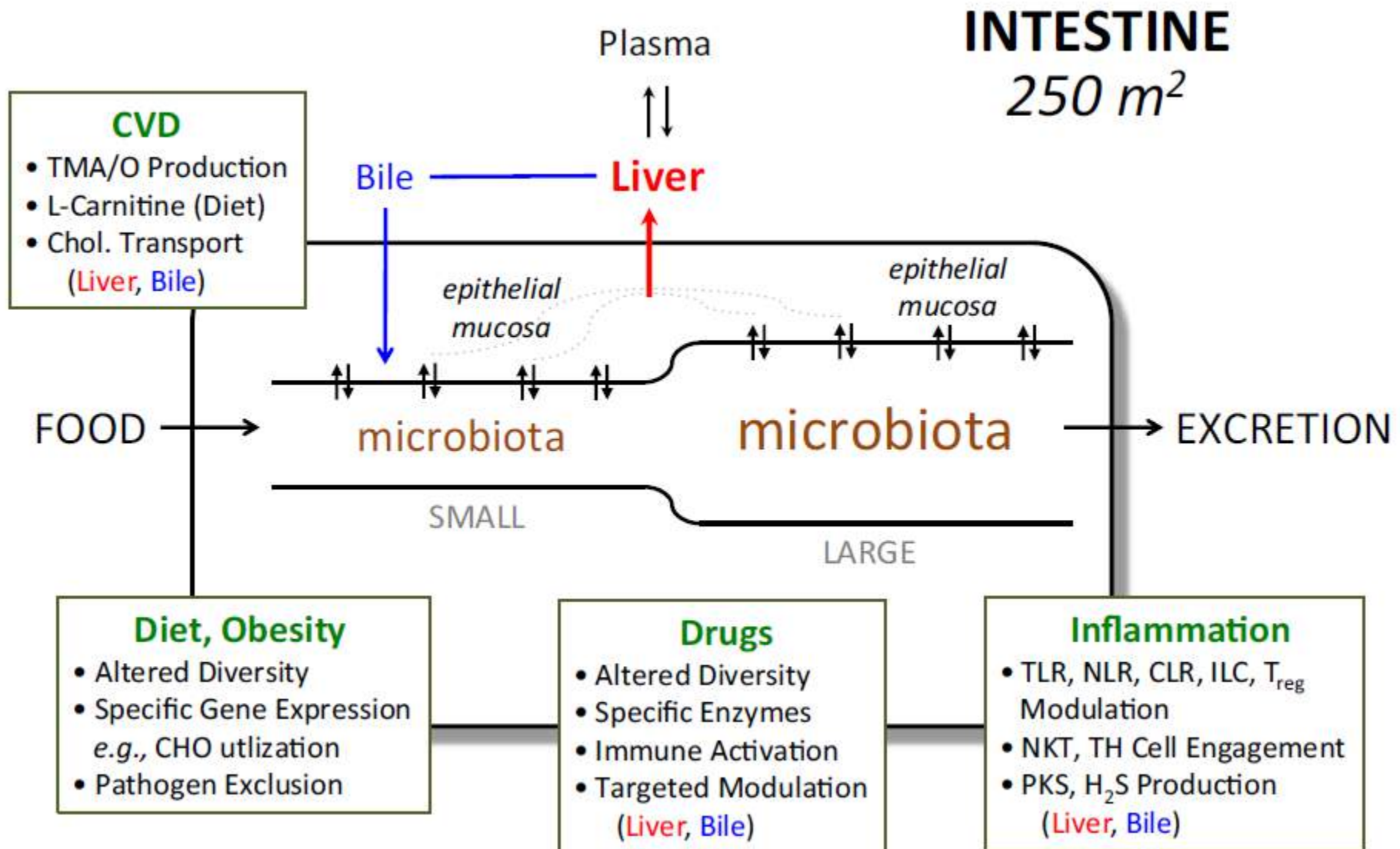


# Barsak Mikrobiyotasının İşlevleri

- **Koruyuculuk işlevi**
  - Patojenlerin uzaklaştırılması
  - Besin rekabeti
  - Reseptör rekabeti
  - Antimikrobiyal faktörlerin üretimi
- **Metabolik işlevler**
  - Sindirilemeyen maddelerin fermentasyonu
  - Kısa zincirli yağ asitlerinin üretimi
  - Enerji kaynaklarının kurtarılması
  - Esansiyel vitaminlerin sentezi (K, B12, niasin, biotin, folat)
- **Yapısal işlevler**
  - Epitel hücre döngüsünün düzenlenmesi
  - Epitel hücre diferansiyasyonunun harekete geçirilmesi
  - Epitel engelin güçlendirilmesi
  - Sıkı bileşkelerin dayanıklılaştırılması
- **İmmün işlevler**
  - Sekretuar IgA'nın uyarılması
  - Oral toleransın uyarılması
  - İmmün mikroçevrenin şekillendirilmesi

