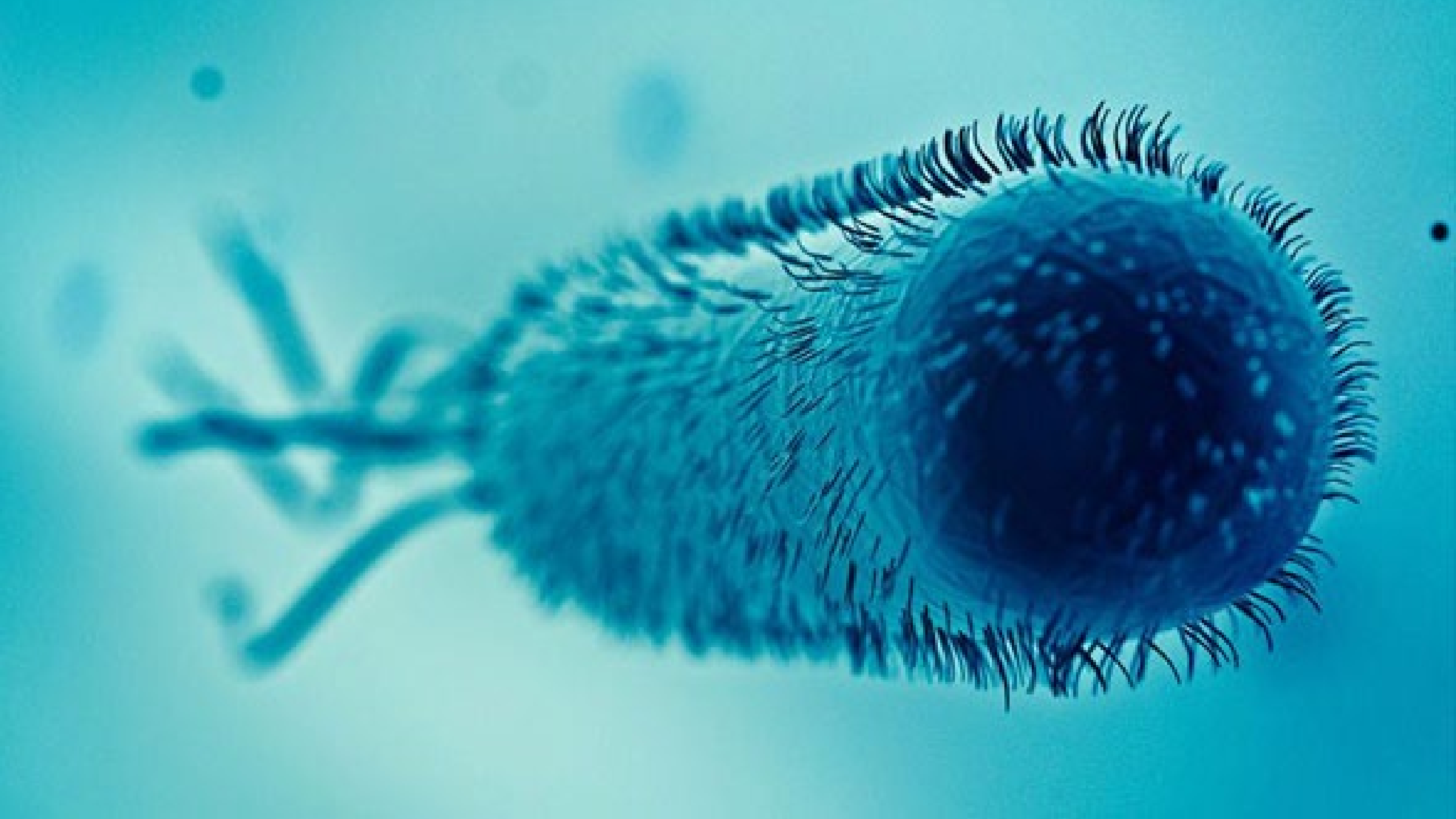
Das menschliche Mikrobiom

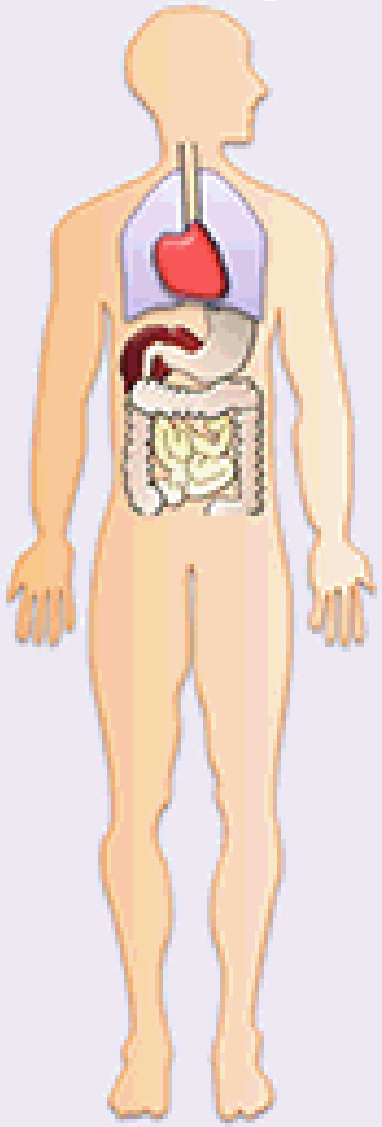
Mehr, als wir erwartet haben

Tom Fox

16.04.2021



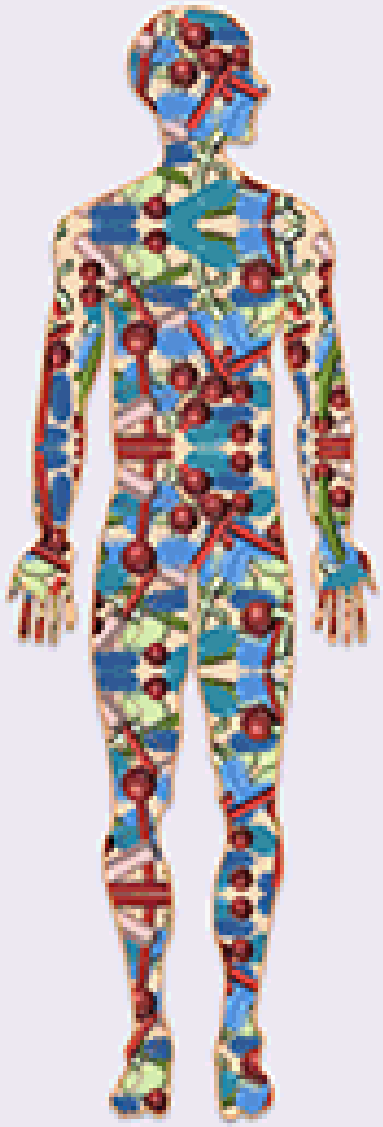
Visible Organs



- ~10^{-14} cells
- ~ 23000 genes

+

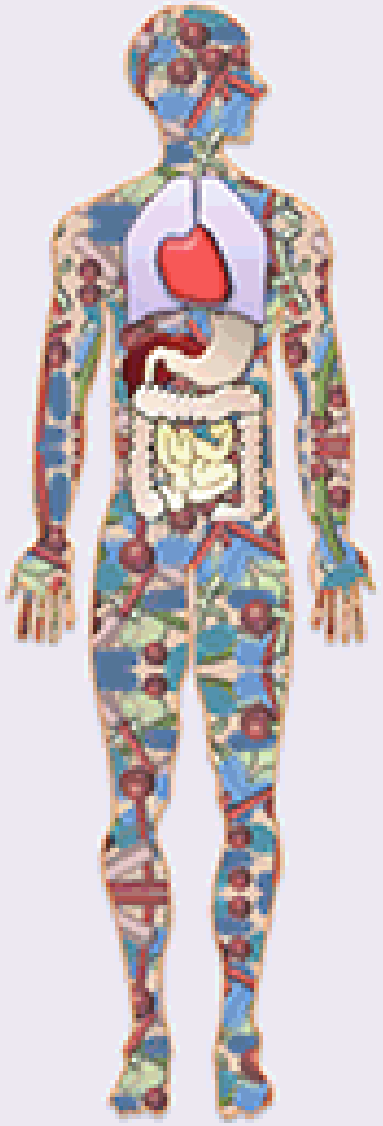
Invisible Microbiome



- ~10^{-14} million microbes
- ~ 9 million genes

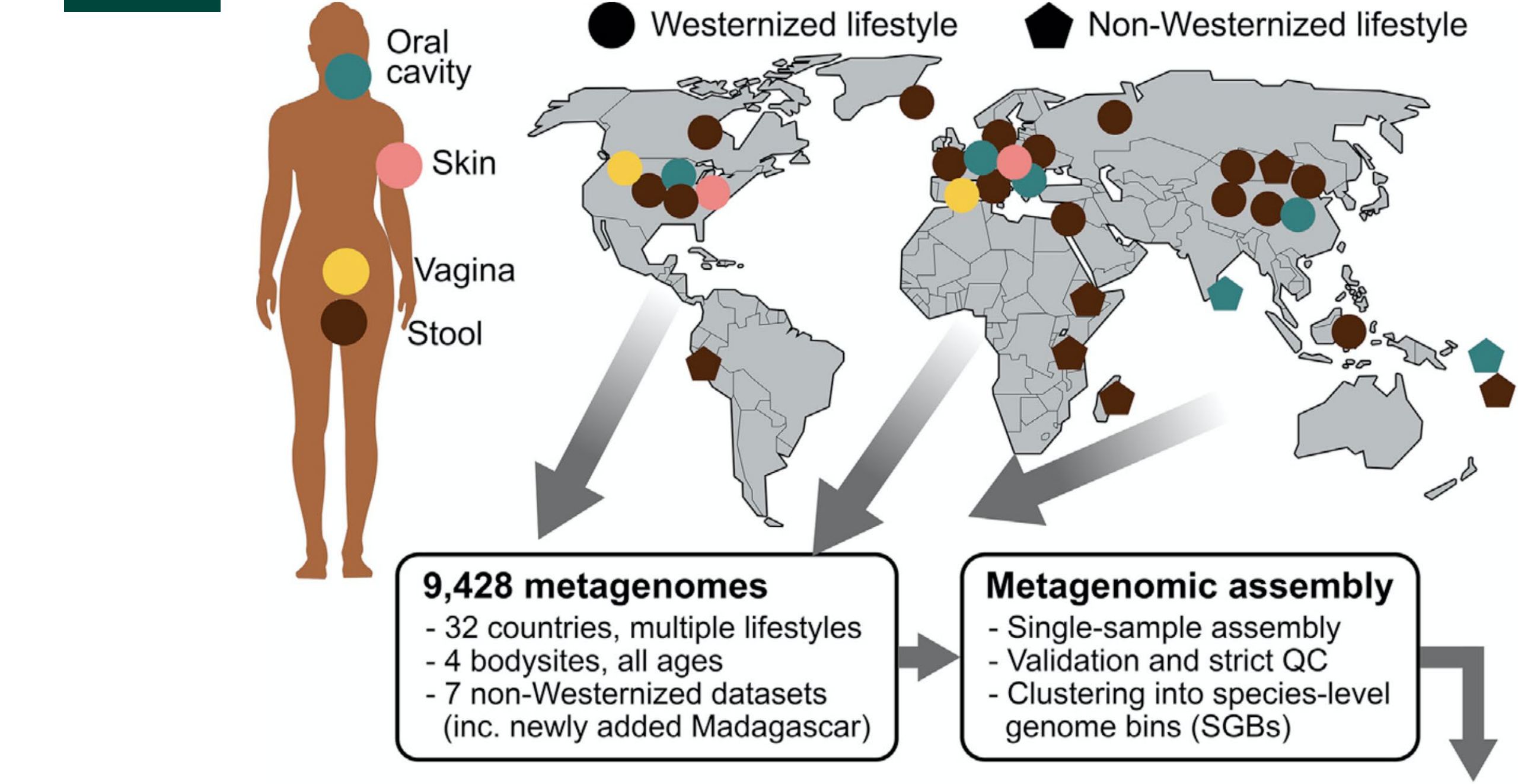
=

Complete Human



Normal functioning body

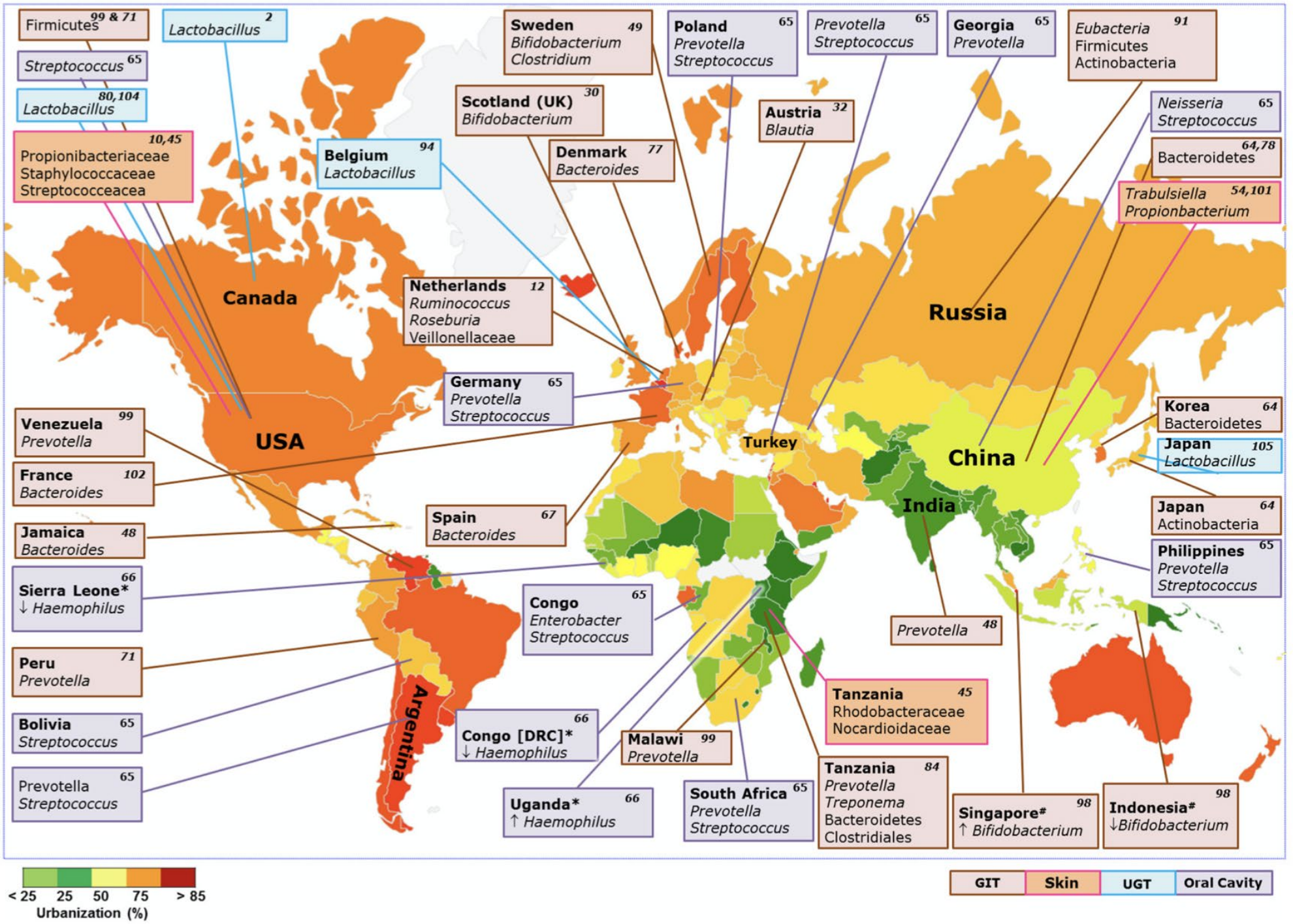
Appanna 2018



Pasolli 2019

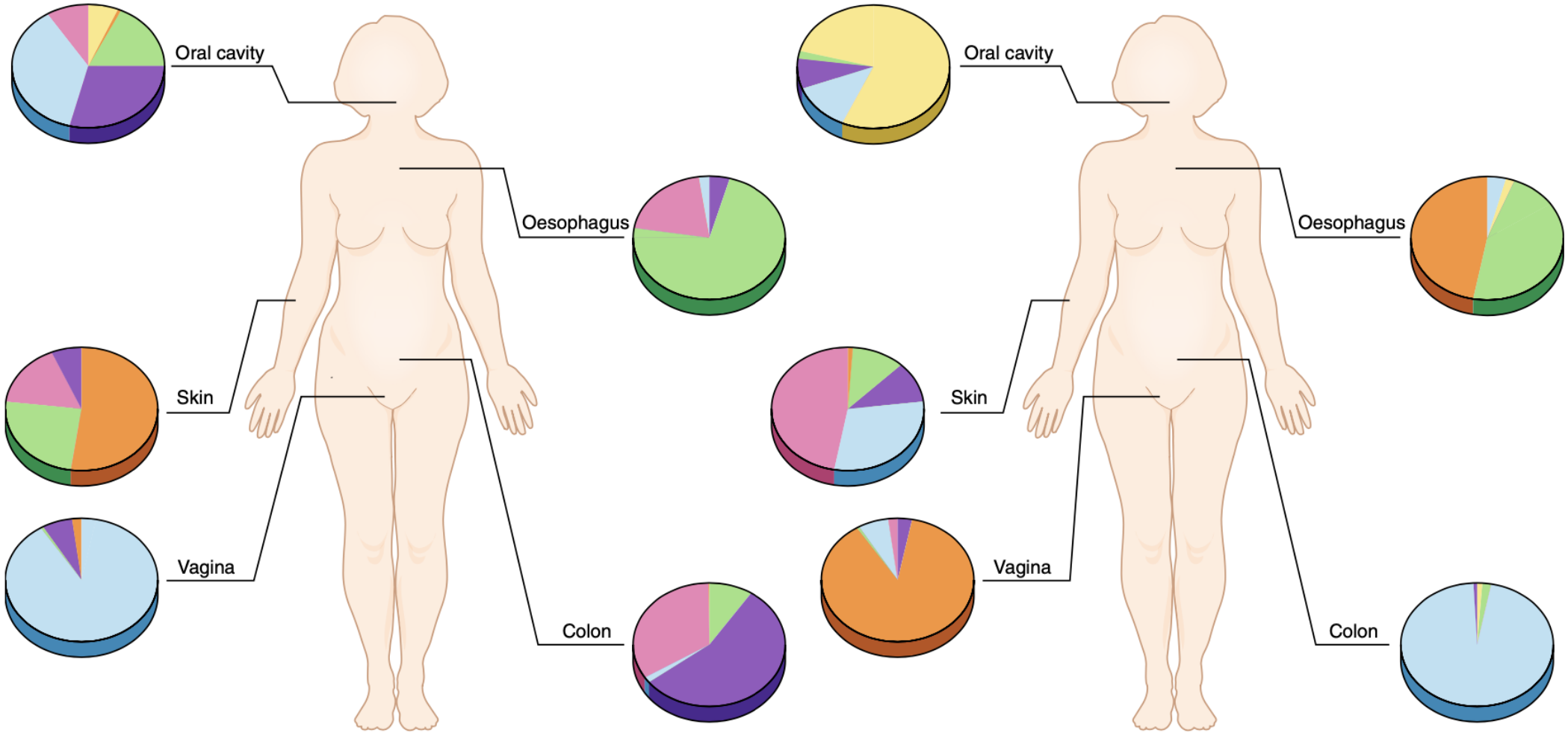
154,723 microbial genomes from metagenomes

Man kann schnell die Übersicht verlieren …



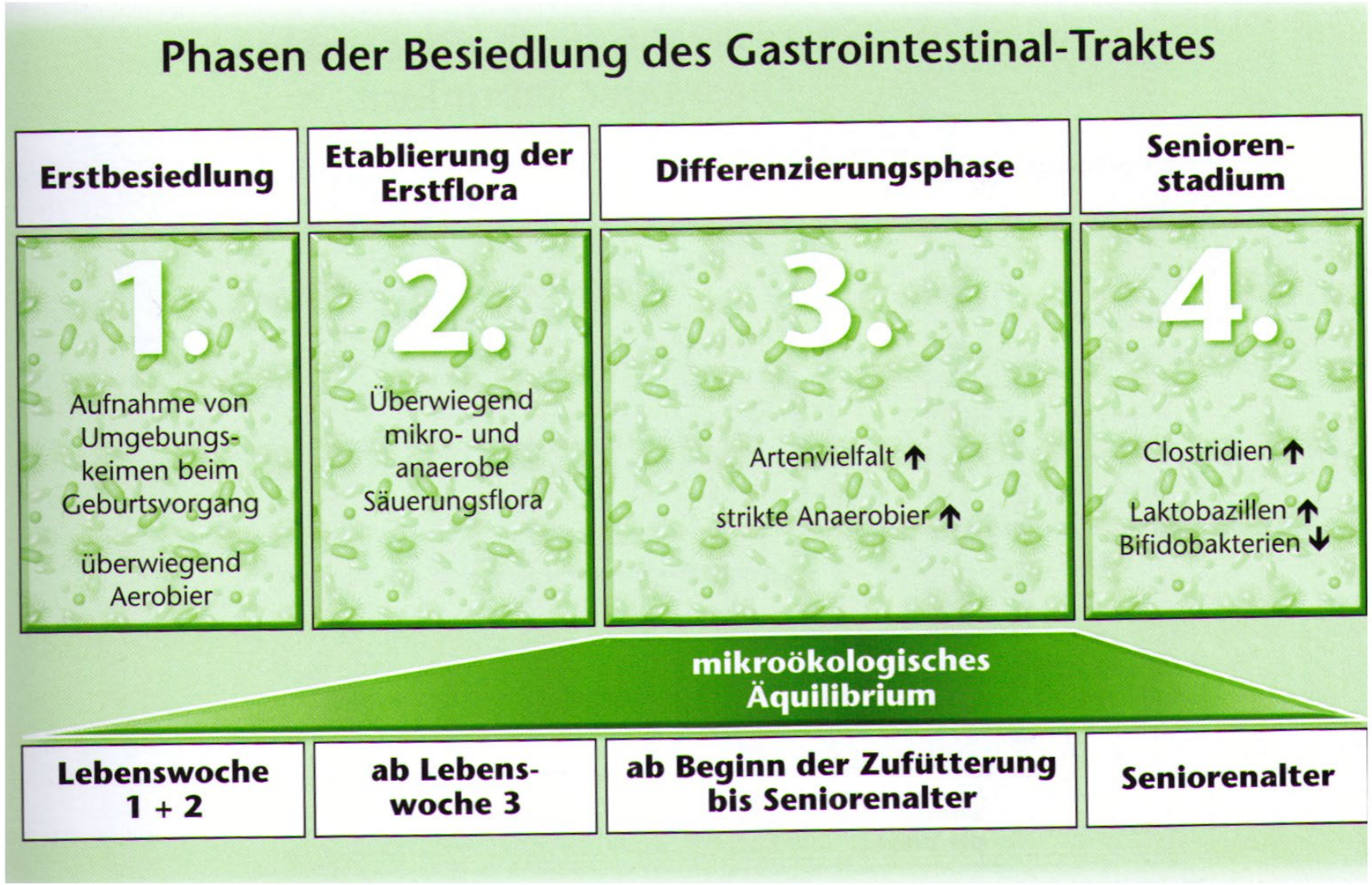
Gupta 2017

Dennoch: das Mikrobiom ist sehr individuell



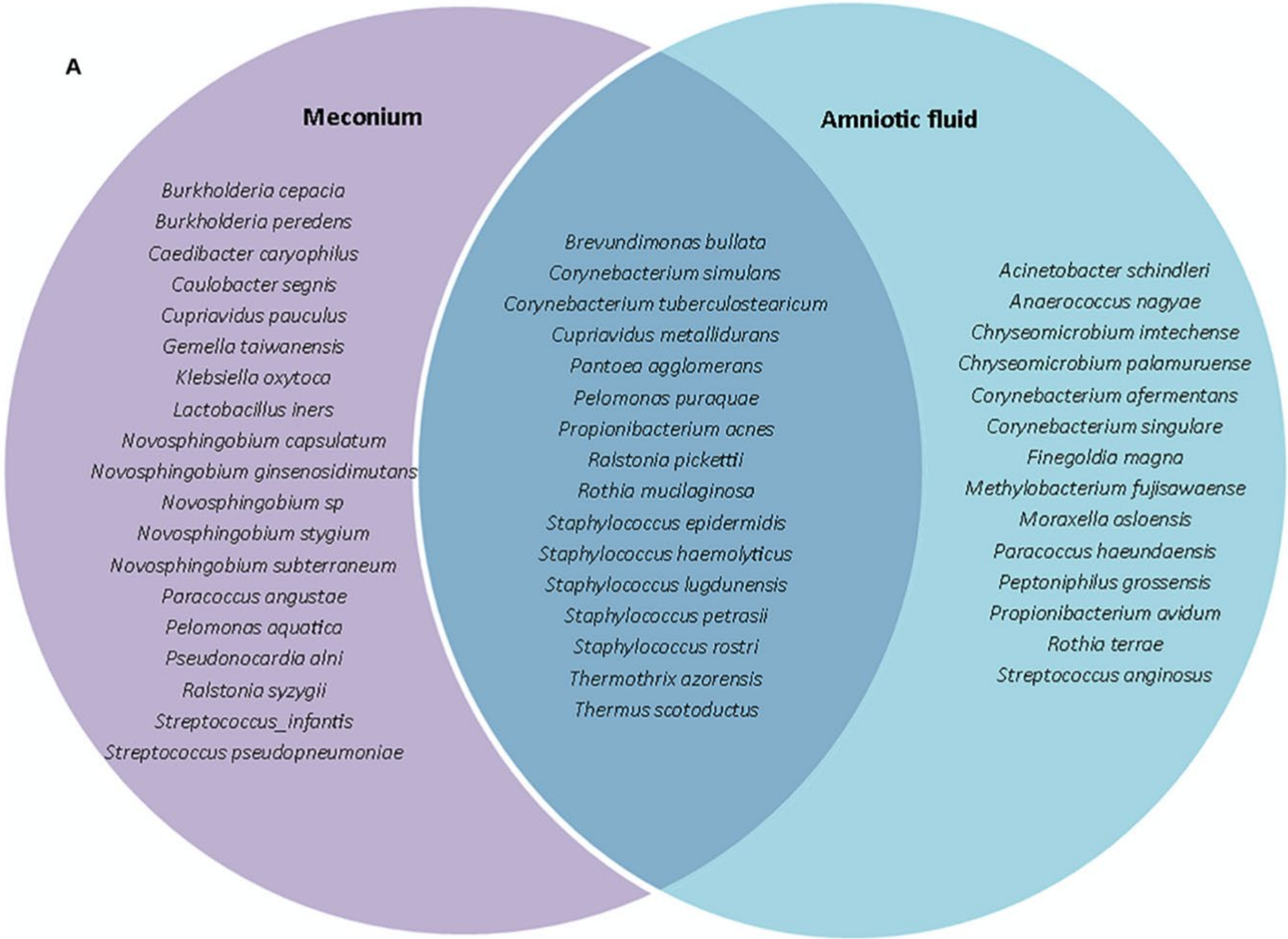
Gilbert 2018

Besiedelung: die klassische Erklärung …



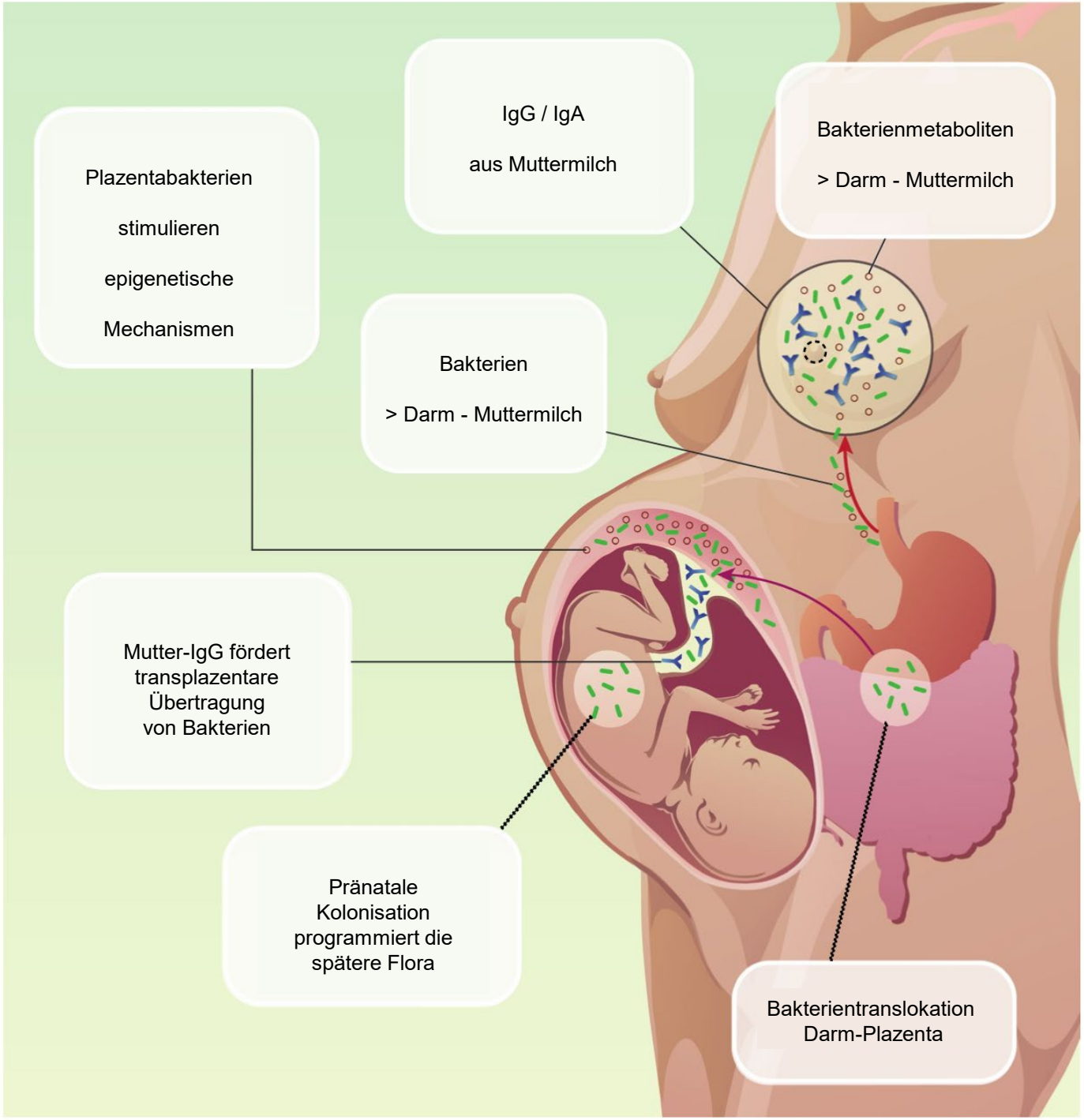
Beckmann / Rüffler 2007

… reicht nicht mehr



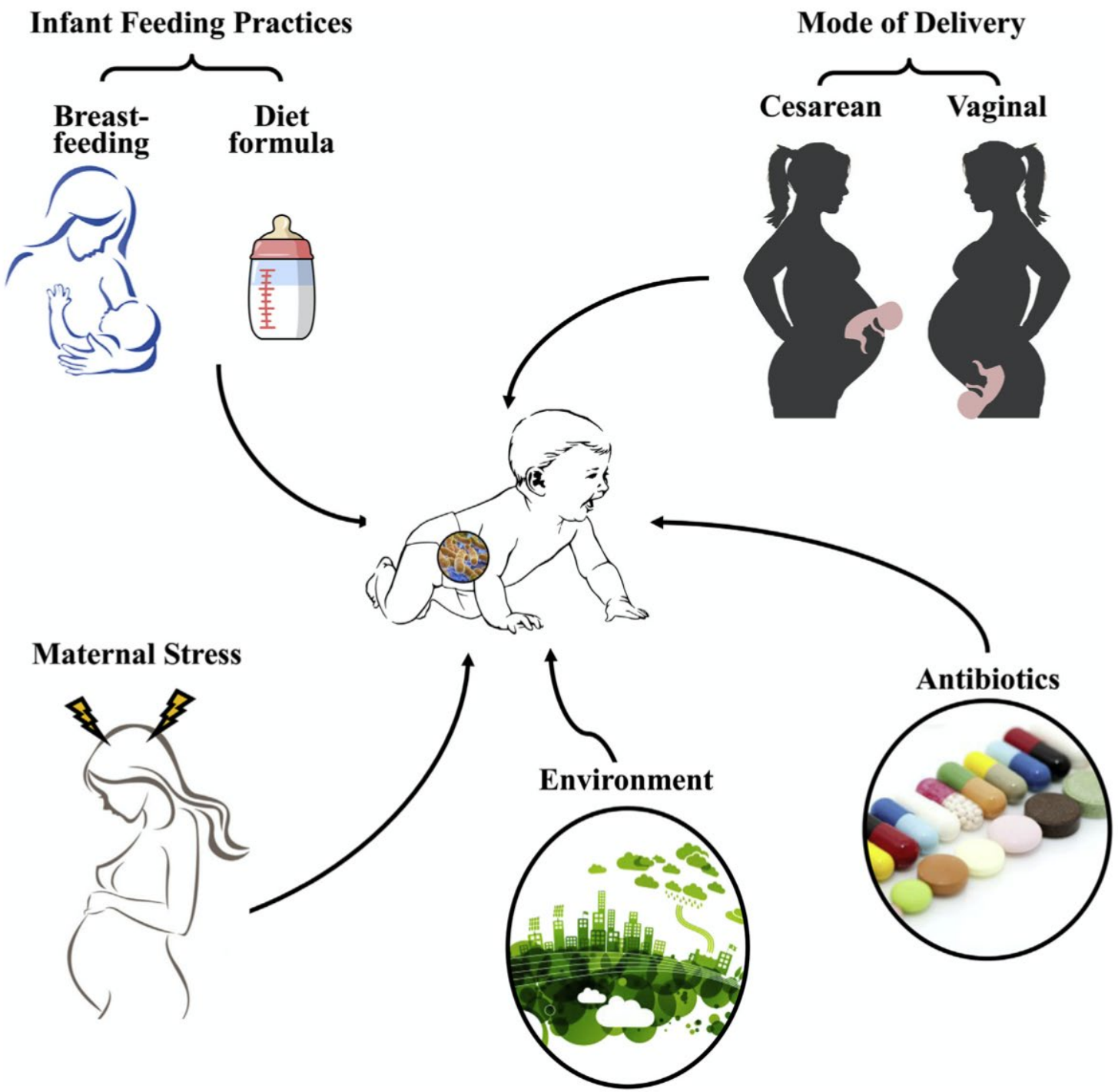
Stinson 2019

Potentielle Mechanismen



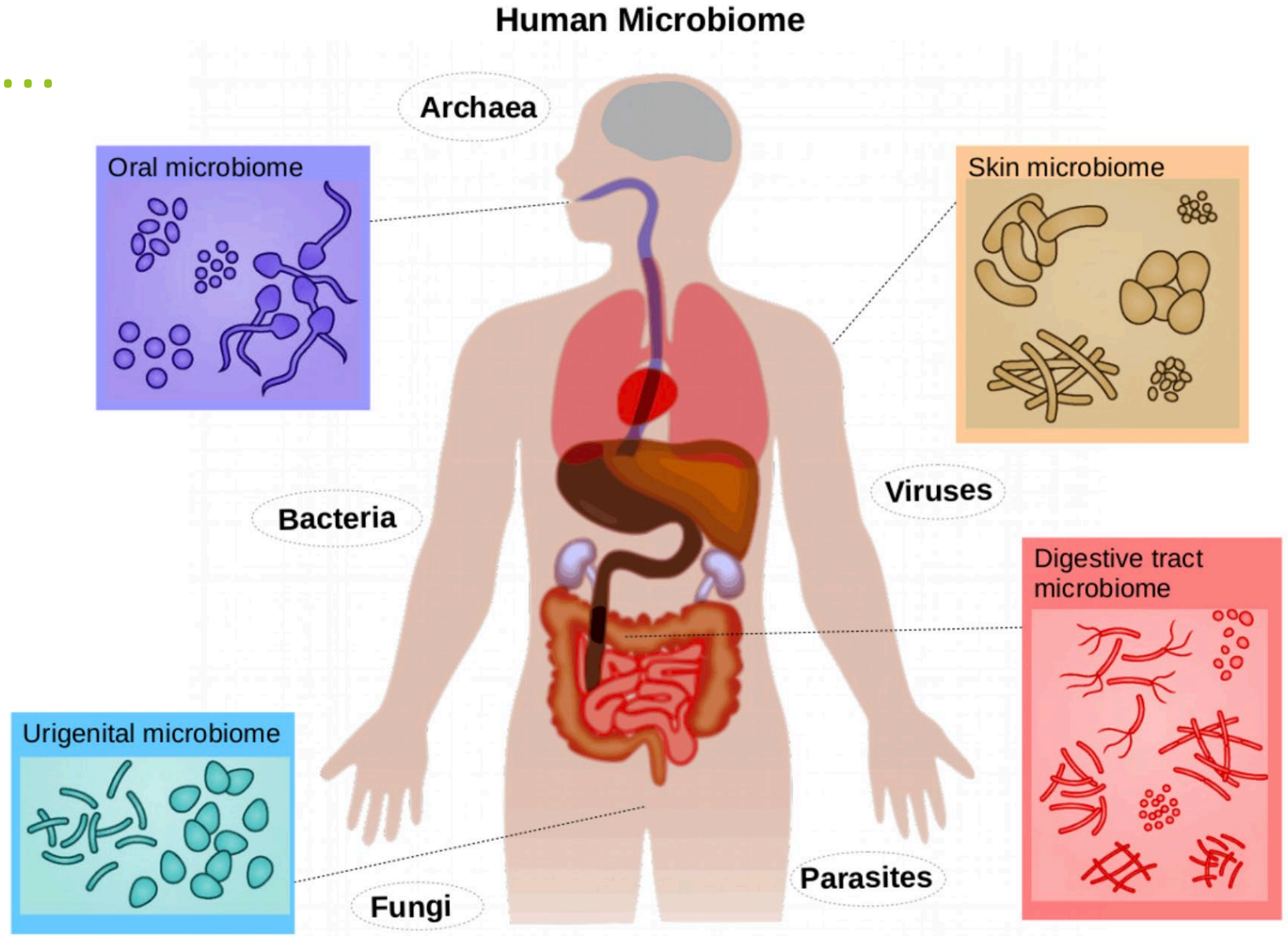
Nyangahu 2019

Weitere Einflussfaktoren



Heijtz 2016

Das Mikrobiom ist mehr …



Marks 2018

Bakterien: Hauptgruppen (99%)