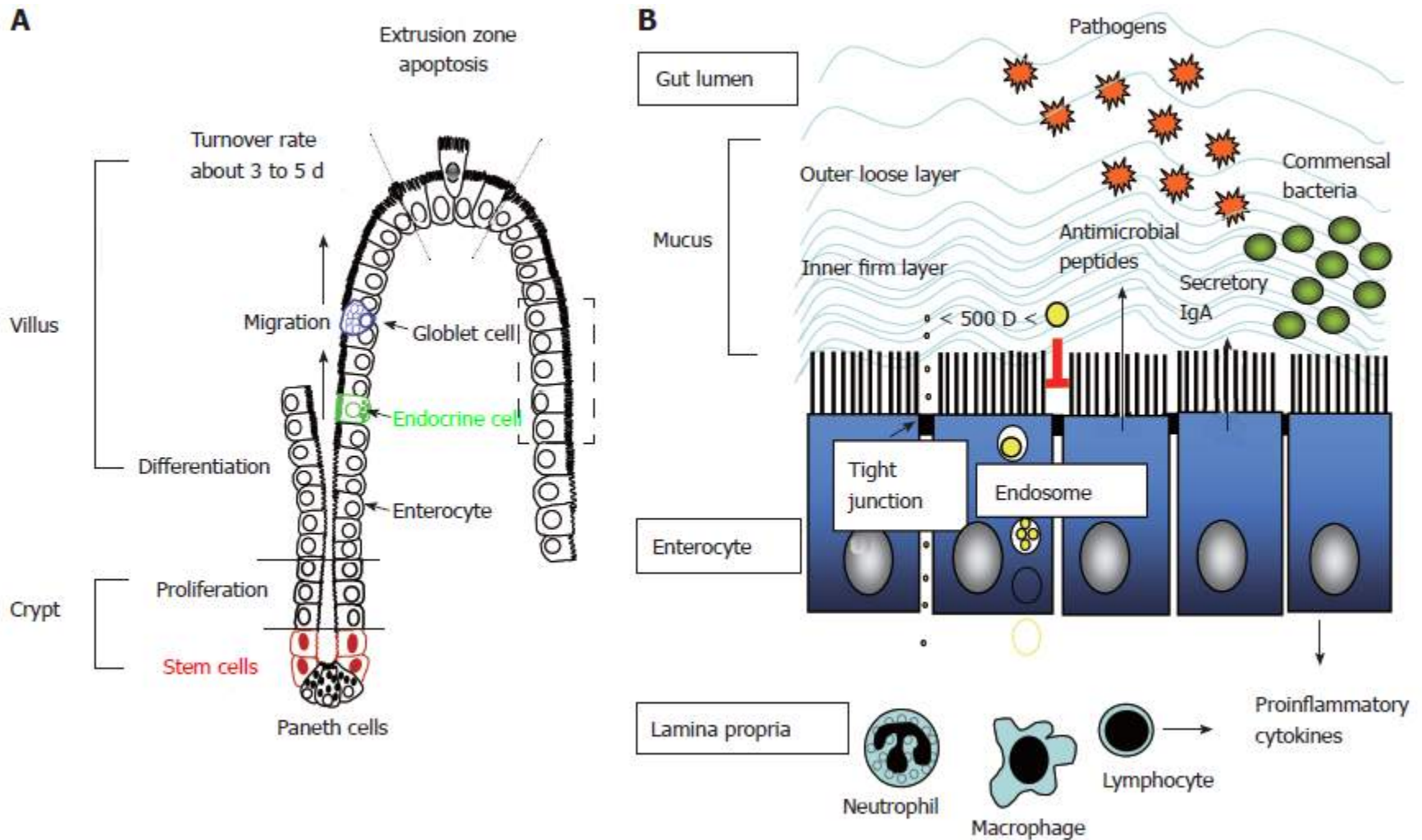


Some examples of the effects of intestinal microbiota and host physiology



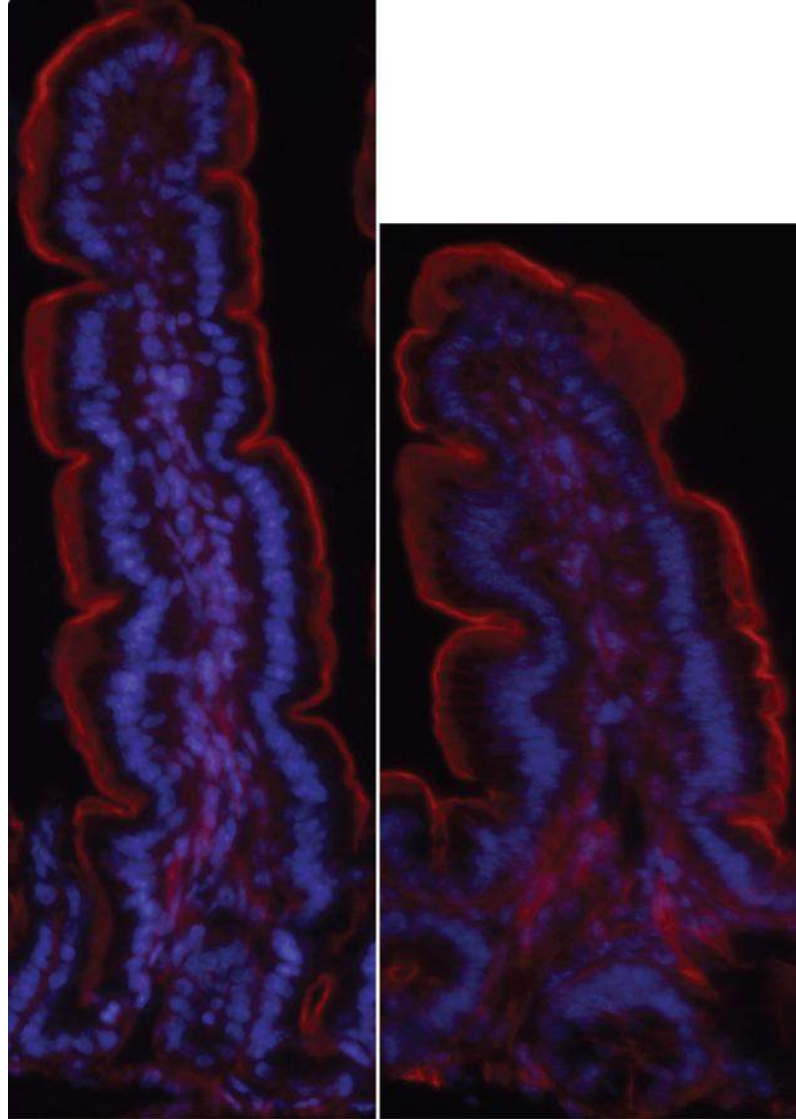
Features associated with the microbiota and diet and obesity, cardiovascular disease (CVD), inflammation, and drug toxicity





## Intestinal crypt-villus axis and formation of intestinal barriers for luminal confinement of commensal bacteria

**Mikropsuz  
ortamda  
yetiřtirilmiř  
fare**

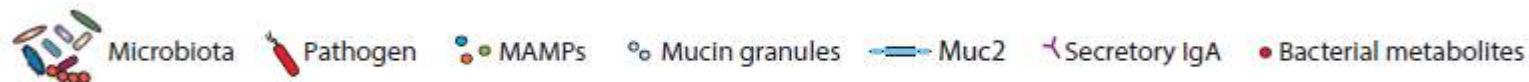
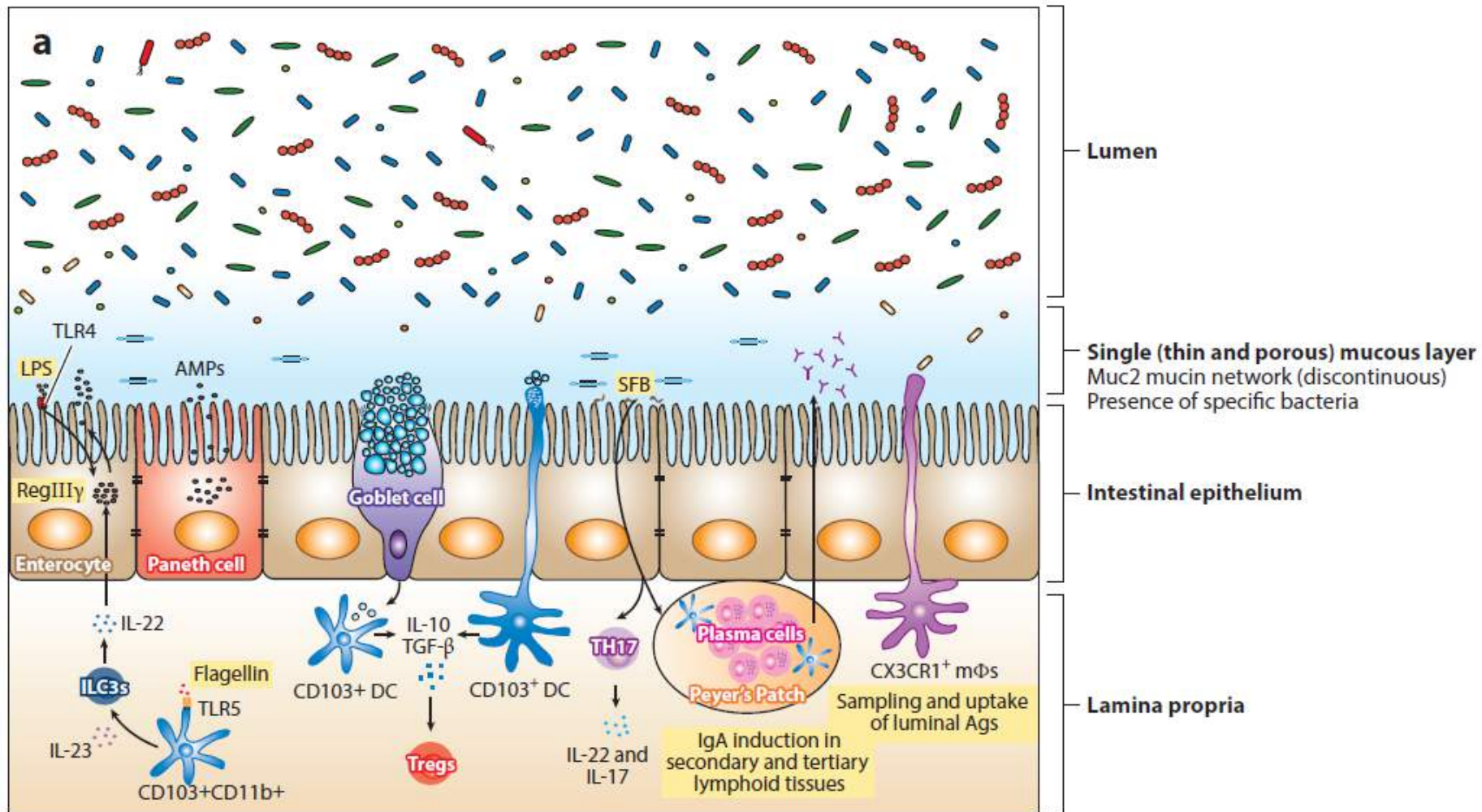