Actinobakterien

Bacteroidetes

Firmicuten

Proteobakterien

Bevor wir total verrückt werden - ein Beispiel:

- Stamm (Phyla)
  - Klasse
    - Ordnung
      - Familie
        - Gattung
          - Art

- Bacteroidetes
  - Bacteroidia
    - Bacteroidales
      - Bacteroidaceae
        - Bacteroides
          - Bacteroides faeces

Beispiel: Stamm Actinobakterien

- Klasse Acidimicrobiia
  - Ordnung Acidimicrobiales
    - Unterordnung „Acidimicrobineae“
      - Familie Acidimicrobiaceae
      - Familie Iamiaceae
- Klasse Actinobacteria
  - Ordnung Acidothermales
    - Familie Acidothermaceae
  - Ordnung Actinomycetales
    - Unterordnung Actinomycineae
      - Familie Actinomycetaceae
    - Unterordnung Actinopolysporineae
      - Familie Actinopolysporaceae
    - Unterordnung Catenulisporineae
      - Familie Actinospicaceae
      - Familie Catenulisporaceae
    - Unterordnung Corynebacterineae
      - Familie Corynebacteriaceae
      - Familie Dietziaceae
      - Familie Mycobacteriaceae
      - Familie Nocardiaceae
      - Familie Segniliparaceae
      - Familie Tsukamurellaceae
    - Unterordnung Glycomycineae
      - Familie Glycomycetaceae
    - Unterordnung Jiangellineae
      - Familie Jiangellaceae
    - Unterordnung Micromonosporineae
      - Familie Micromonosporaceae
    - Unterordnung Propionibacterineae
      - Familie Nocardioidaceae
      - Familie Propionibacteriaceae
    - Unterordnung Pseudonocardineae
      - Familie Pseudonocardiaceae
    - Unterordnung Streptomycineae
      - Familie Streptomycetaceae
    - Unterordnung Streptosporangineae
      - Familie Nocardiopsaceae
      - Familie Streptosporangiaceae
      - Familie Thermomonosporaceae
  - Ordnung Actinopolysporales
    - Familie Actinopolysporaceae
  - Ordnung Bifidobacteriales
    - Familie Bifidobacteriaceae
  - Ordnung Catenulisporales
    - Familie Actinospicaceae
    - Familie Catenulisporaceae
  - Ordnung Cryptosporangiales
    - Familie Cryptosporangiaceae
  - Ordnung Frankiales (alternativ: Motilibacterales)
    - Familie Frankiaceae
    - Familie Motilibacteraceae
  - Ordnung Geodermatophilales
    - Familie Antricoccaceae
    - Familie Geodermatophilaceae
  - Ordnung Glycomycetales
    - Familie Glycomycetaceae
  - Ordnung Jatrophihabitantales
    - Familie Jatrophihabitantaceae
  - Ordnung Jiangellales
    - Familie Jiangellaceae
  - Ordnung Kineosporiales
    - Familie Kineosporiaceae
  - Ordnung Micrococcales
    - Familie Beutenbergiaceae
    - Familie Bogoriellaceae
    - Familie Brevibacteriaceae
    - Familie Cellulomonadaceae
    - Familie Demequinaceae
    - Familie Dermabacteraceae
    - Familie Dermacoccaceae
    - Familie Dermatophilaceae
    - Familie Intrasporangiaceae
    - Familie Jonesiaceae (inklusive ehemaliger Sanguibacteraceae)
    - Familie Kytococcaceae
    - Familie Microbacteriaceae
    - Familie Micrococcaceae
    - Familie Ornithinimicrobiaceae
    - Familie Promicromonosporaceae
    - Familie Rarobacteraceae
    - Familie Ruaniaceae
    - Familie Tropherymataceae
    - Familie Yaniellaceae
  - Ordnung Micromonosporales
    - Familie Micromonosporaceae
  - Ordnung Mycobacteriales (alternativ: Corynebacteriales)
    - Familie Corynebacteriacea
    - Familie Dietziaceae
    - Familie Gordoniaceae
    - Familie Lawsonellaceae
    - Familie Mycobacteriaceae
    - Familie Nocardiaceae
    - Familie Segniliparaceae
    - Familie Tsukamurellaceae
  - Ordnung Nakamurellales
    - Familie Nakamurellaceae
  - Ordnung Propionibacteriales
    - Familie Actinopolymorphaceae
    - Familie Kribbellaceae
    - Familie Nocardioidaceae
    - Familie Propionibacteriaceae
  - Ordnung Pseudonocardiales
    - Familie Pseudonocardiaceae
  - Ordnung Sporichthyales
    - Familie Sporichthyaceae
  - Ordnung Streptosporangiales
    - Familie Streptomycetaceae
- Klasse Coriobacteriia
  - Ordnung Coriobacteriales
    - Unterordnung „Coriobacterineae“
      - Familie Atopobiaceae
      - Familie Coriobacteriaceae
  - Ordnung Eggerthellales
    - Familie Eggerthellaceae
- Klasse Nitriliruptoria
  - Ordnung Egibacterales
    - Familie Egibacteraceae
  - Ordnung Egicoccales
    - Familie Egicoccaceae
  - Ordnung Euzebyales
    - Familie Euzebyaceae
  - Ordnung Nitriliruptorales
    - Familie Nitriliruptoraceae
- Klasse Rubrobacteria
  - Ordnung Gaiellales
    - Familie Gaiellaceae
  - Ordnung Rubrobacterales
    - Unterordnung „Rubrobacterineae“
      - Familie Rubrobacteraceae
  - Ordnung Solirubrobacterales
    - Familie Baekduiaceae
    - Familie Conexibacteraceae
    - Familie Paraconexibacteraceae
    - Familie Parviterribacteraceae
    - Familie Patulibacteraceae
    - Familie Solirubrobacteraceae
- Klasse Thermoleophilia
  - Ordnung Thermoleophilales
    - Familie Thermoleophilaceae

Allein die Mundflora beherbergt 12 verschiedene „phylae (= Stämme)“

Firmicutes

Fusobacteriae

Proteobacteriae

Actinobacteriae

Bacteroidetes

Chlamydiae

Chloroflexi

Spirochaetes

SR1

Synergistetes

Saccharibacteria

Gracilibacteria

Bakterien: wer ist wo?

Esophagus pH
< 4.0

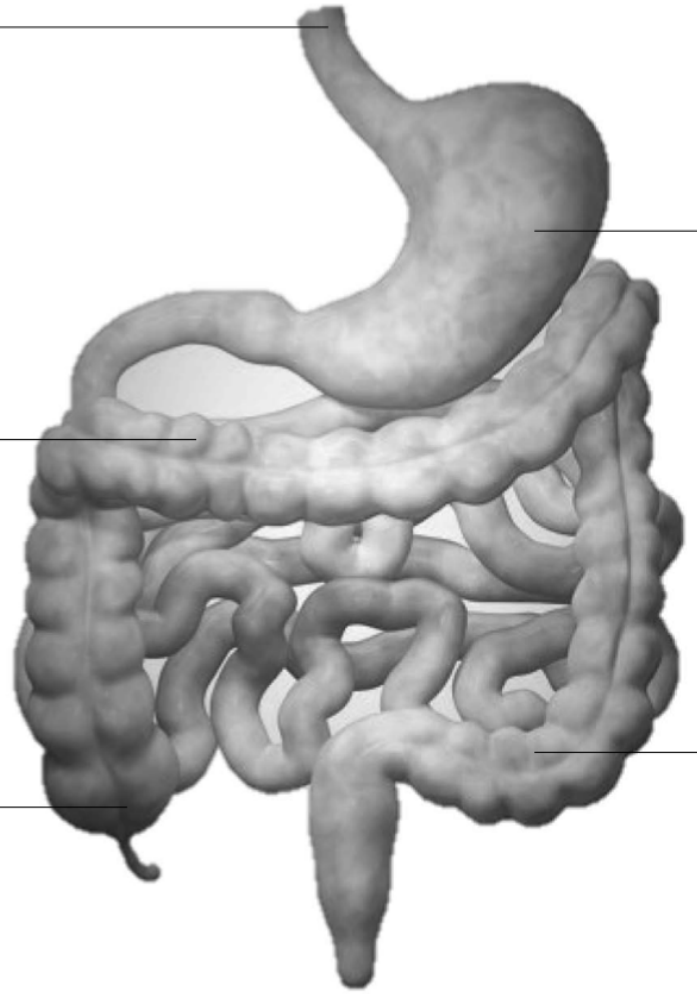
Bacteroides, *Gemella*, *Megasphaera*, *Pseudomonas*, *Prevotella*, *Rothia* sps., *Streptococcus*, *Veillonella*

Colon pH
5-5.7

Bacteroides, *Clostridium*, *Prevotella*, *Porphyromonas*, *Eubacterium*, *Ruminococcus*, *Streptococcus*, *Enterobacterium*, *Enterococcus*, *Lactobacillus*, *Peptostreptococcus*, *Fusobacteria*

Cecum pH
5.7

Lachnospira, *Roseburia*, *Butyrivibrio*, *Ruminococcus*, *Fecalibacterium*, *Fusobacteria*



Stomach pH
2

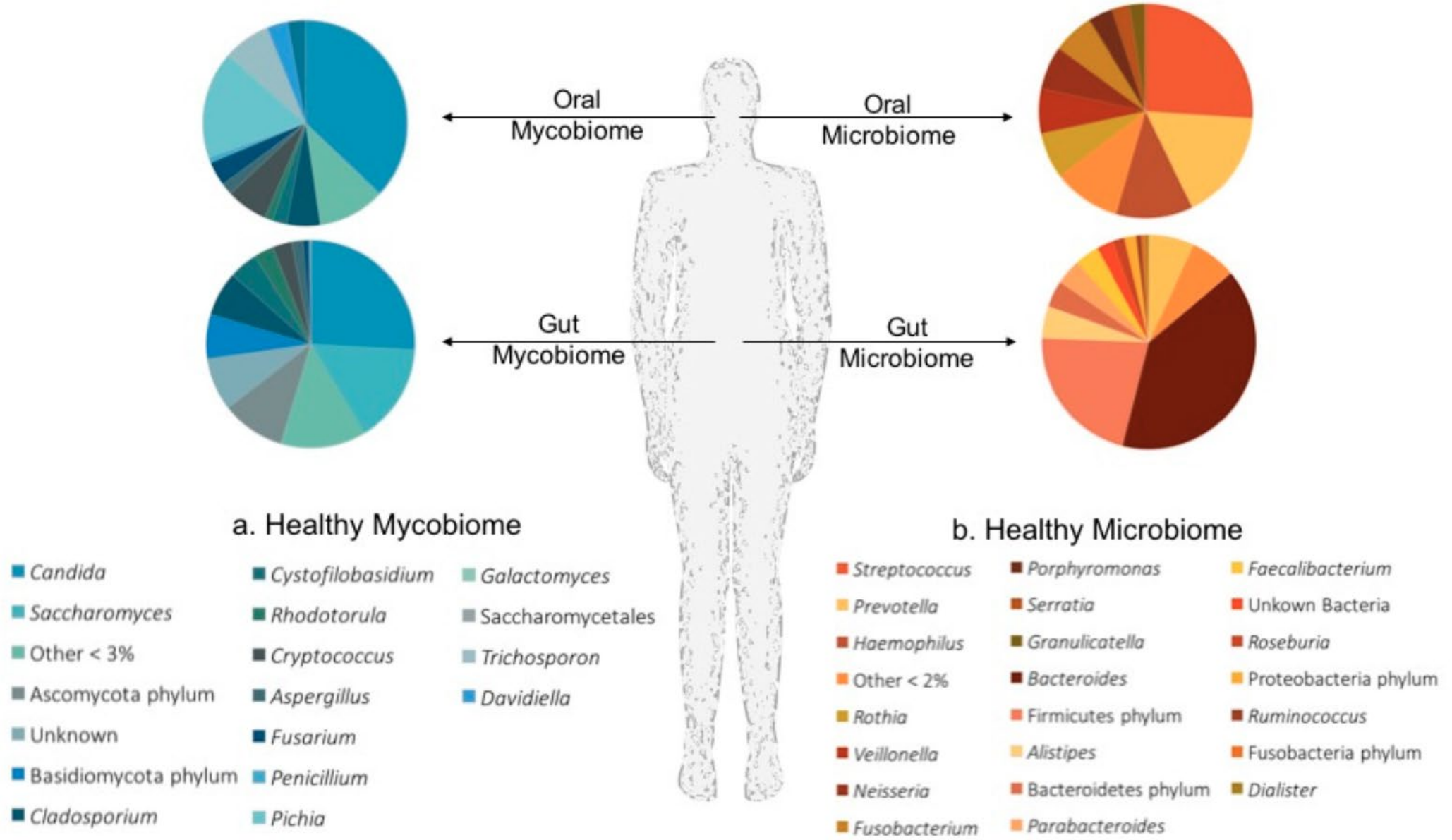
Streptococcus, *Lactobacillus*, *Prevotella*, *Enterococcus*, *Helicobacter pylori*

Small intestine pH
5-7

Bacteroides, *Clostridium*, *Streptococcus*, *Lactobacillus*, *γ-Proteobacteria*, *Enterococcus*

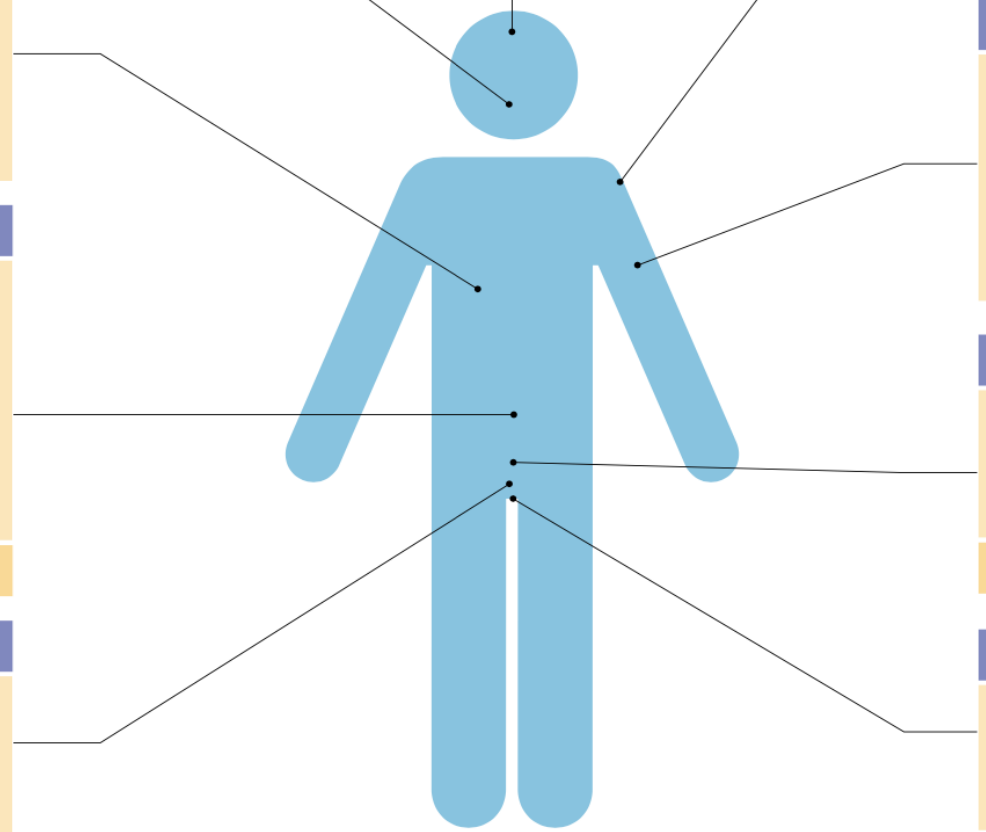
Jandhyala 2015

Pilze …



Witherden 2017

Viren ...