**Klasik  
kořullarda  
yetiřtirilmiř  
kolonize  
fare**

### **İnce bağırsak villus morfolojisi**

Jejunal sections from germ-free and colonized mice stained with phalloidin (F-actin; red) and DAPI (nuclei; blue).

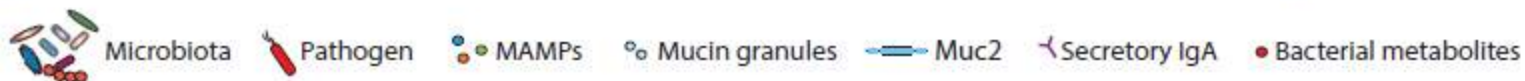
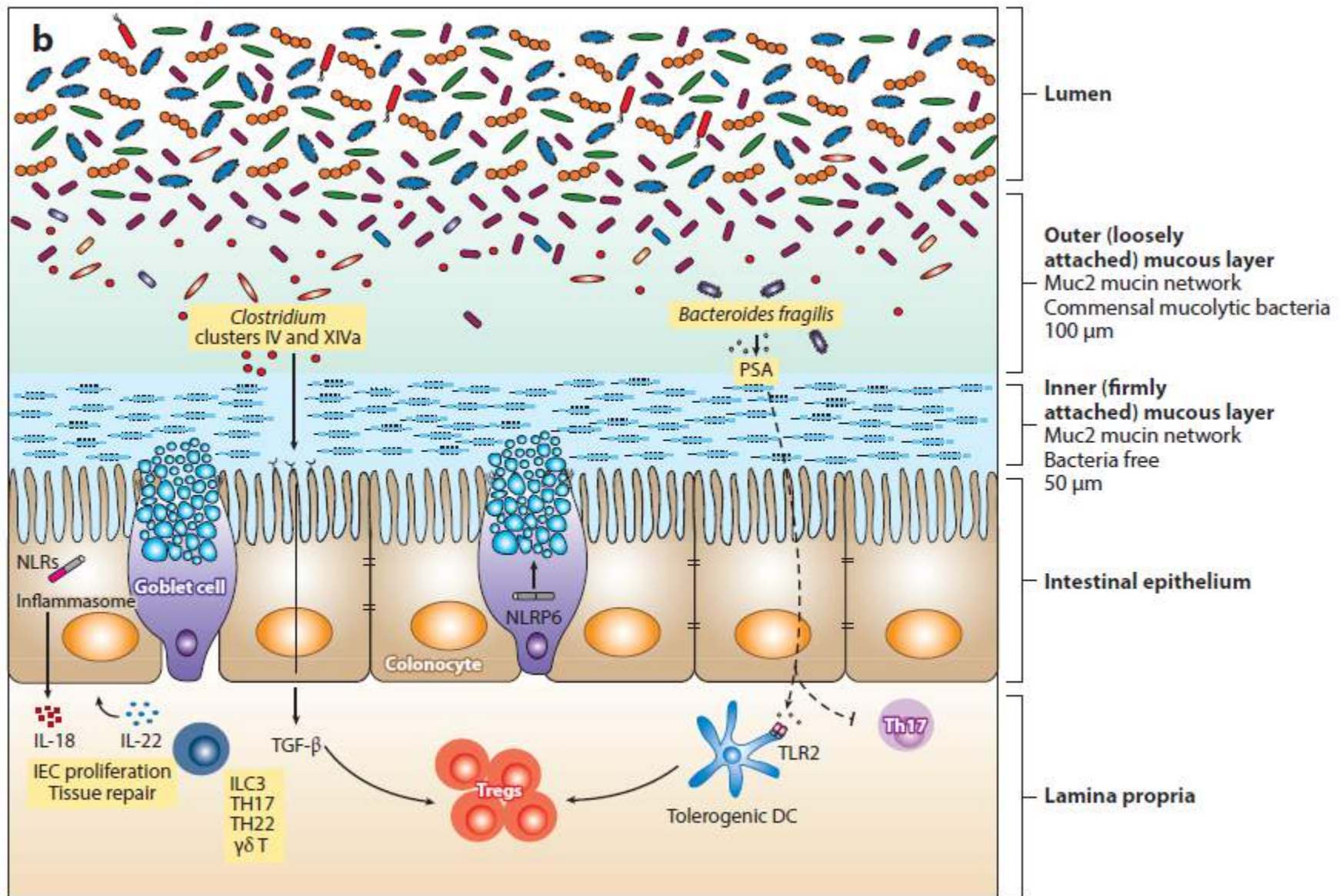
*(Bäckhed F: 2012)*



## Maintenance of intestinal homeostasis in the gastrointestinal tract

(Caballero S, Pamer EG: 2015)



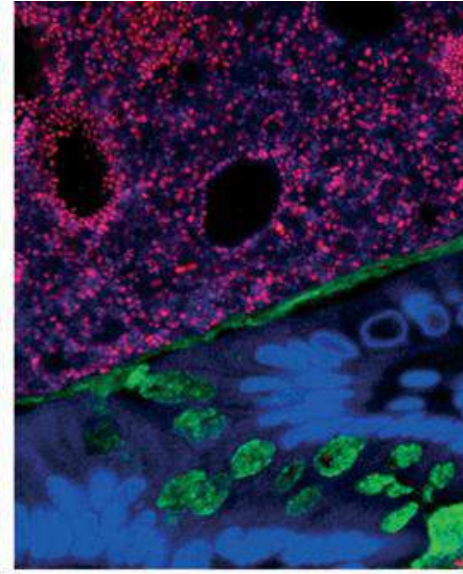
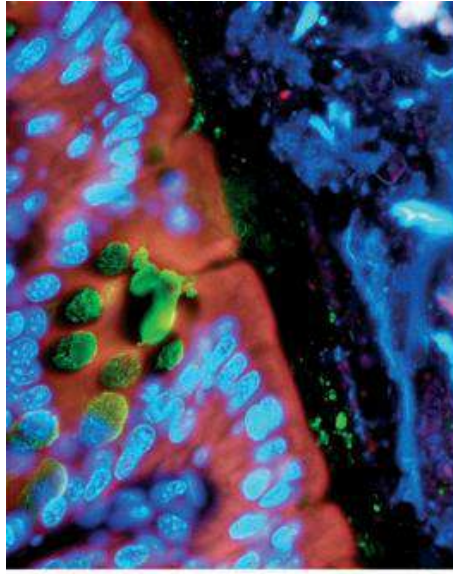


## Maintenance of intestinal homeostasis in the gastrointestinal tract

(Caballero S, Pamer EG: 2015)

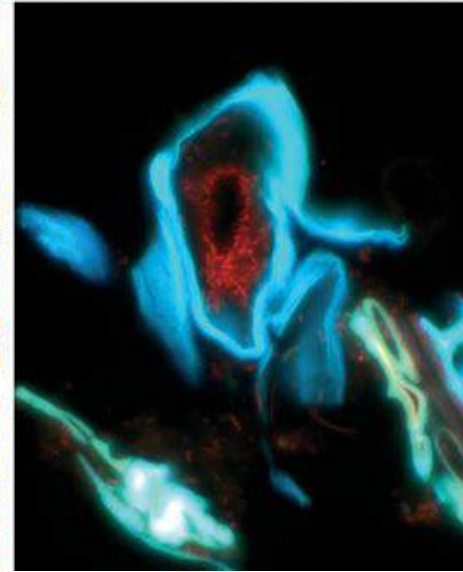
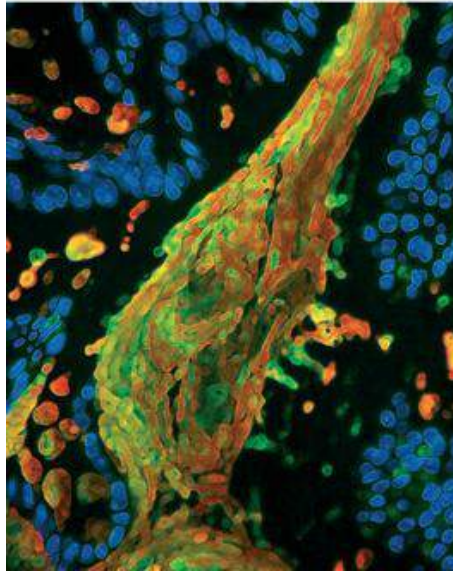


Kadeh hücreleri (yeşil),  
epitel hücreleri  
(kırmızı), epitel  
nükleusu (mavi) ve  
lüminal bağırsak içeriği  
ile bakterileri (mavi ve  
pembe) göstermek  
üzere boyanmış  
bağırsak epitel  
yüzeyinin fluoresans  
mikrografı



Carnoy fiksatifini  
kullanılarak korunmuş  
müsinü gösteren epitel  
yüzeyleri ve üniversal  
16S rRNA probu  
(Eub338 probu)  
fluoresans in situ  
hibridizasyon (FISH)  
kullanılarak ortaya  
çıkartılmış bakteriler

Besin partiküllerine  
tutunmuş çok sayıda  
luminal bakteriyi  
sekestre eden  
bağırsak lümeninde  
(epitel hücreleriyle  
çevrelenmiştir)  
görülen büyük bir  
müsin tıkacı

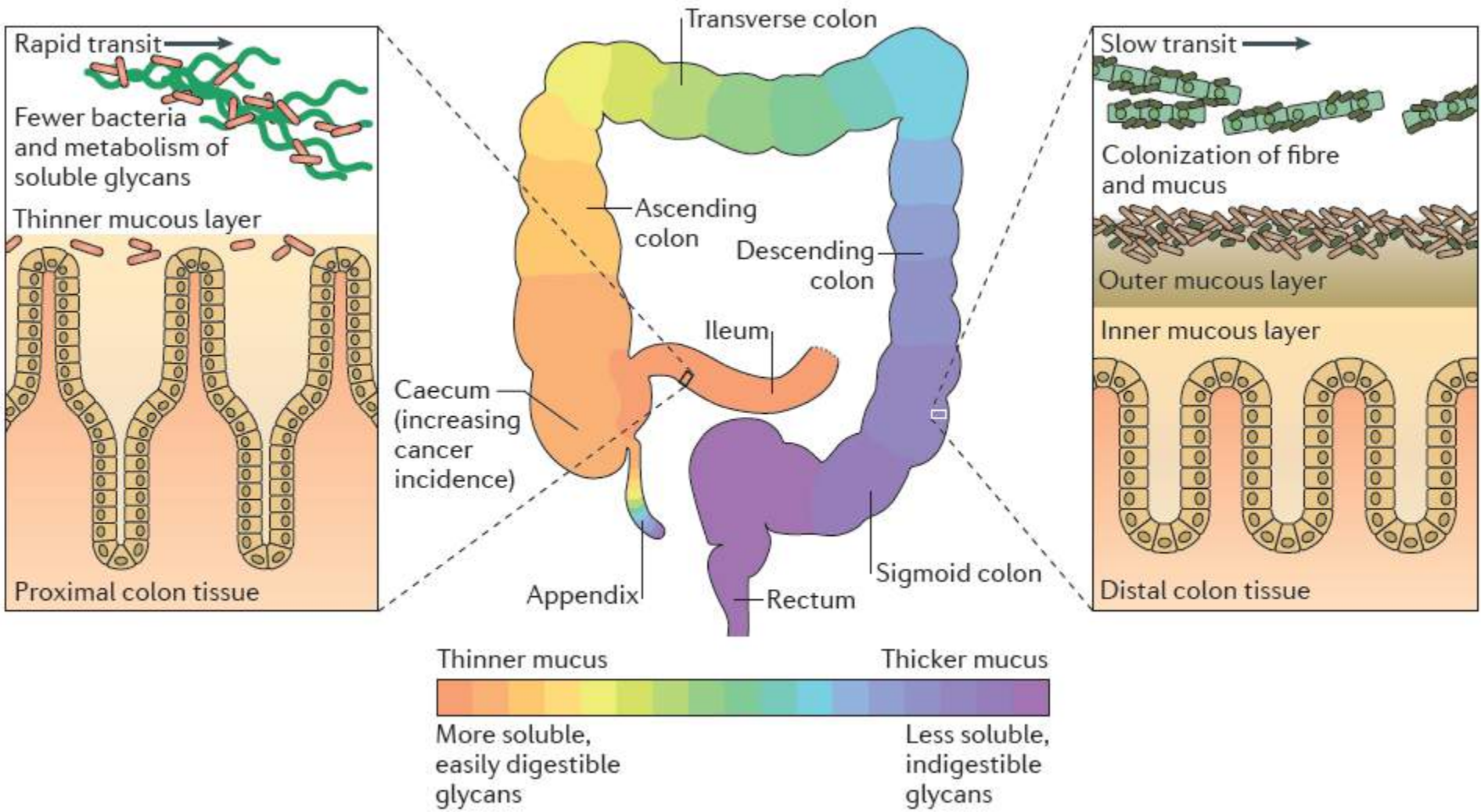


Bağırsak lümeninde  
bir besin partikülünü  
kolonize etmiş  
bakterileri gösteren  
büyük büyütme.  
Bakteriler Eub 338  
probonun kullanıldığı  
FISH ile ortaya  
çıkartılmıştır.