Oral cavity

Eukaryotic viruses	Phages
Herpesviridae	*Siphoviridae*
Redondoviridae	*Podoviridae*
Anelloviridae	*Myoviridae*
Papillomaviridae	

~10^8 VLPs per millilitre of saliva

Lung

Eukaryotic viruses	Phages
Anelloviridae	*Siphoviridae*
Redondoviridae	*Podoviridae*
Adenoviridae	*Myoviridae*
Herpesviridae	*Microviridae*
Papillomaviridae	*Inoviridae*

Gastrointestinal tract

Eukaryotic viruses	Phages
Anelloviridae	*Siphoviridae*
Adenoviridae	*Podoviridae*
Caliciviridae	*Myoviridae*
Picornaviridae	*Microviridae*
Herpesviridae	*Inoviridae*
Circoviridae	
Virgaviridae	

~10^9 VLPs per gram of faeces

Vagina

Eukaryotic viruses	Phages
Anelloviridae	*Siphoviridae*
Herpesviridae	*Podoviridae*
	Myoviridae
	Microviridae

Nervous system

Eukaryotic viruses	Phages
Herpesviridae	*Siphoviridae*
	Podoviridae
	Myoviridae

~10^4 VLPs per millilitre of cerebrospinal fluid

Blood

Eukaryotic viruses	Phages
Anelloviridae	*Siphoviridae*
Herpesviridae	*Podoviridae*
Picornaviridae	*Myoviridae*
	Microviridae
	Inoviridae

~10^8 VLPs per millilitre of saliva

Skin

Eukaryotic viruses	Phages
Adenoviridae	*Siphoviridae*
Anelloviridae	*Podoviridae*
Circoviridae	*Myoviridae*
Herpesviridae	
Papillomaviridae	
Polyomaviridae	

Urinary system

Eukaryotic viruses	Phages
Papillomaviridae	*Siphoviridae*
Polyomaviridae	*Podoviridae*
Herpesviridae	*Myoviridae*

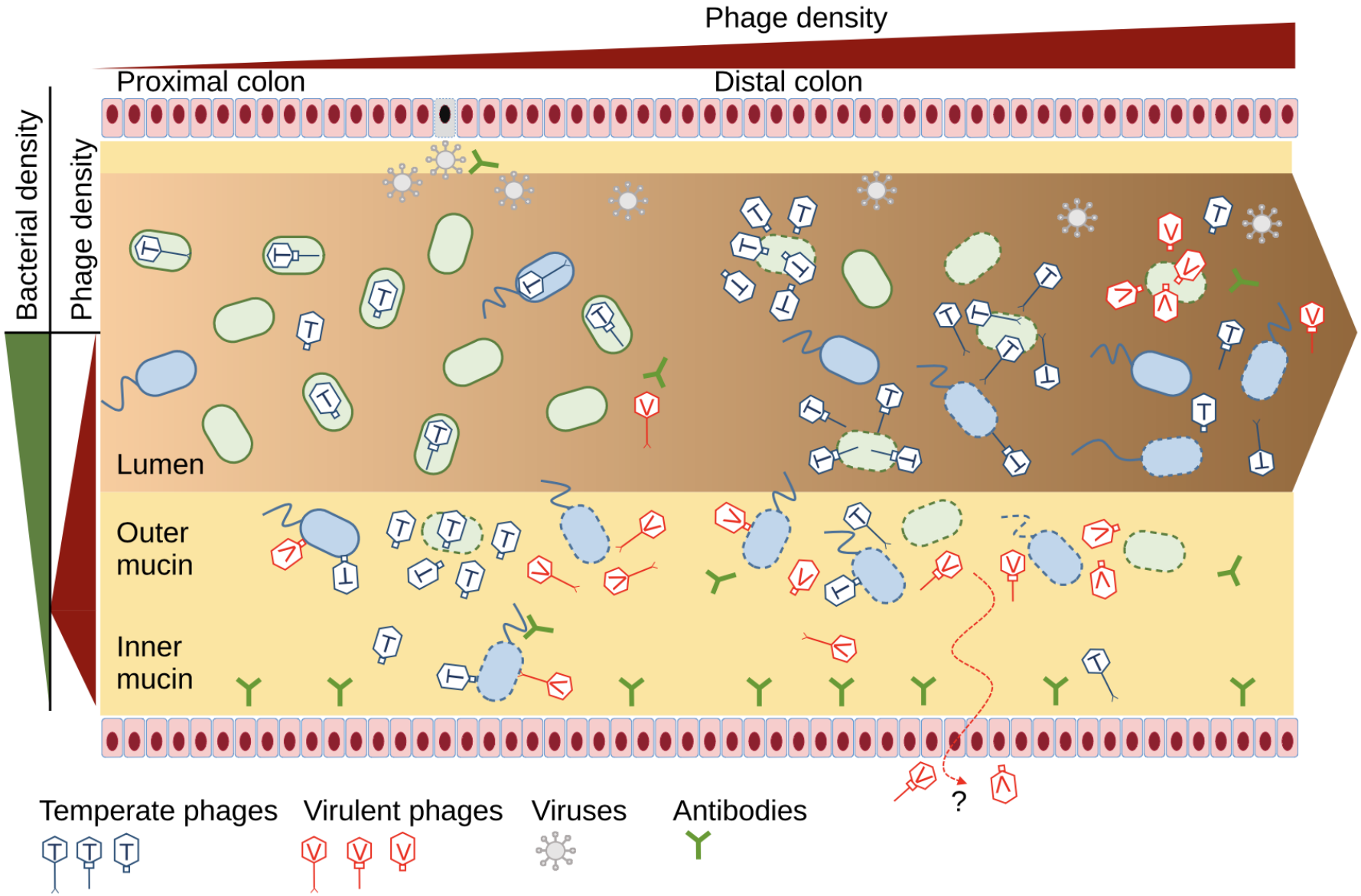
~10^7 VLPs per millilitre of urine

Semen

Eukaryotic viruses	Phages
Anelloviridae	Unknown
Papillomaviridae	
Herpesviridae	

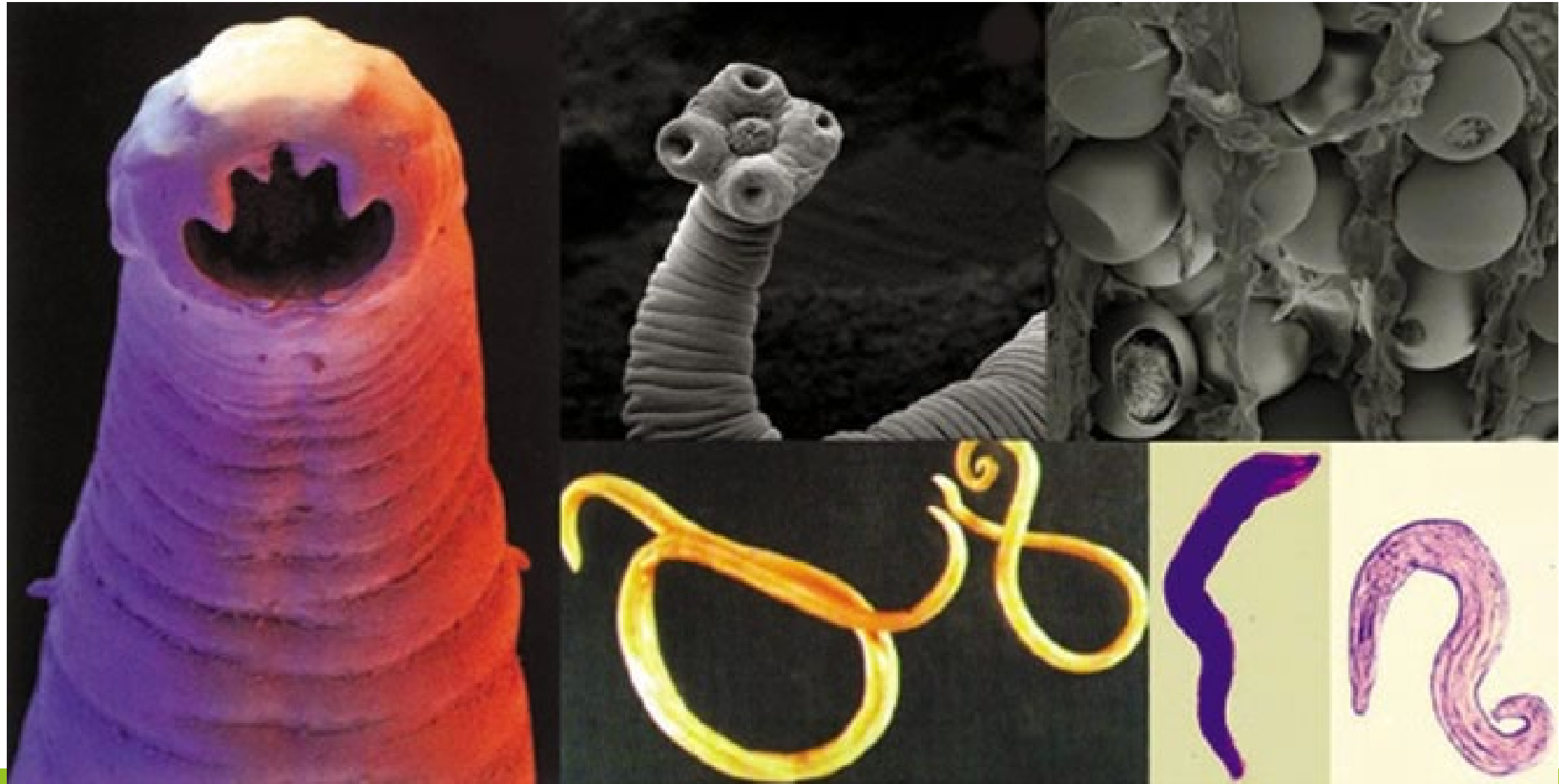
Liang 2021

Die grösste Gruppe Viren: Bakteriophagen



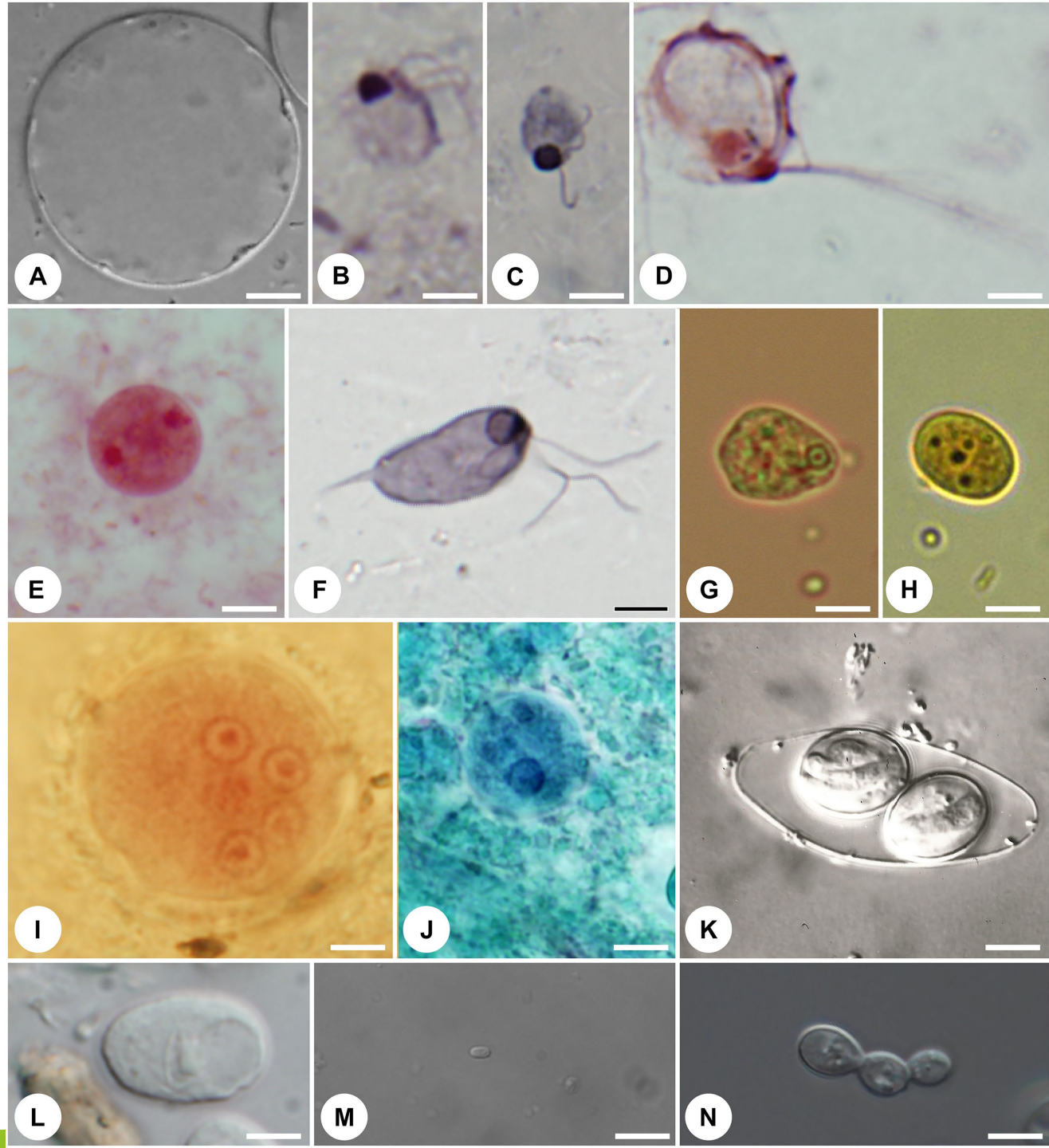
Shkoporov 2019

Parasiten …



Das menschliche Parasitom

A Blastocystis hominis
B Enteromonas hominis
C Retortamonas intestinalis
D Pentratrichomonas hominis
E Dientamoeba fragilis
F Chilomastix mesnili
G Entamoeba hartmani
H Endolimax nana
I Entamoeba coli
J Entamoeba dispar
K Isospora belli
L Iodamoeba buetschli
M Encephalitozoon cuniculi
N Candida albicans



Lukeš 2015

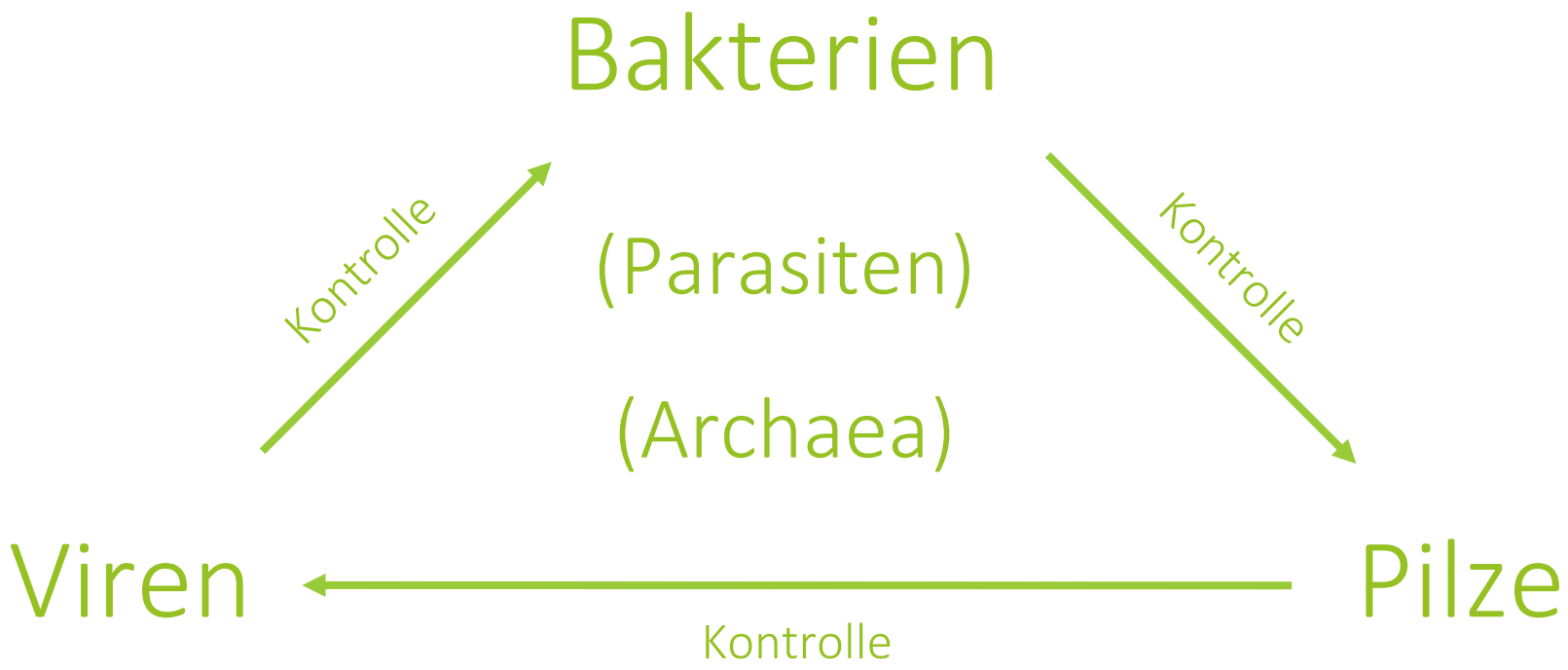
Parasiten …

Definition:

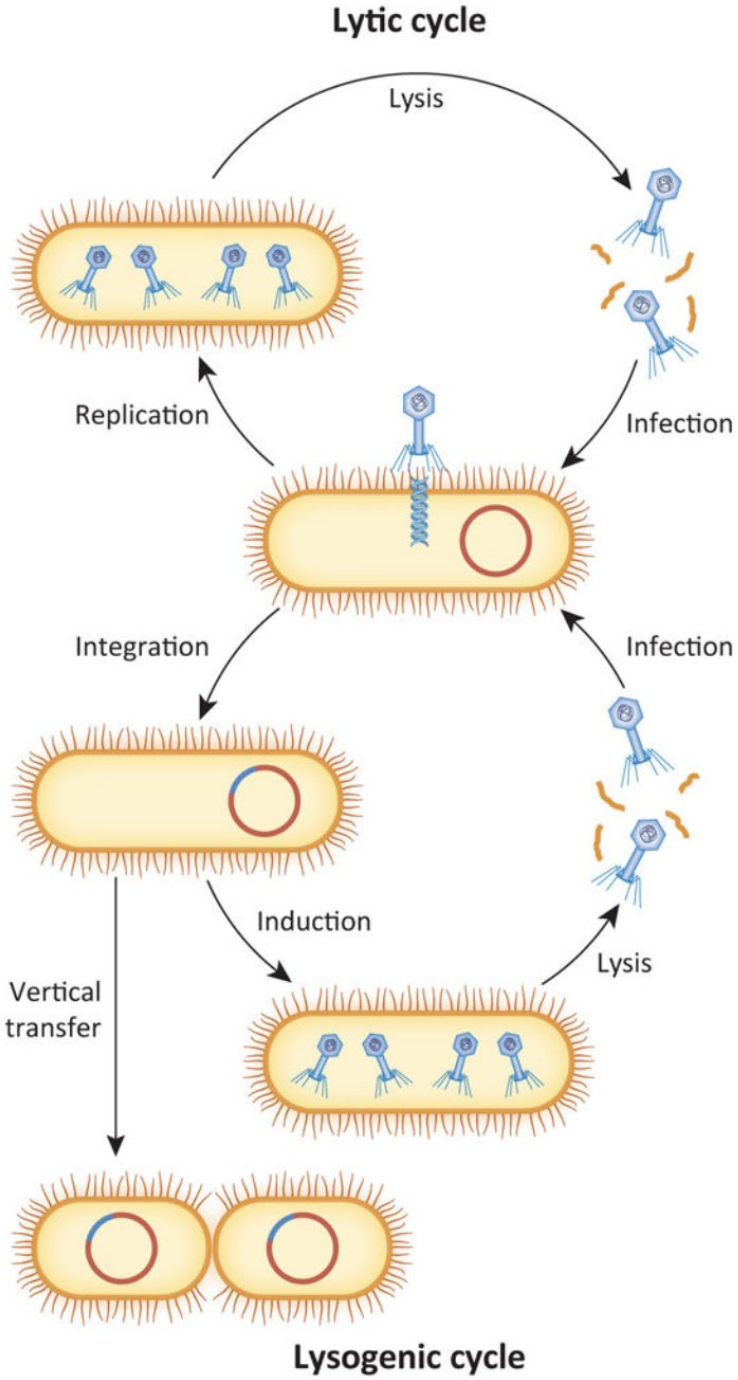
„Lebewesen, das aus dem Zusammenleben mit anderen Lebewesen einseitig Nutzen zieht, die es oft auch schädigt und bei denen es Krankheiten hervorrufen kann.“


Healthy - Dec 2014
Dying - Feb 2015
Dead - Aug 2015

Im Prinzip ist es dann doch einfach:

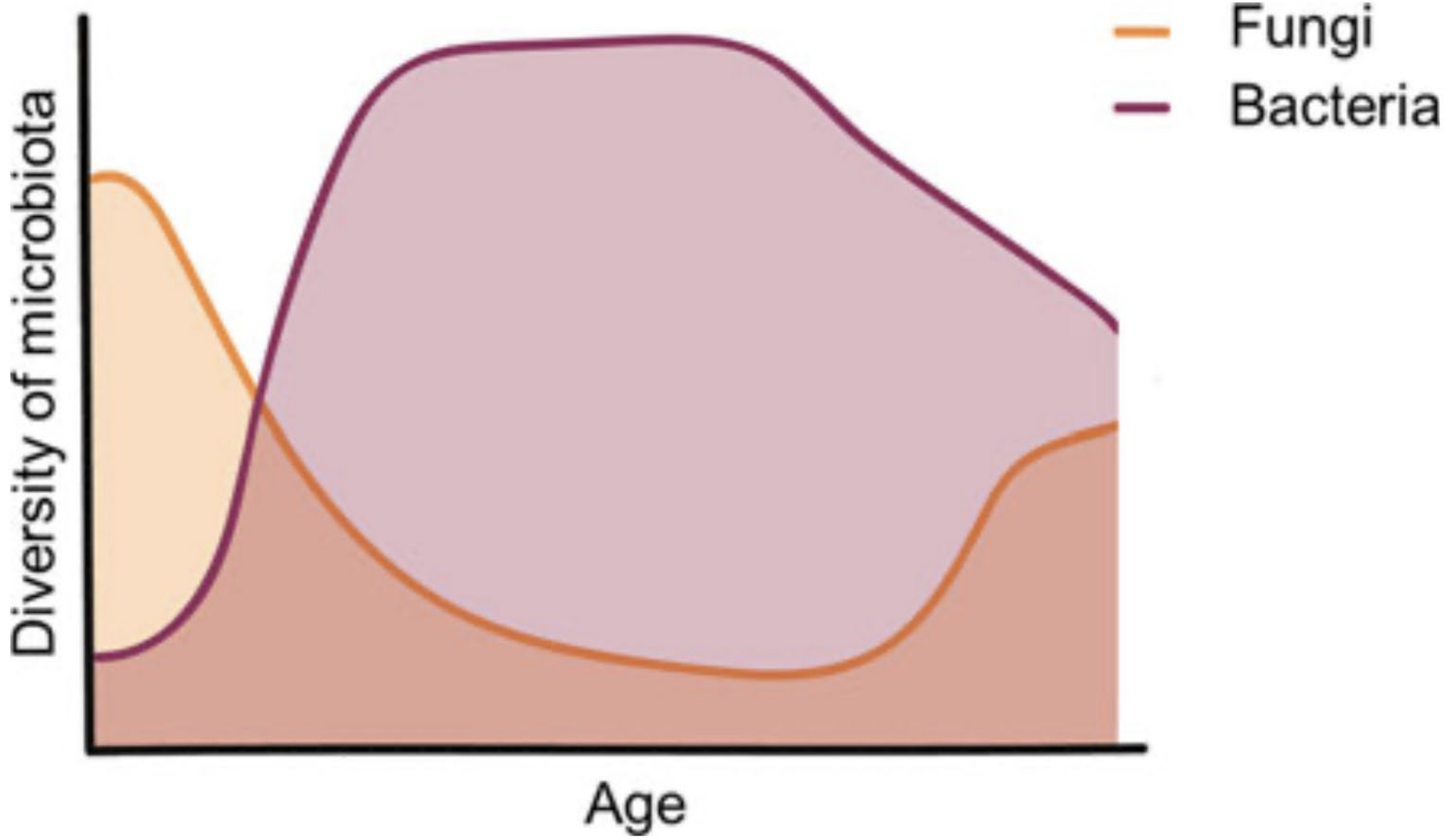


Phagen kontrollieren Bakterien



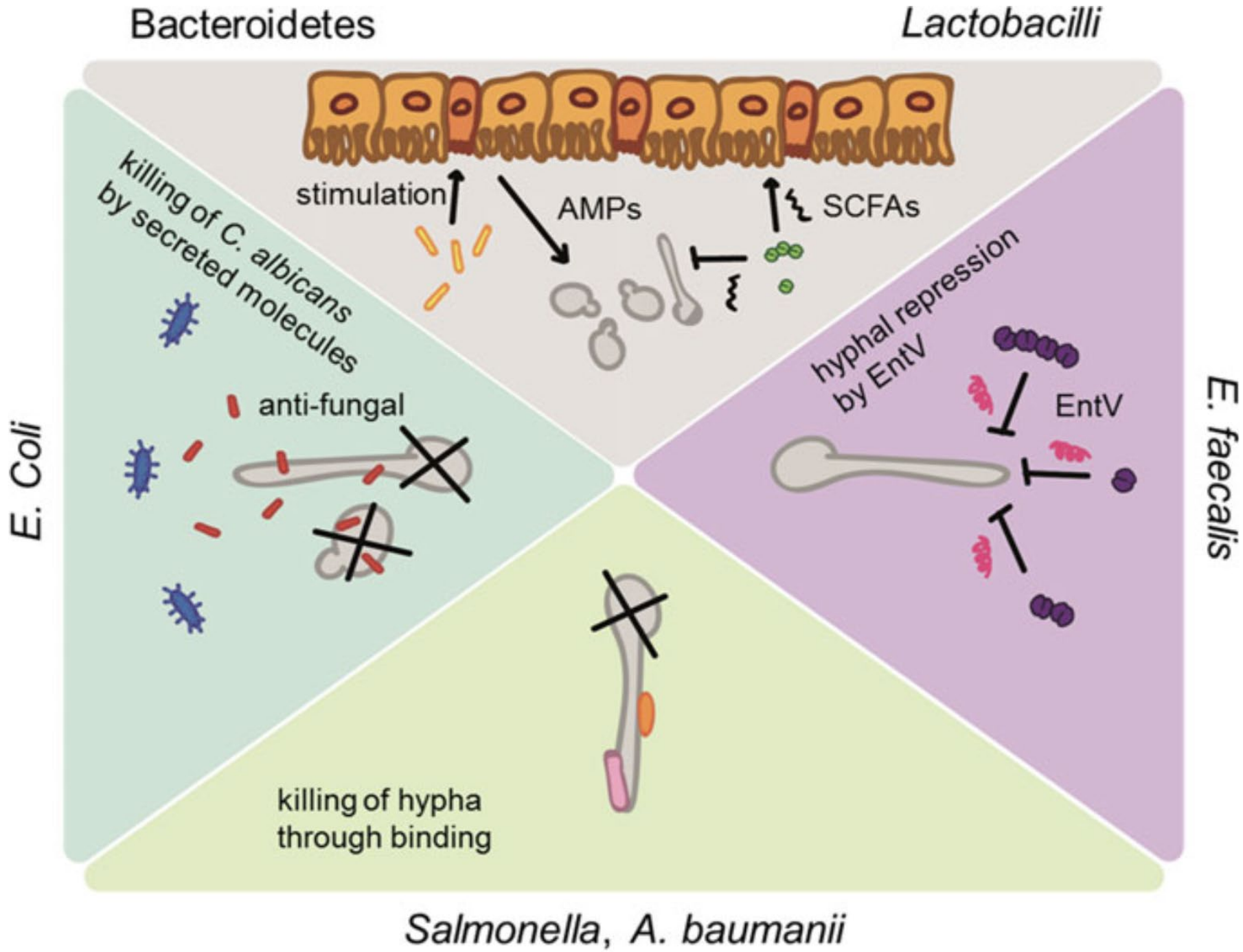
Keen 2018

Die Diversität ändert sich im Laufe des Lebens



Kapitan 2019

Beispiel: Kontrolle des Candida albicans



Kapitan 2019

Pilze kontrollieren Viren

Linnakoski 2018

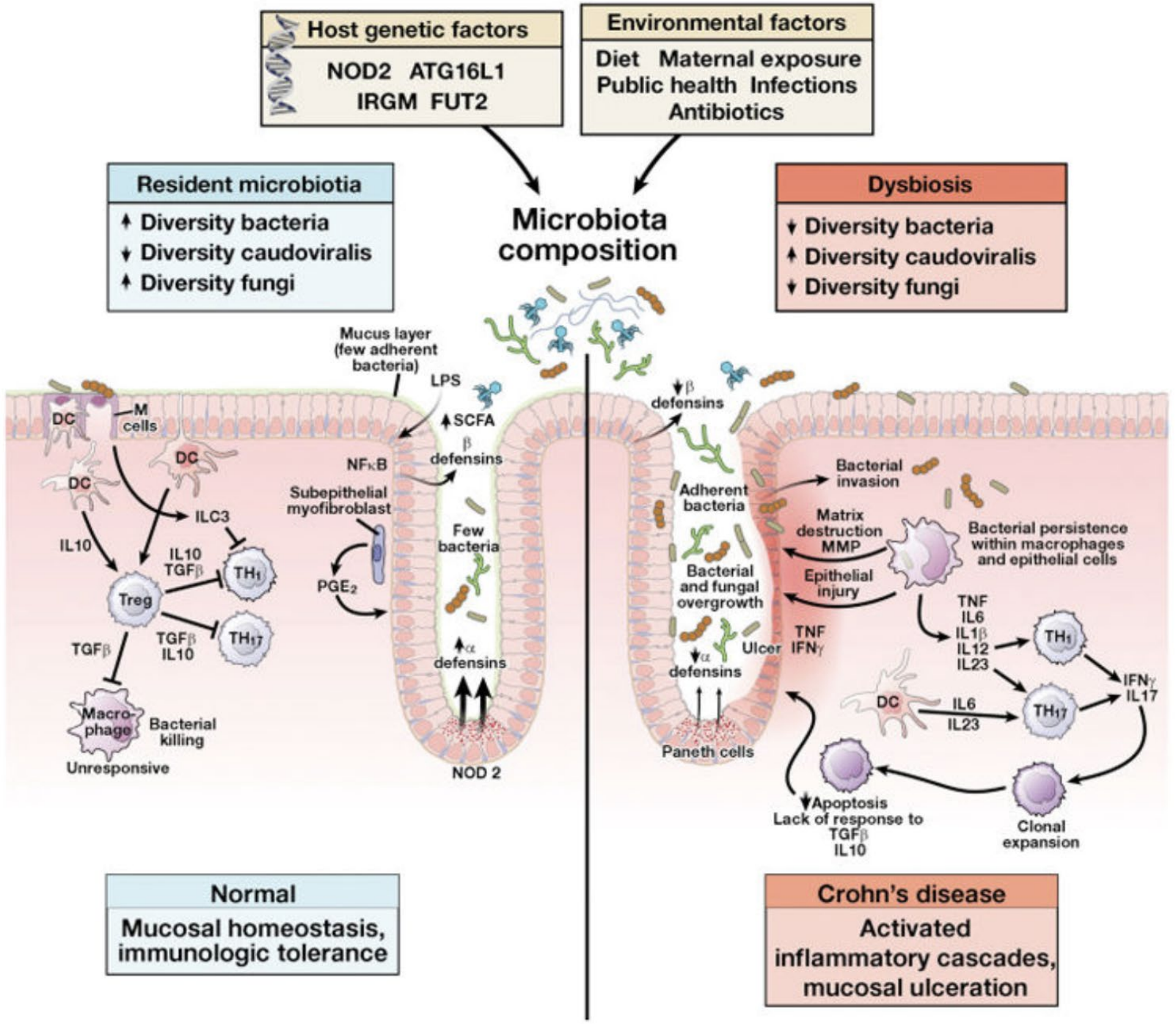
Phylum	Order	Virus*	Reference
Ascomycota	Amphisphaeriales	EV71[1], HIV-I[1]	Li et al., 2008; Wang J. et al., 2014; Jia et al., 2015
	Capnodiales	H1N1[1]	Peng et al., 2013; Wu et al., 2014
	Chaetothyriales	HIV-I[4]	Ondeyka et al., 2003; Mlinaric et al., 2005
	Diaporthales	HIV-1[4], HSV-1[1]	Jayasuriya et al., 2003; Bunyapaiboonsri et al., 2010
	Dothideales	HSV-1[5]	Isaka et al., 2007
	Eurotiales	EV71[2], DENV[3], H1N1[2], HIV-1[4], H3N2[2], JEV[1], Zika virus[2]	Omura et al., 1993; Matsuzaki et al., 1995; Singh et al., 2003a; Shiomi et al., 2005; Sebastian et al., 2011; Zhang et al., 2011; Gao et al., 2013a; He et al., 2013; Bashyal et al., 2014; Fang et al., 2014; Peng et al., 2014; Wang J.-F. et al., 2014; Stierle and Stierle, 2015; Yu et al., 2016; Raekiansyah et al., 2017
	Glomerellales	HIV-1[4]	Mlinaric et al., 2005
	Helotiales	HSV-1[1]	Rowley et al., 2003
	Hypocreales	EV71[2], HIV-1[4], HSV-1[1], H1N1[1,4], H3N2[1,4]	Hazuda et al., 1999; Yoshimoto et al., 1999; Minagawa et al., 2002; Singh et al., 2003a,b; Sawadjoon et al., 2004; Mlinaric et al., 2005; Jiang et al., 2011; Ma et al., 2013; Li et al., 2014; Zhao et al., 2017; Pang et al., 2018
	Microascales	HIV-1[4]	Mlinaric et al., 2005
	Ophiostomatales	HIV-1[4]	Mlinaric et al., 2005
	Pezizales	HIV-1[4]	Pérez et al., 2014
	Pleosporales	HIV-1[4], HSV-1[1]	Hazuda et al., 1999; Singh et al., 2002; Guo et al., 2009; Shushni et al., 2011; Bashyal et al., 2014; Zhang et al., 2015
	Saccharomycetales	HIV-1[4]	Mlinaric et al., 2005
	Sordaliales	HIV-1[4], influenza A and B[4]	Mlinaric et al., 2005; Sacramento et al., 2015
	Xylariales	H1N1[2], HIV-1[4], HSV-1[1]	Hazuda et al., 1999; Pittayakhajonwut et al., 2005; Zhang et al., 2016
Basidiomycota	Agaricales	BoHV-1[1,3], H1N1[2], HCV[5], HBV[4,5], HCV[5], HIV-1[2], HSV-1[1,2,3], HSV-2[1,2], influenza A[2], polio[2], RSV[1,2], vaccinia[1], VS[1], VZV[2], WEE[2]	Kandefer-Szerszeń et al., 1980; Amoros et al., 1997; Saboulard et al., 1998; Piraino and Brandt, 1999; Wang and Ng, 2000, 2001; Sorimachi et al., 2001; Lehmann et al., 2003; Chen et al., 2004; Mlinaric et al., 2005; Bruggemann et al., 2006; Grinde et al., 2006; Faccin et al., 2007; Razumov et al., 2010; Zhu et al., 2010; Cardozo et al., 2011, 2014; Gao et al., 2013b; Yamamoto et al., 2013; Krupodorova et al., 2014
	Boletales	HIV-1[4], HSV-1[5], vaccinia[1], VS[1]	Kandefer-Szerszeń et al., 1980; Kanokmedhakul et al., 2003; Mlinaric et al., 2005
	Cantharellales	HIV-1[4], vaccinia[1]	Kandefer-Szerszeń et al., 1980; Mlinaric et al., 2005
	Gomphales	vaccinia[1]	Kandefer-Szerszeń et al., 1980
	Hymenochaetales	influenza A and B[4]	Ichimura et al., 1998; Awadh Ali et al., 2003;
	Polyporales	BoHV-1[1], EBV-A[3], EV71$_2$, H1N1[2], H3N2[2], HCV[2], HHV-1[2,4], HIV[4], HSV-1[1,2,4], HSV-2[1,2], influenza A[2], MCMV[1,2], measles[2], mumps[2], polio[1,2,3], PV-1[1], VSV[2], WEE[2], EMCV[2,4]	Hirose et al., 1987; Okada and Minamishima, 1987; Tochikura et al., 1987, 1988; Suzuki et al., 1989; Sorimachi et al., 1990; Sarkar et al., 1993; Amoros et al., 1997; Collins and Ng, 1997; El-Mekkawy et al., 1998; Min et al., 1998; Eo et al., 1999a,b, 2000; Kim et al., 2000; Iwatsuki et al., 2003; Mothana et al., 2003; Ngai and Ng, 2003; Singh et al., 2003a; Mlinaric et al., 2005; Niedermeyer et al., 2005; Gu et al., 2007; El Dine et al., 2008; Sato et al., 2009; Razumov et al., 2010; Rincão et al., 2012; Teplyakova et al., 2012; Krupodorova et al., 2014; Zhang et al., 2014; Matsuhisa et al., 2015; Mizerska-Dudka et al., 2015
	Russulales	HIV-1[4], vaccinia[1], VS[1]	Kandefer-Szerszeń et al., 1980; Mlinaric et al., 2005; Wang et al., 2007

Und wir wissen auch wie …

Chemical class	Source (fungal order)	Phylum	Reference
High molecular weight compounds			
Lignin derivatives	Polyporales	Basidiomycota	Suzuki et al., 1989; Sorimachi et al., 1990; Sarkar et al., 1993
Polysaccharides	Agaricales, Polyporales	Basidiomycota	Faccin et al., 2007; Razumov et al., 2010; Cardozo et al., 2011; Yamamoto et al., 2013
Proteins	Agaricales, Polyporales	Basidiomycota	Piraino and Brandt, 1999; Wang and Ng, 2000; Ngai and Ng, 2003; Gu et al., 2007
Polysaccharide-protein/amino acid complex	Polyporales	Basidiomycota	Hirose et al., 1987; Okada and Minamishima, 1987; Tochikura et al., 1988; Collins and Ng, 1997; Eo et al., 1999a,b, 2000; Kim et al., 2000; Wang and Ng, 2000
Small molecular weight compounds (secondary metabolites)			
Indole alkaloids	*Capnodiales, Eurotiales, Hypocreales, Pleosporales*	*Ascomycota*	Guo et al., 2009; Zhang et al., 2011; Ma et al., 2013; Peng et al., 2013; Li et al., 2014; Zhao et al., 2017
Non-ribosomal peptides (NRPS)	*Dothideales, Helotiales, Xylariales*	*Ascomycota*	Rowley et al., 2003; Pittayakhajonwut et al., 2005; Isaka et al., 2007
	Russulales	*Basidiomycota*	Wang et al., 2007
Polyketides (PKS)	*Amphisphaeriales, Diaporthales, Eurotiales, Hypocreales, Pezizales, Pleosporales, Sordaliales*	*Ascomycota*	Singh et al., 2002, 2003a; Jayasuriya et al., 2003; Li et al., 2008; Bunyapaiboonsri et al., 2010; Shushni et al., 2011; Gao et al., 2013a; Bashyal et al., 2014; Peng et al., 2014; Pérez et al., 2014, Wang J.-F. et al., 2014; Jia et al., 2015; Sacramento et al., 2015; Pang et al., 2018
	Polyporales	*Basidiomycota*	Awadh Ali et al., 2003; Singh et al., 2003a
NRPS-PKS hybrids	*Capnodiales, Eurotiales, Helotiales, Hypocreales, Pleosporales*	*Ascomycota*	Krohn et al., 1997; Hazuda et al., 1999; Bunyapaiboonsri et al., 2010; Sebastian et al., 2011; Wu et al., 2014; Stierle and Stierle, 2015; Zhang et al., 2015
Terpenoids	*Amphisphaeriales, Eurotiales, Hypocreales, Pleosporales, Xylariales*	*Ascomycota*	Hazuda et al., 1999; Yoshimoto et al., 1999; Minagawa et al., 2002; Sawadjoon et al., 2004; Singh et al., 2003b; Fang et al., 2014; Wang J. et al., 2014; Zhang et al., 2014
	Agaricales, Polyporales, Russulales	*Basidiomycota*	El-Mekkawy et al., 1998; Min et al., 1998; Iwatsuki et al., 2003; Kanokmedhakul et al., 2003; Krawczyk et al., 2003; Lehmann et al., 2003; Mothana et al., 2003; Niedermeyer et al., 2005; El Dine et al., 2008; Sato et al., 2009; Zhu et al., 2010; Zhang et al., 2016