## Bağırsakta immün dışlama

# Metabolik özelliklerine göre bakteri toplulukları

- Fibrolitik topluluk
  - *Bacteroides*
  - *Roseburia*
  - *Bifidobacterium*
- Glikolitik topluluk
  - *Lactobacillus*
  - *Enterococcus*
  - *Staphylococcus*
  - *E. coli*
- Mukolitik topluluk
  - *Akkermansia*
  - *Bacteroides*



**Glycan utilization along the length of the human gut**

**Çözünmez bitki hücre duvarı polisakkaritleri (selüloz, arabinoksilan, ksiloglukan,  $\beta$ -glukan, mannan, pektinler ve lignin)**

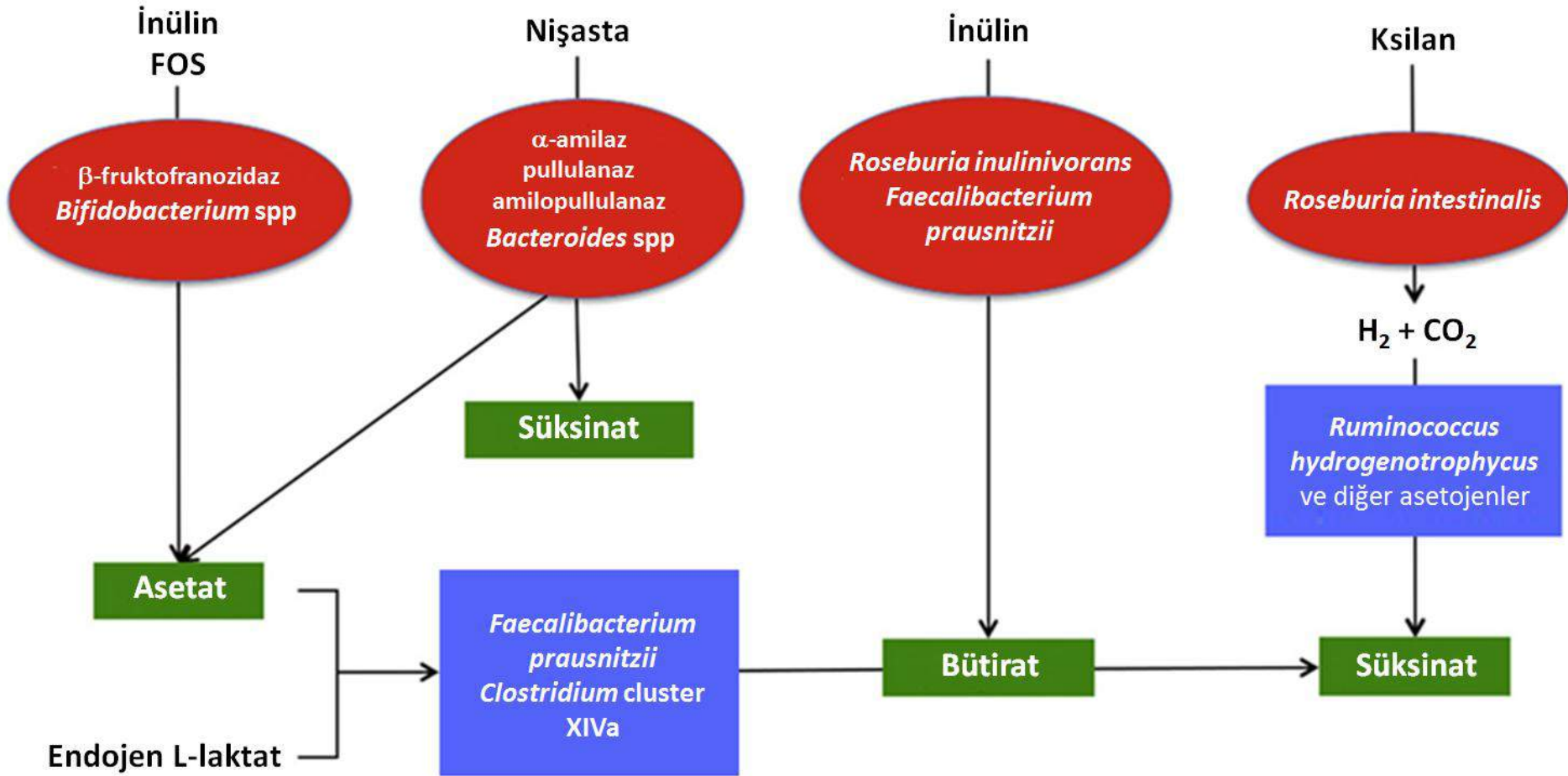
**Diğer kaynaklardan gelen sindirilemez kompleks polisakkaritler**