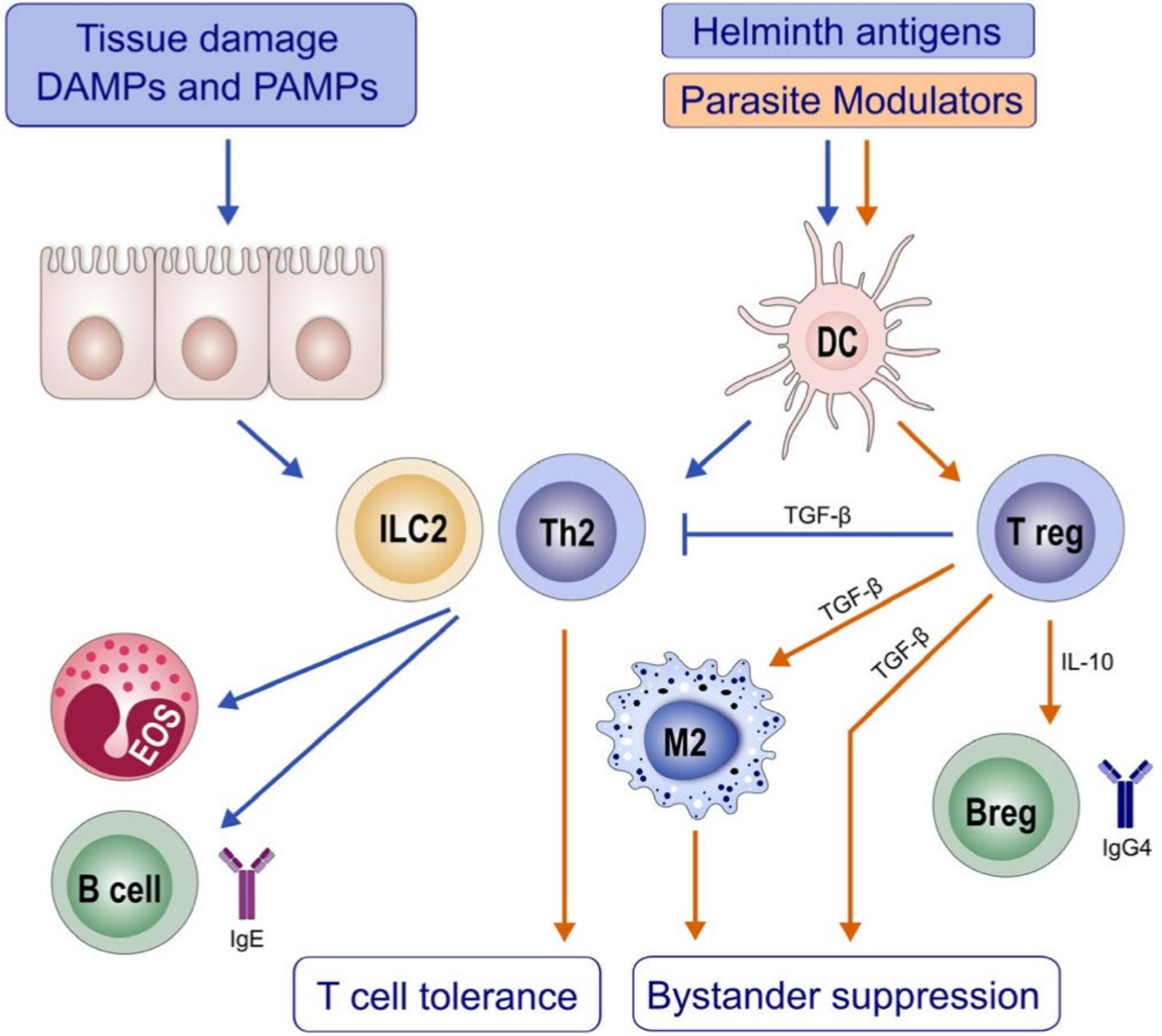
Linnakoski 2018

Störung im Gleichgewicht



Balfour 2016

Parasiten: Die gute Seite



Maizels 2019

Unser Mikrobiom ist sehr, sehr alt …

ARTICLE

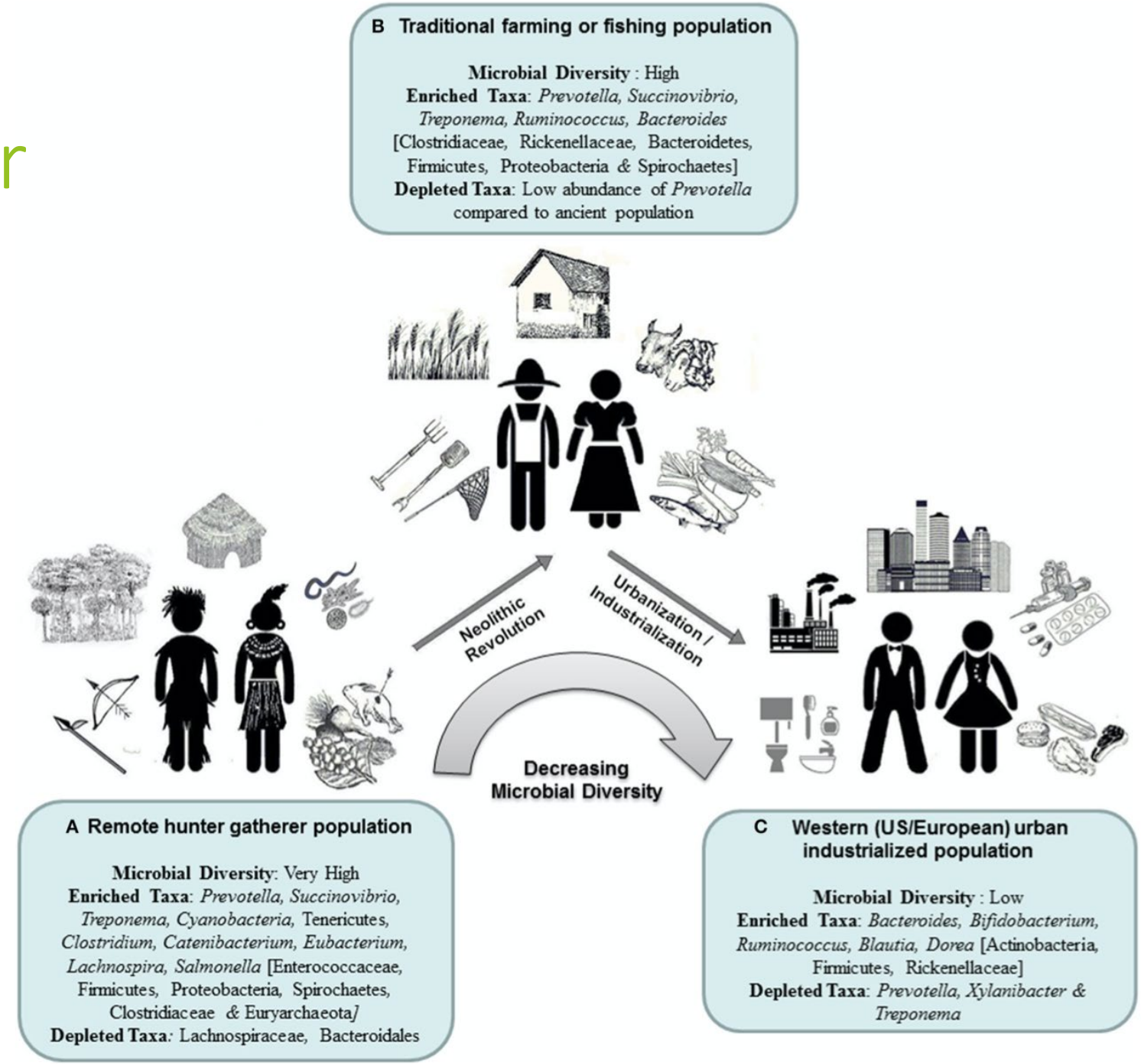
https://doi.org/10.1038/s42003-021-01689-y OPEN

Components of a Neanderthal gut microbiome recovered from fecal sediments from El Salt

Simone Rampelli[1,17], Silvia Turroni[1,17], Carolina Mallol[2,3,4], Cristo Hernandez[2], Bertila Galván[2], Ainara Sistiaga[5,6], Elena Biagi[1], Annalisa Astolfi[7,16], Patrizia Brigidi[8], Stefano Benazzi[9,10], Cecil M. Lewis Jr.[11,12], Christina Warinner[12,13], Courtney A. Hofman[11,12], Stephanie L. Schnorr[14,15,18✉] & Marco Candela[1,18✉]

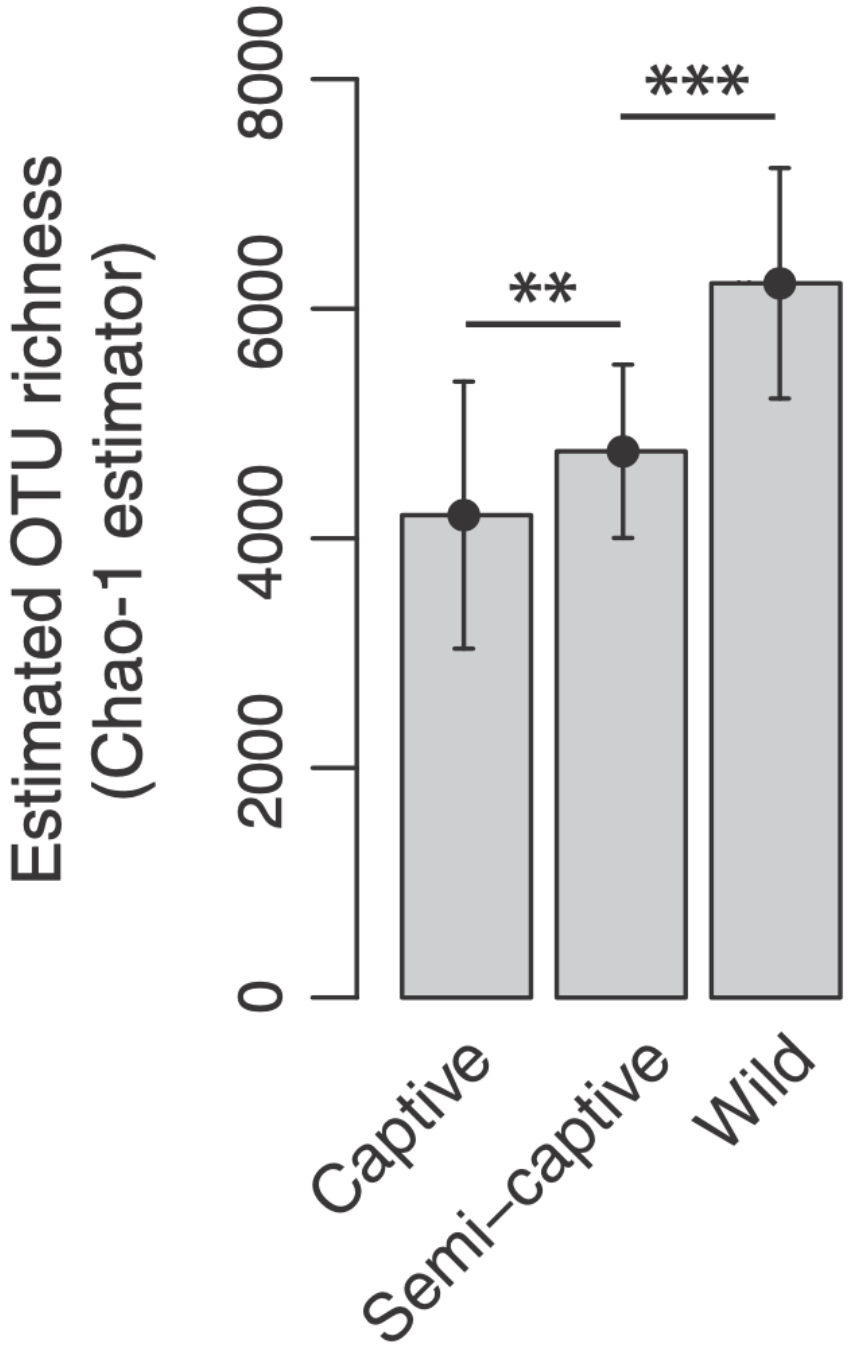
A comprehensive view of our evolutionary history cannot ignore the ancestral features of our gut microbiota. To provide some glimpse into the past, we searched for human gut microbiome components in ancient DNA from 14 archeological sediments spanning four stratigraphic units of El Salt Middle Paleolithic site (Spain), including layers of unit X, which has yielded well-preserved Neanderthal occupation deposits dating around 50 kya. According to our findings, bacterial genera belonging to families known to be part of the modern human gut microbiome are abundantly represented only across unit X samples, showing that well-known beneficial gut commensals, such as *Blautia*, *Dorea*, *Roseburia*, *Ruminococcus*, *Faecalibacterium* and *Bifidobacterium* already populated the intestinal microbiome of *Homo* since as far back as the last common ancestor between humans and Neanderthals.