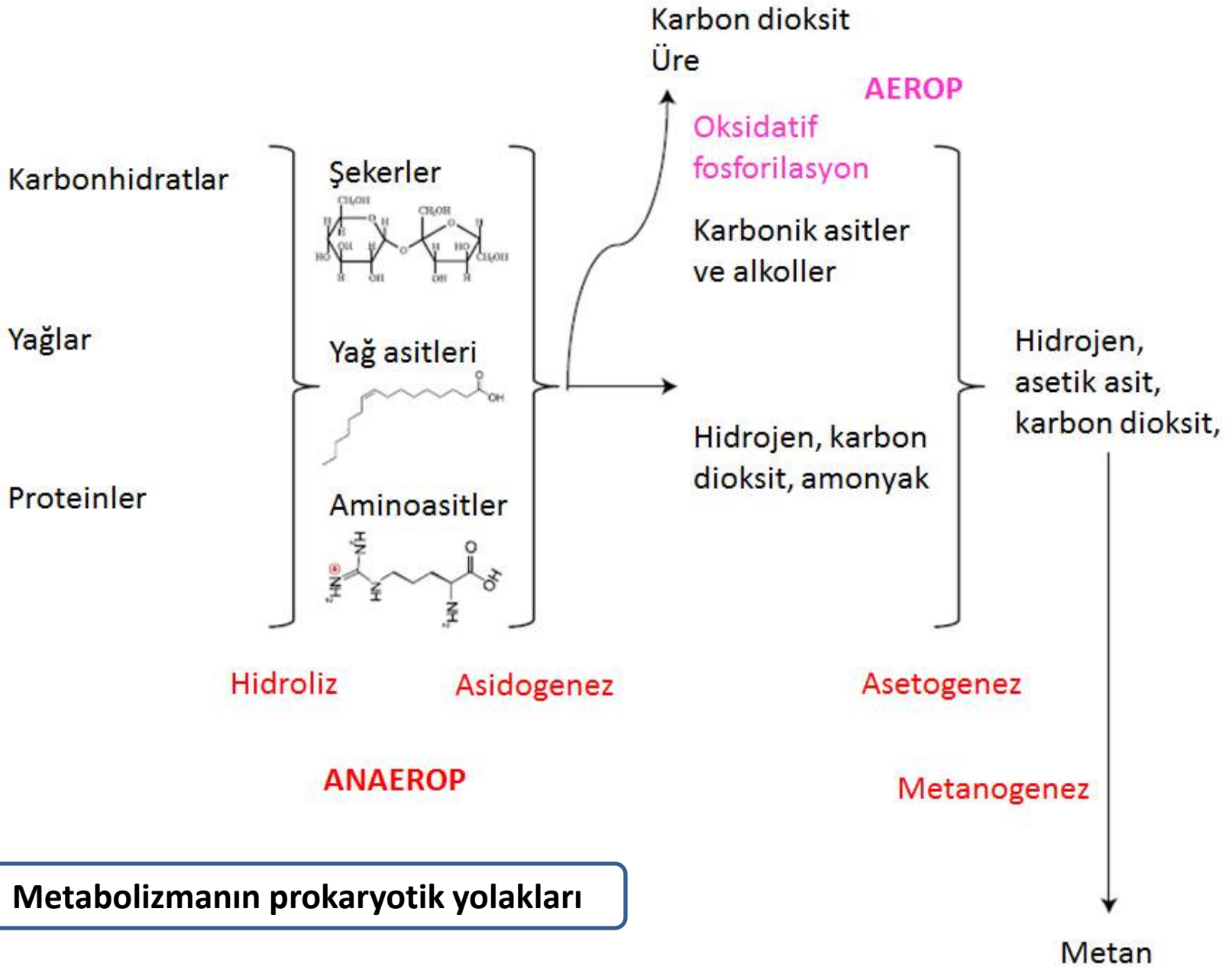


**Çözünür polisakkaritler ve oligosakkaridler**

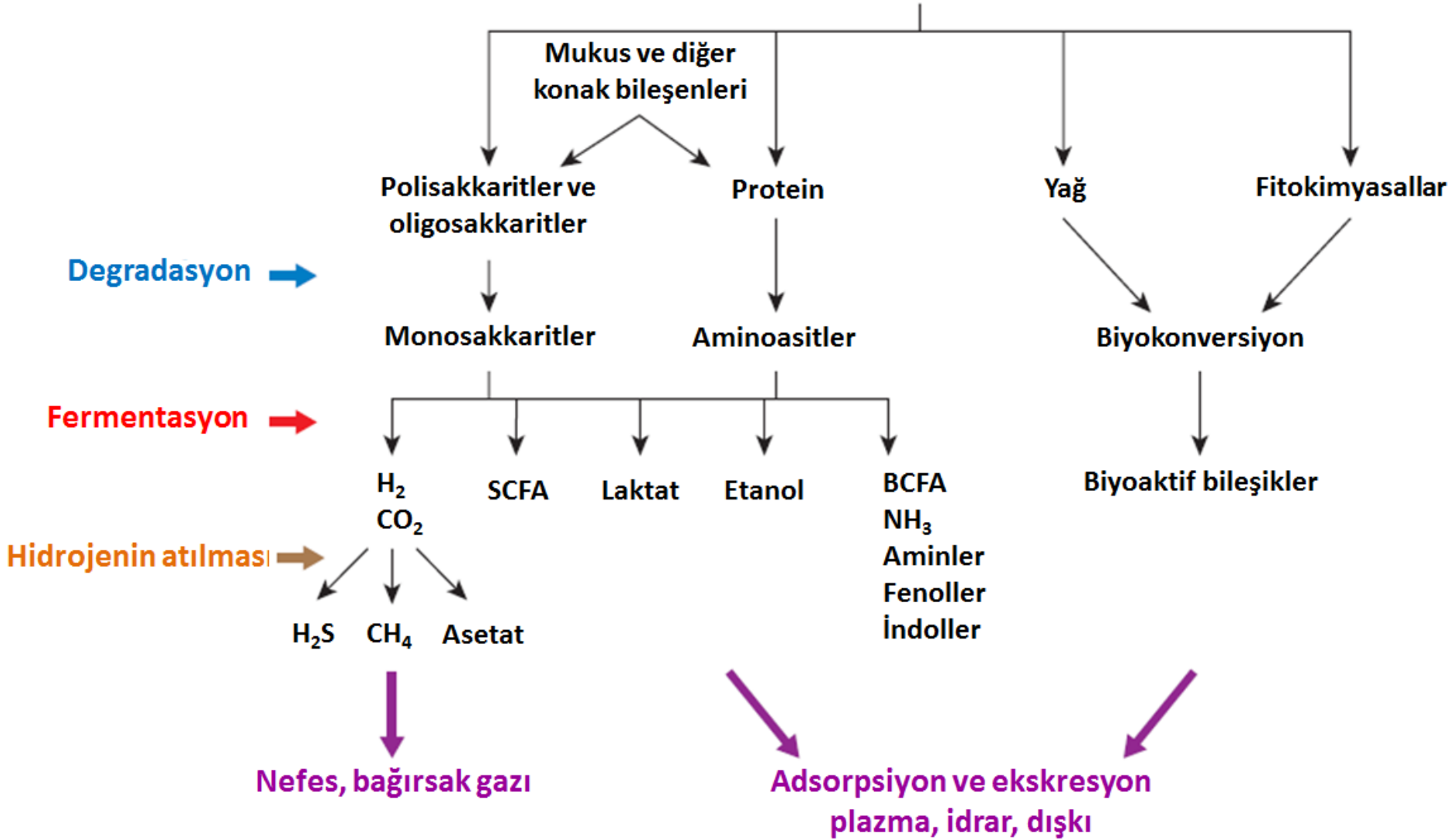




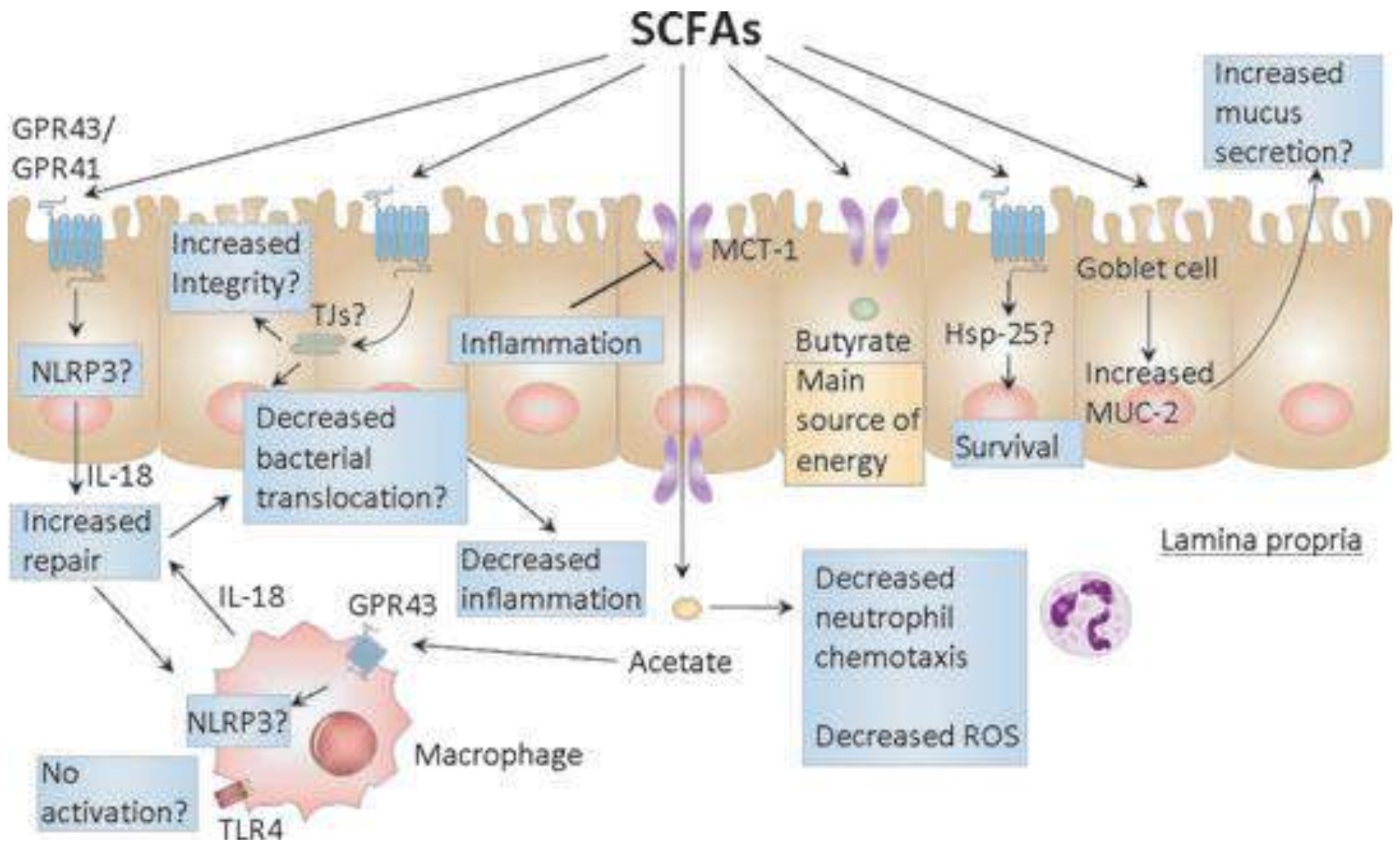