Aber:
der Mensch hat leider ‚wenig' Diversität … entwickelt



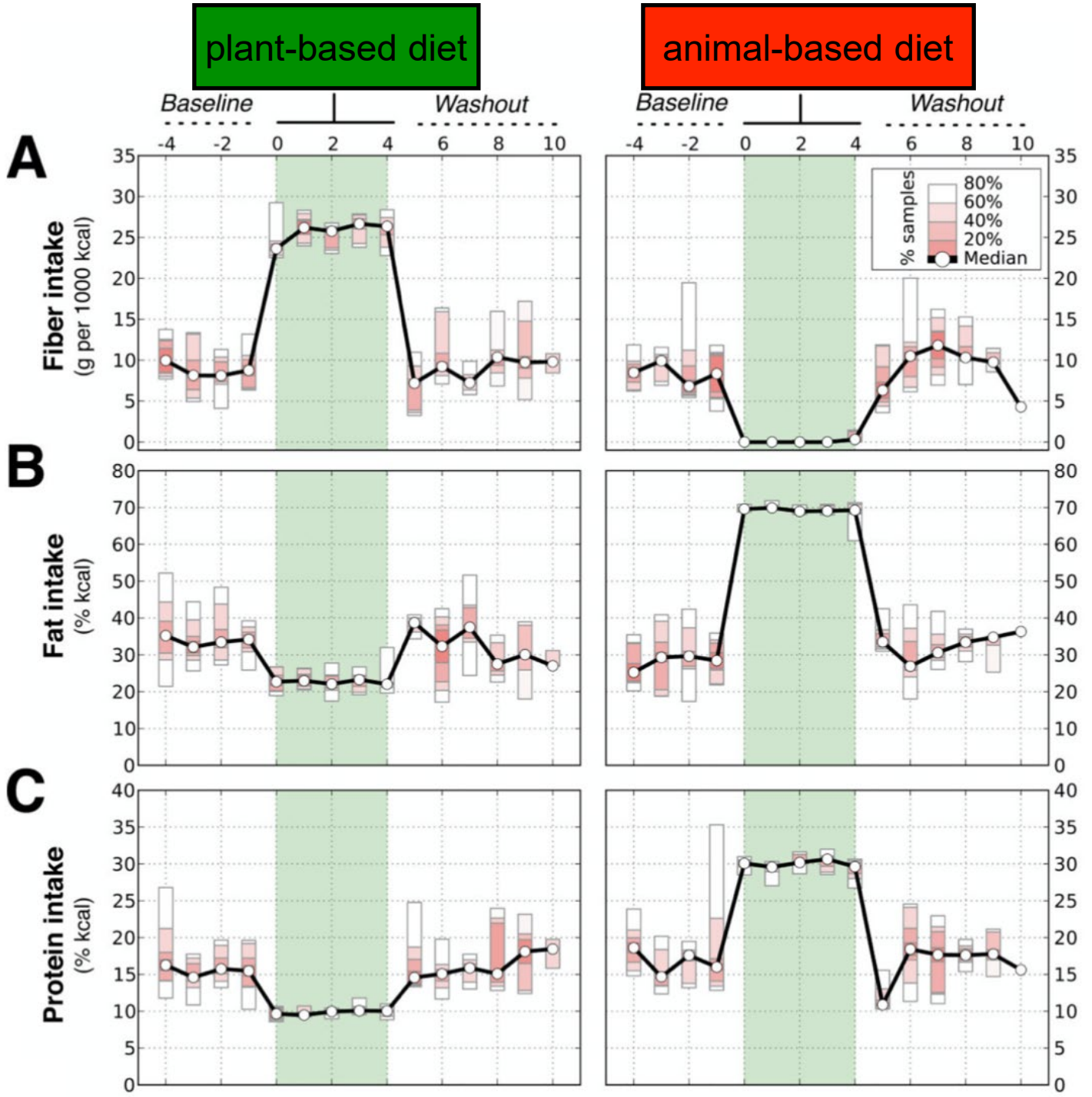
Gupta 2017

Und das fängt schon bei Primaten an …



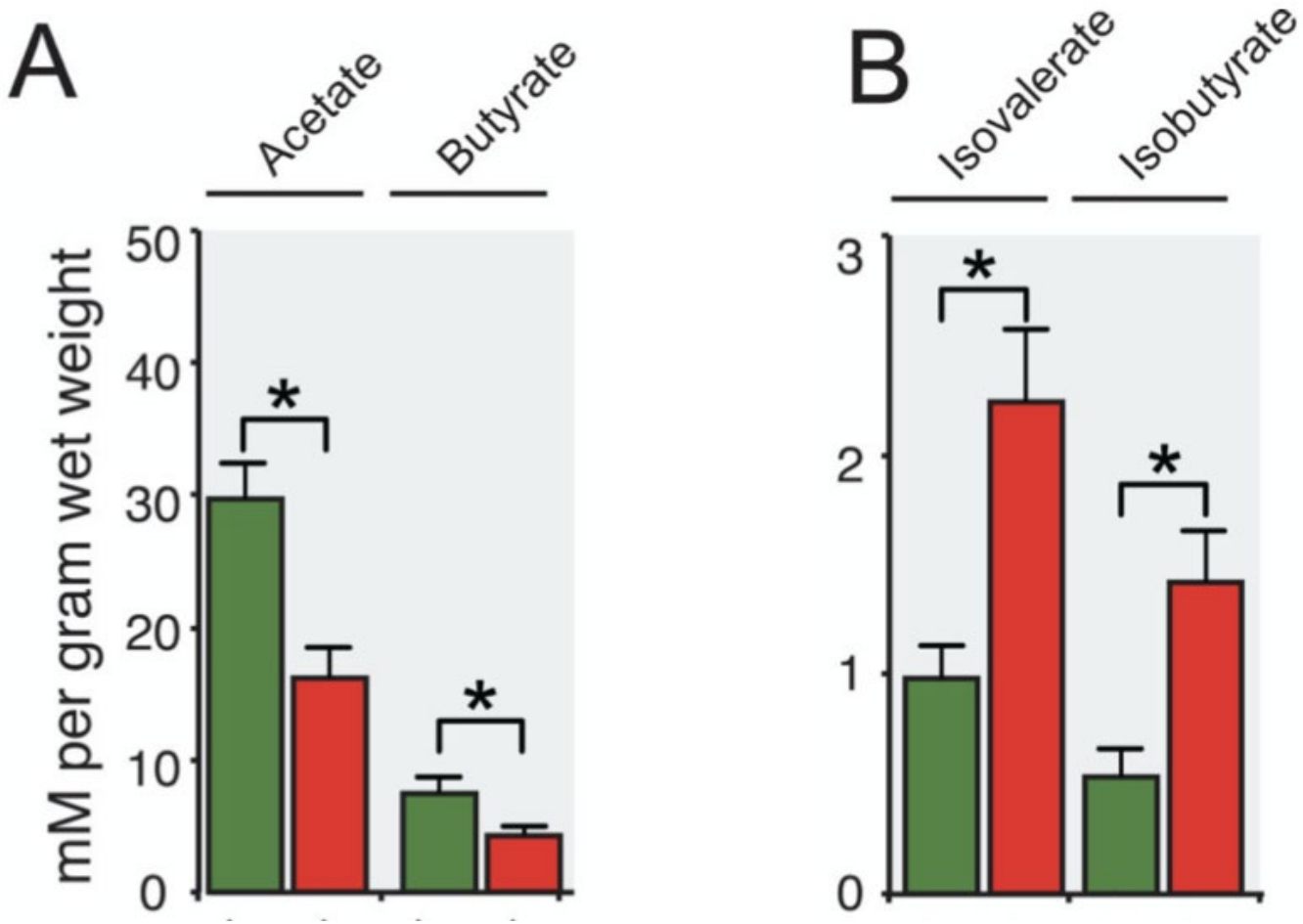
Clayton 2016

Nahrung ändert das Mikrobiom innerhalb von Tagen



David 2014

Dies hat Einfluss auf die kurzkettigen Fettsäuren



plant-based diet

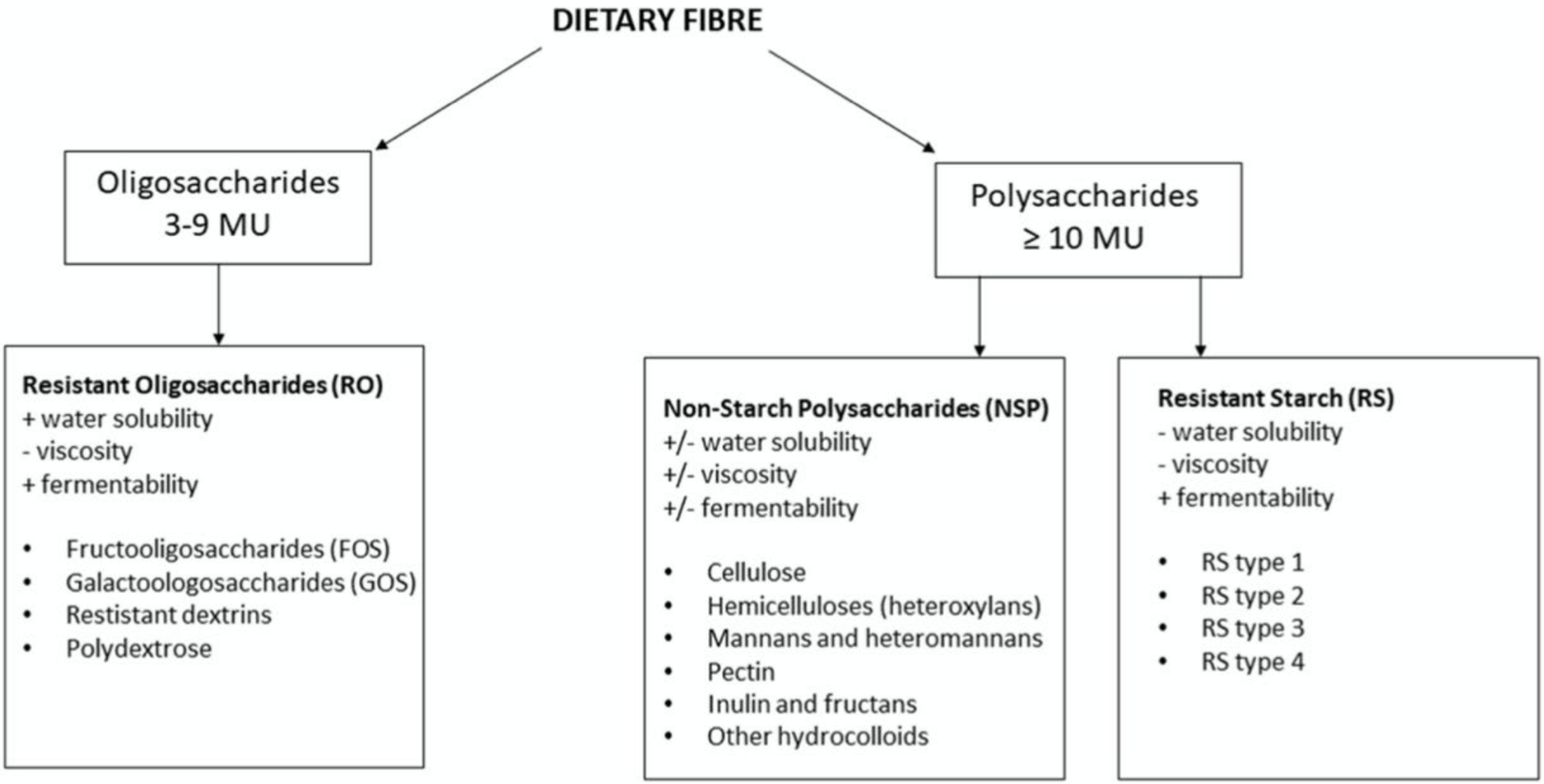
animal-based diet

A: KKFS aus Polysaccharid-Fermentation

B: KKFS aus Aminosäuren-Fermentation

David 2014

Faserstoffe: der Treibstoff für Bakterien



Myhrstad 2020

Das Ergebnis der Fermentation: Kurzkettige Fettsäuren

Butyrat — *Hauptsächlich durch Firmicuten*

Acetat, Propionat — *Hauptsächlich durch Bakteroidetes*

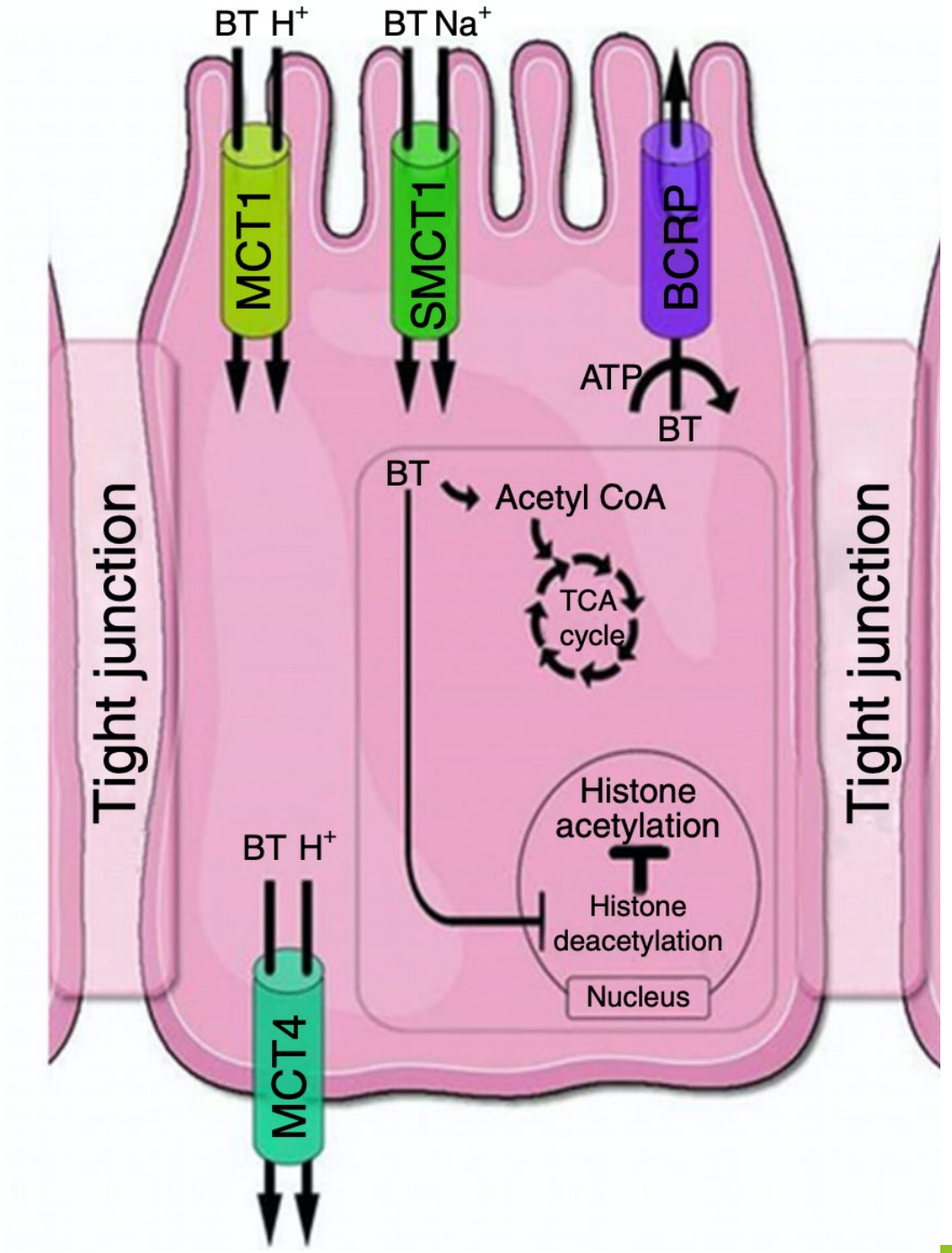
Hauptaufgaben dieser Fettsäuren

- Energieversorgung
- Signalgebung

Wie werden diese Fettsäuren aufgenommen?

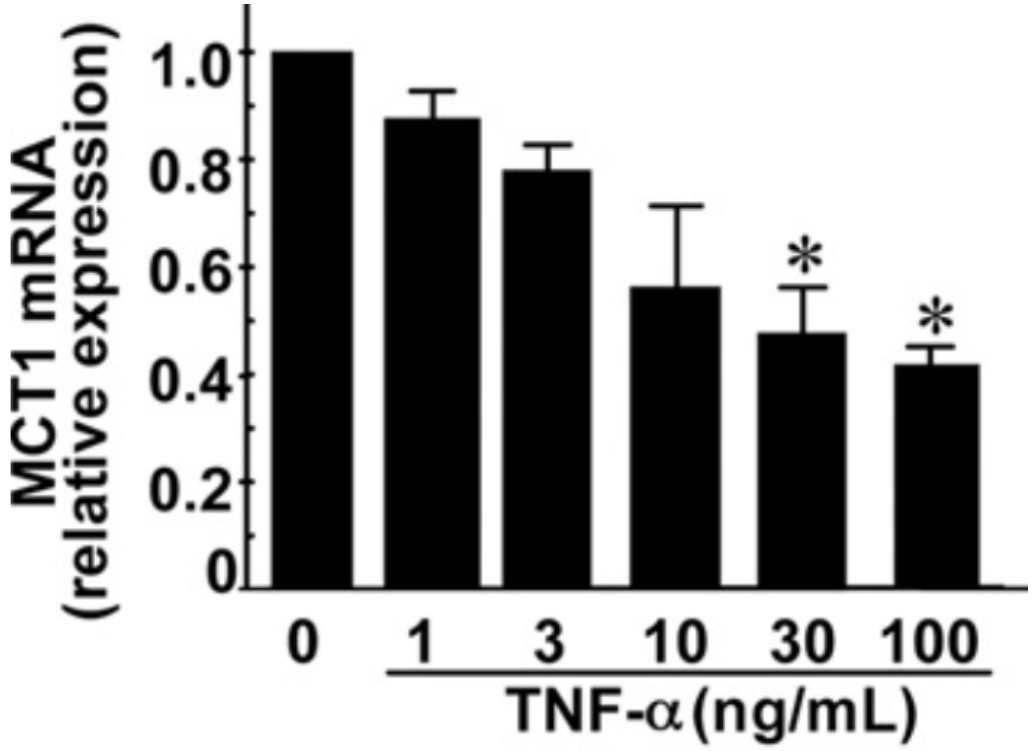
- passiver Membrantransport
- MCT-1
- SMCT-1