# Diyet bileşenleri



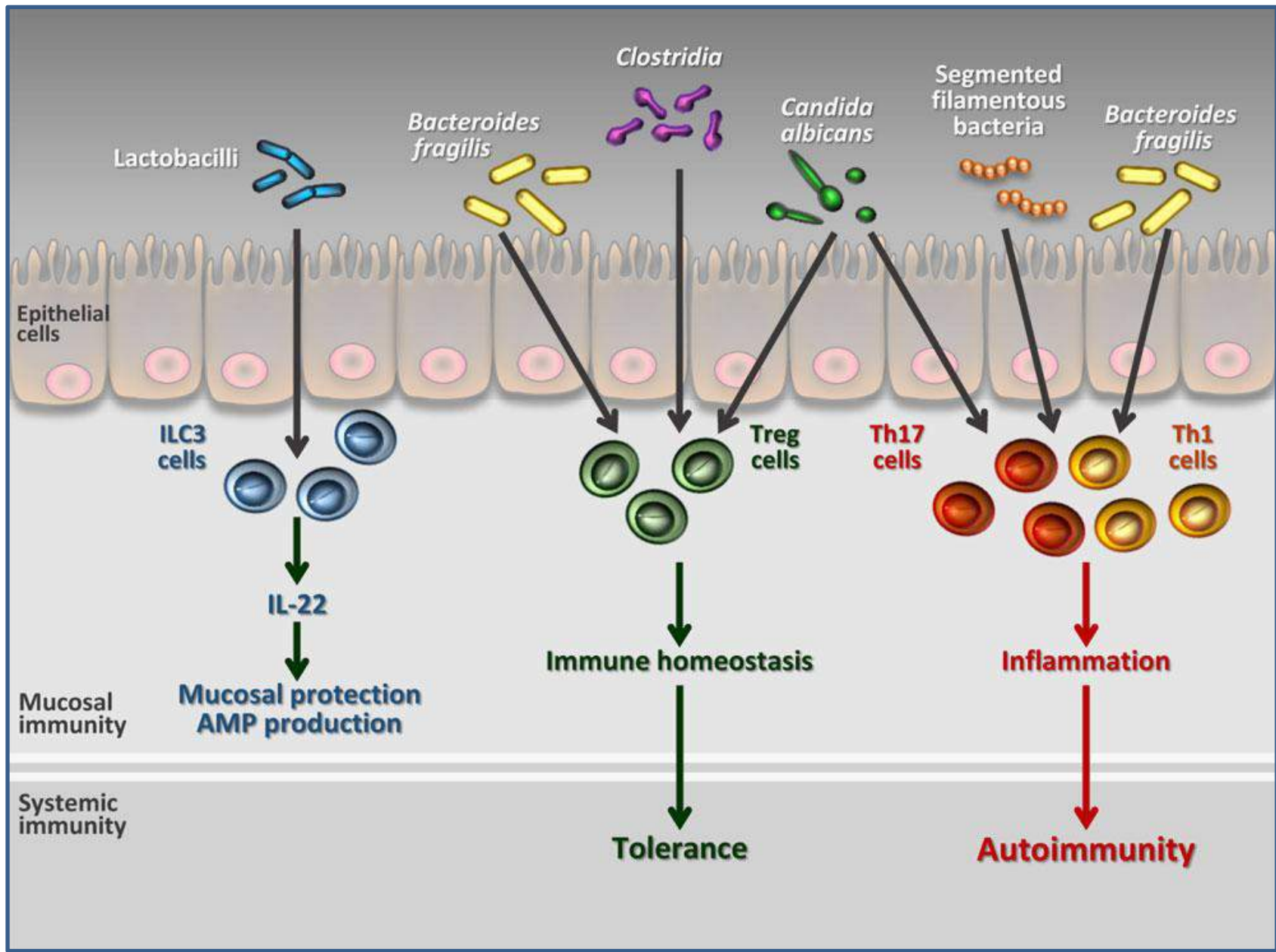
**Bağırsak mikrobiyotası karbonhidrat ve proteinleri degrade eder, yağ ve fitokimyasalları biyoaktif bileşiklere dönüştürür**



**Potential effects of SCFAs on gut epithelial biology and immune cells**

MCT-1 monocarboxylate transporter

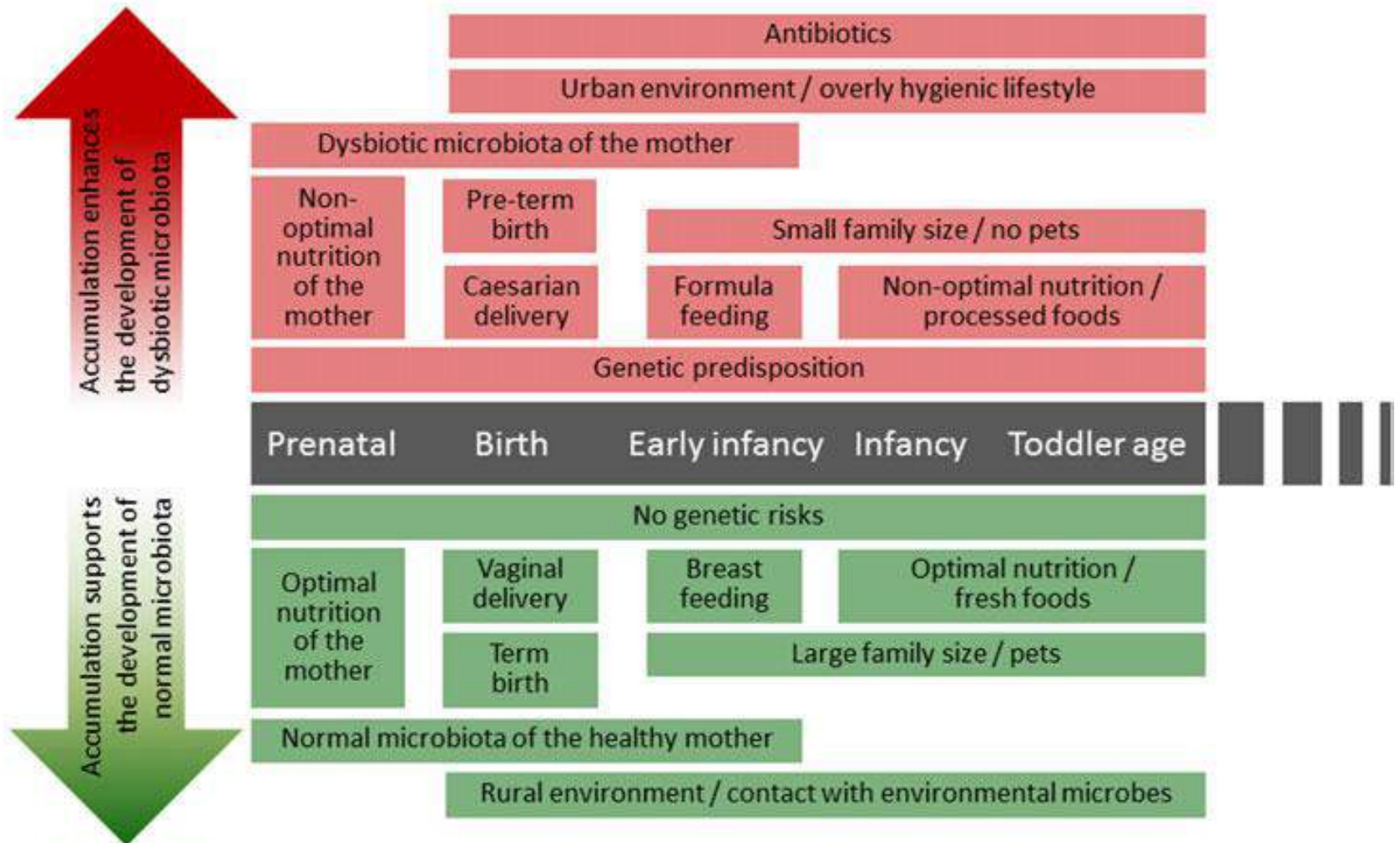




Examples of how microbiota shape host mucosal and systemic immunity

(Romani L et al: 2014)

# Increased risk of disease



Modern life style factors associated with the development of intestinal microbiota and later life health

**‘Life would not long remain possible in the absence of microbes.’**

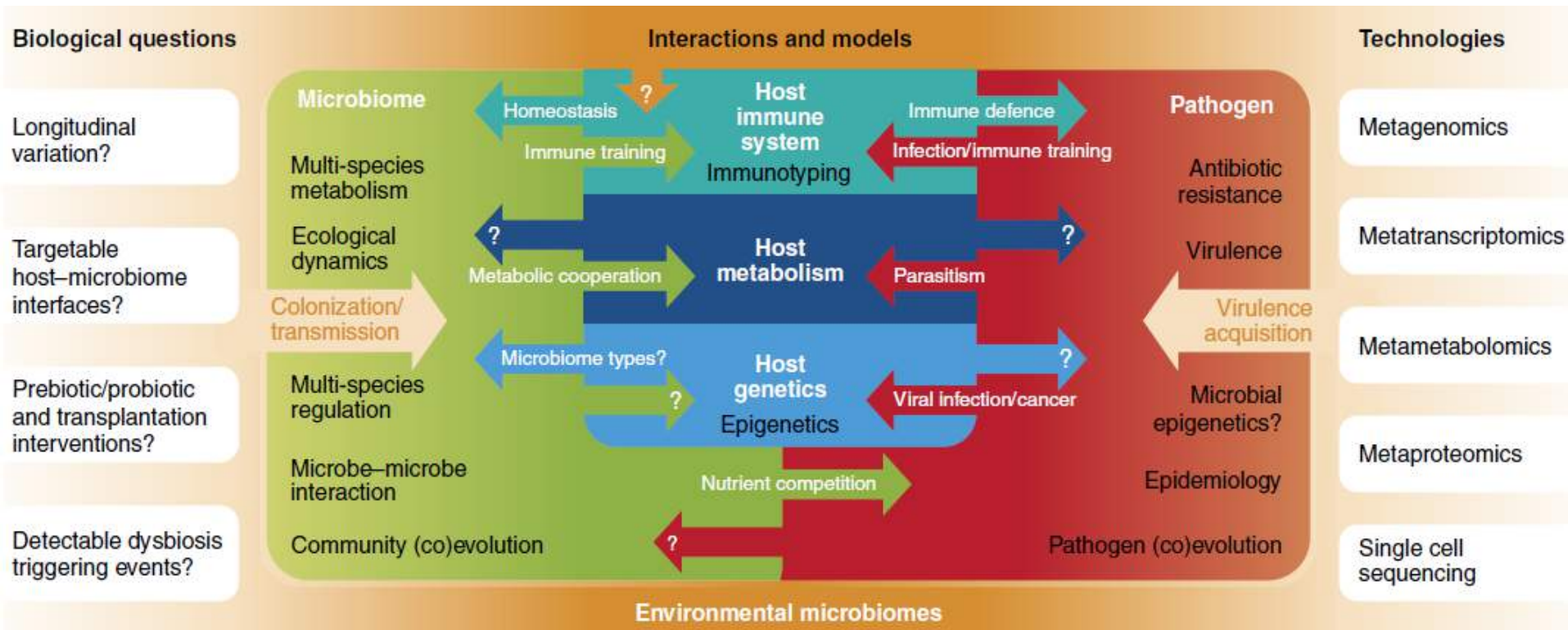
Louis Pasteur, 1883

**‘Without understanding the environment in which cells or species exist, life cannot be understood. An organism’s environment is ultimately as unique as its genetic code.’**

J. Craig Venter, 2007

**‘There is increasing evidence that the microbiome and its output (our interactome) touch many, if not most, pathways that affect health, disease, and aging. The composition of the microbiome and its activities are involved in most, if not all, of the biological processes that constitute human health and disease, as we proceed through our own life cycle.’**

Martin J. Blaser, 2014



**Open biological questions in microbial community biology, and emerging technologies and models for their exploration. Microbial communities are complex biological entities interacting with the environment, host organisms, and transient microbes. Predictive models for most of the interactions within these ecosystems are currently rare, but several studies have begun to provide key insights.**



# Sorular

- Hayvan modellerinden elde edilen veriler insanlar için ne kadar geçerlidir?
- Sonuçlar insan sađlığı için nasıl kullanılacaktır?
- Mikrobiyata üyelerinin sadece türler arası deđil bireyler arasında da deđişmesi elde edilen verilerin geçerliliđini nasıl etkiler?
- Diyet alışkanlıklarının etkisi nasıl deđerlendirilmelidir?

**Mikrobiyomolojiye  
hoş geldiniz!**

Teşekkürler...