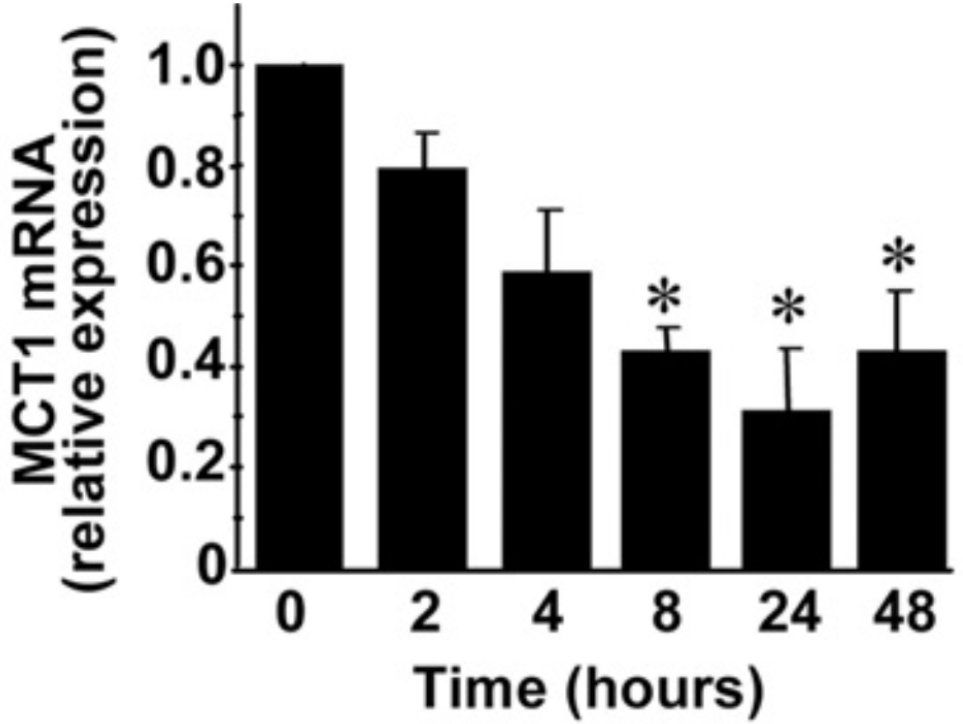
MCT-1 und SMCT-1



Goncalves 2016

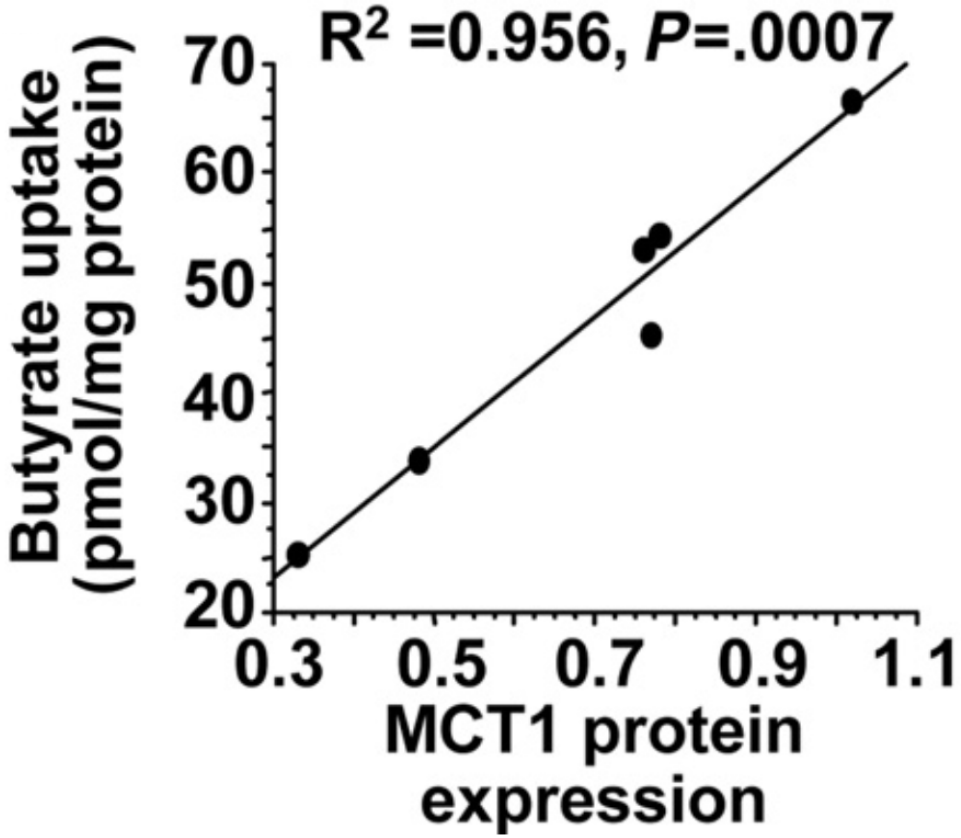
Anzahl MCT-1 bei Entzündung …

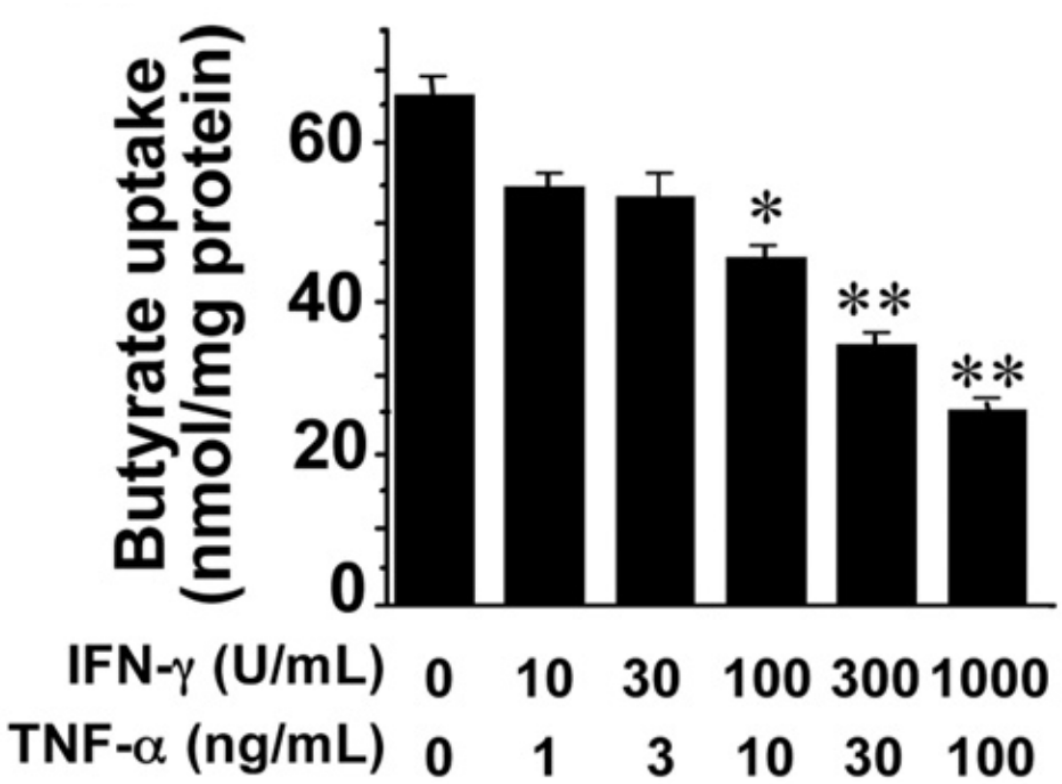




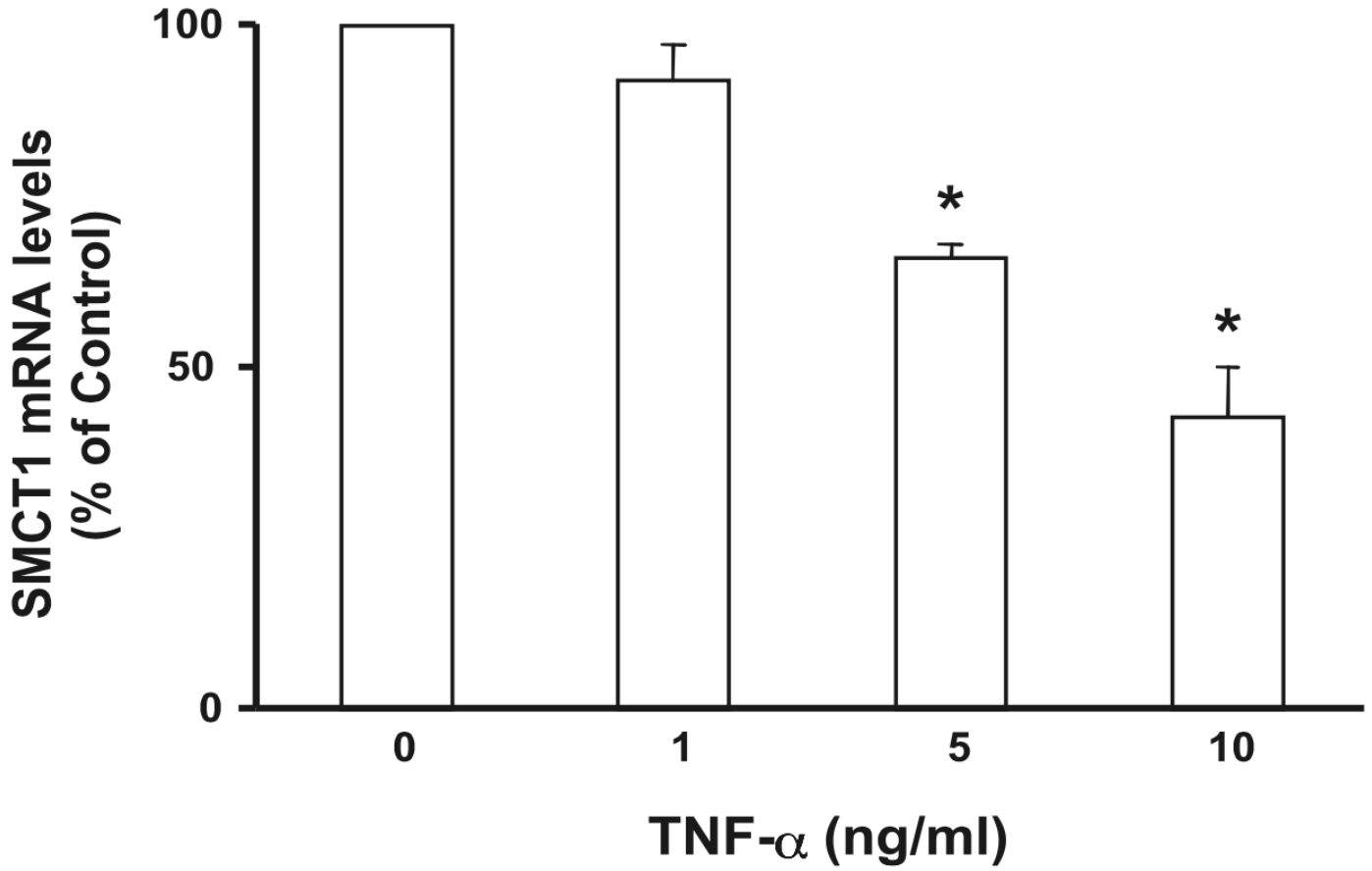
Thibault 2007

… führt zu weniger KKFS Aufnahme



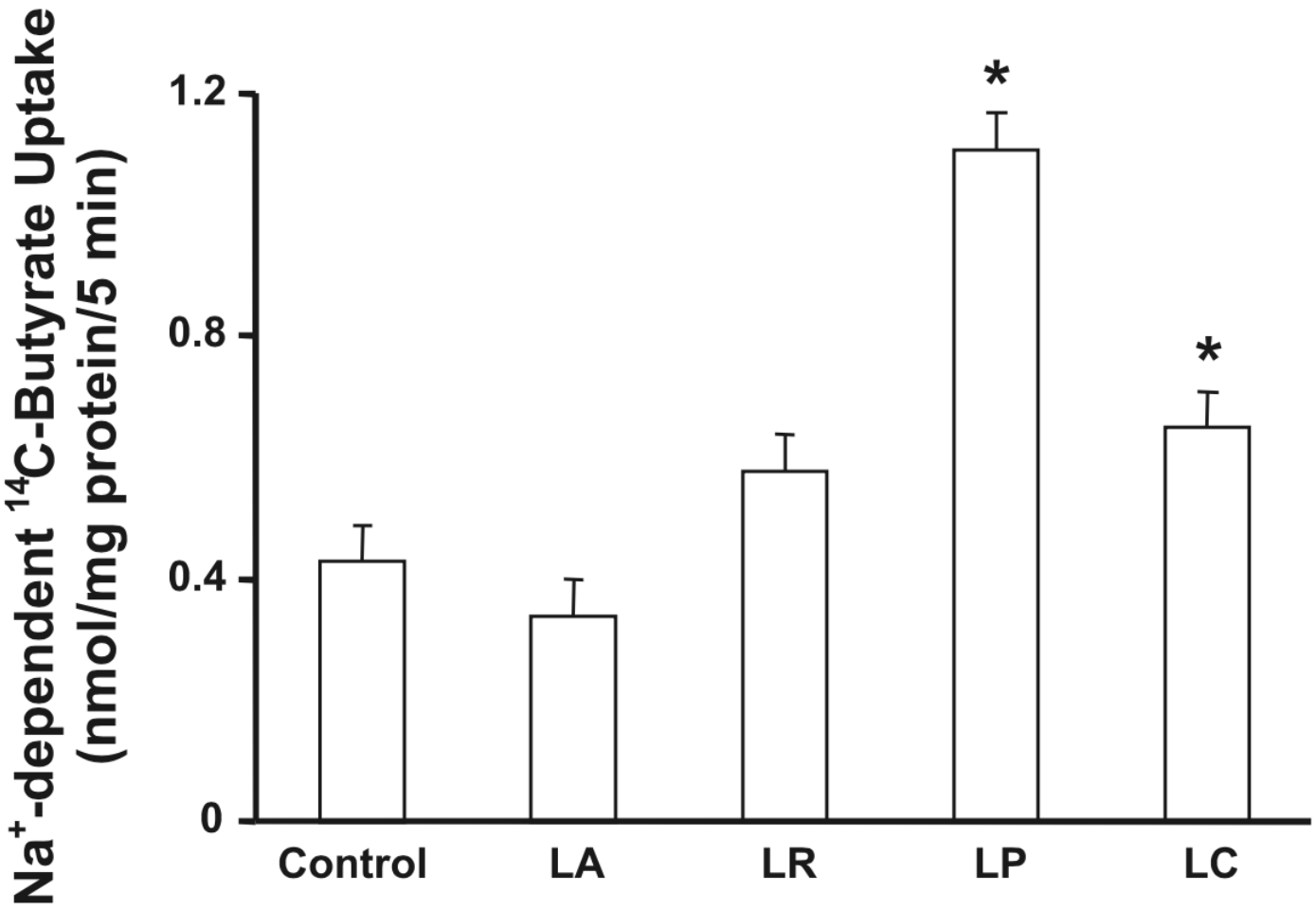


Anzahl SMCT-1 bei Entzündung …



Borthakur 2010

… und in Anwesenheit von Laktobazillen

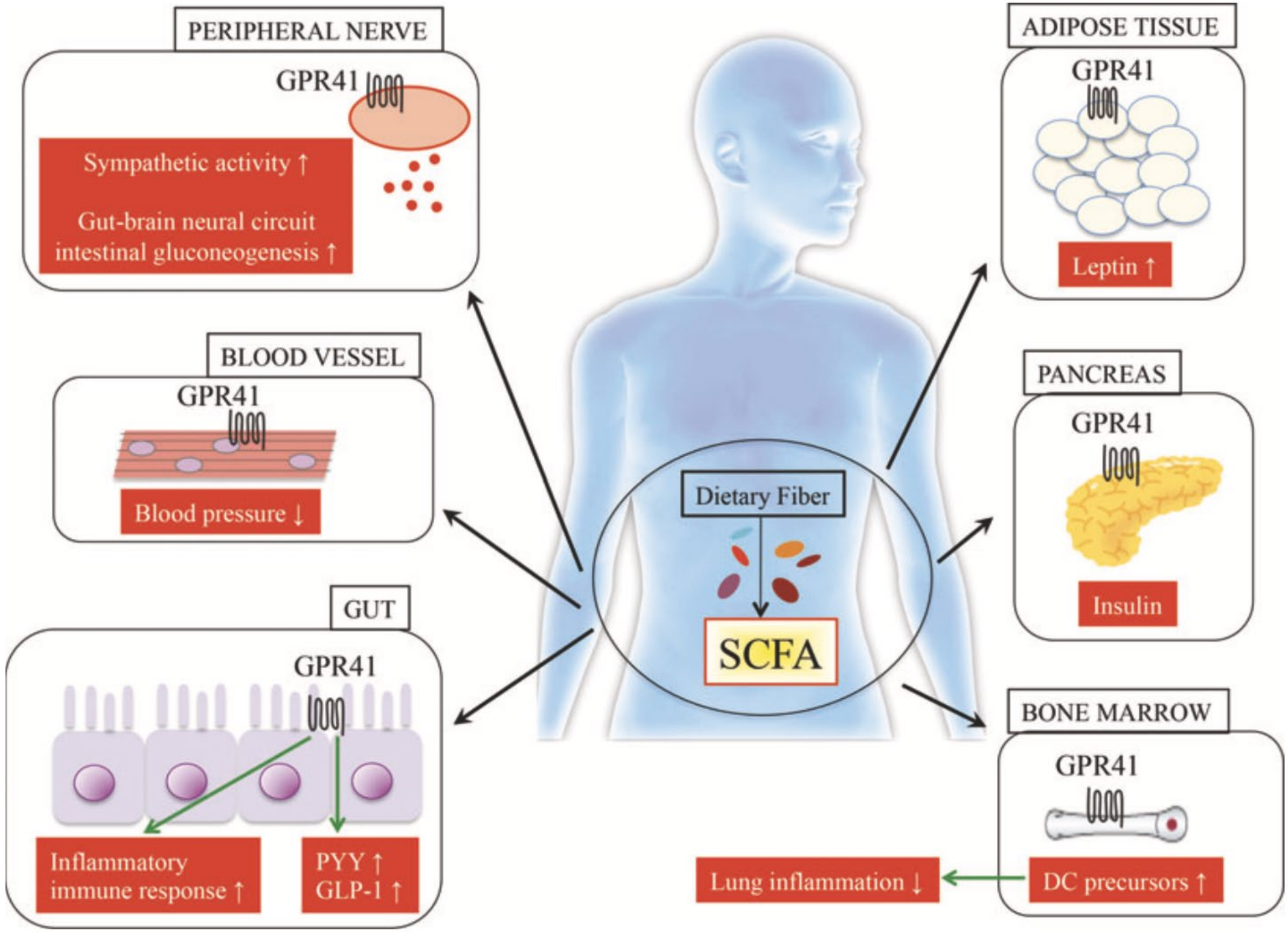


Borthakur 2010

KKFS als Botenstoffe
G protein-coupled receptors (GPR):

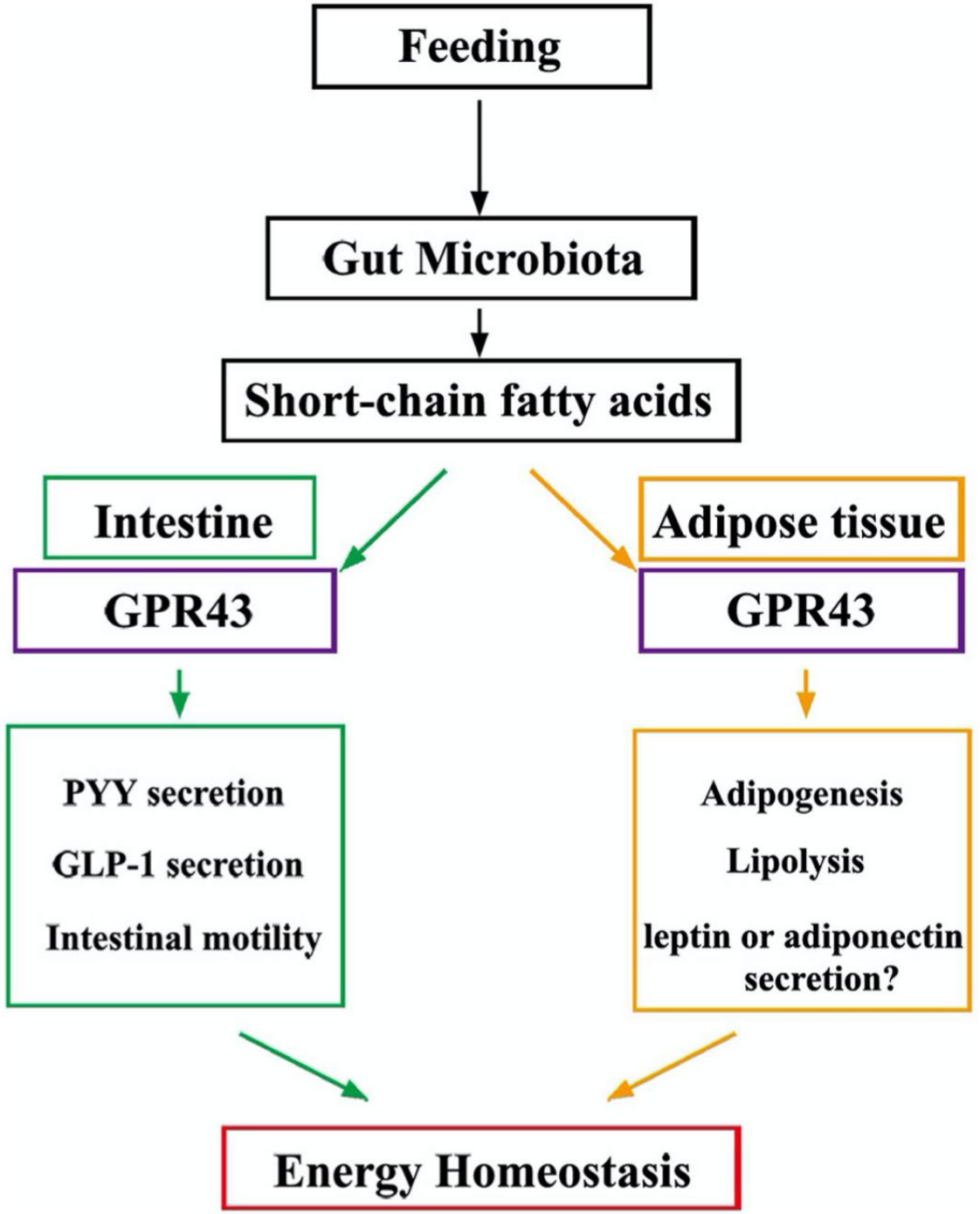
- GPR41
- GPR43
- GPR109a

GPR41



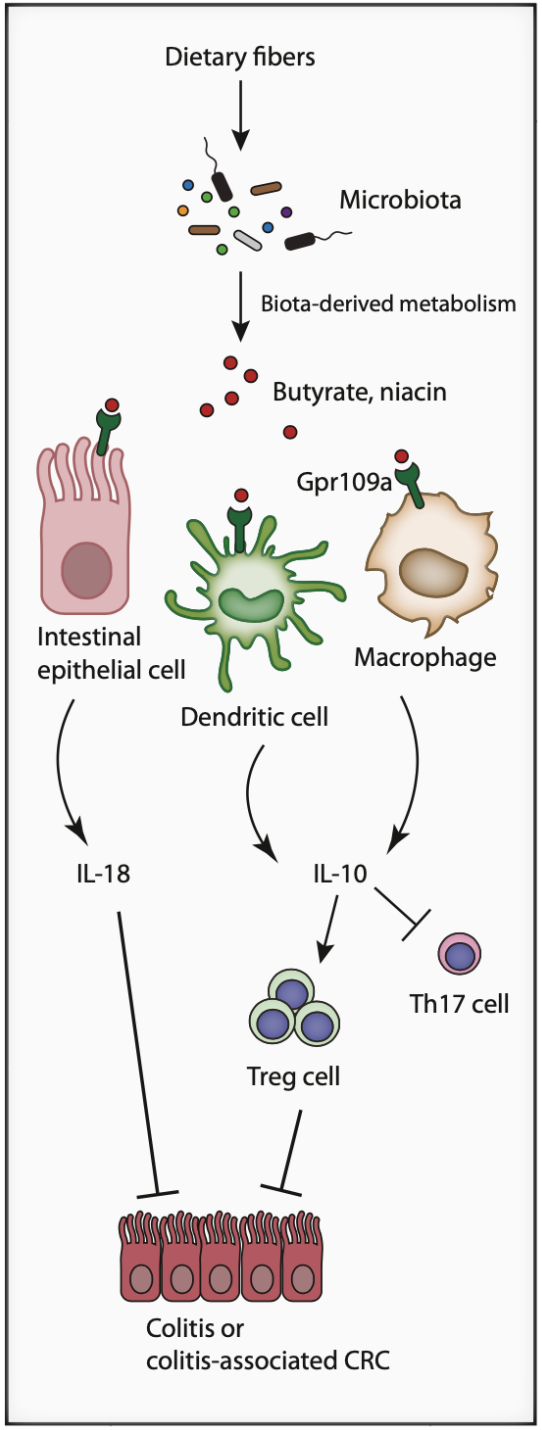
Nakajima 2018

GPR43



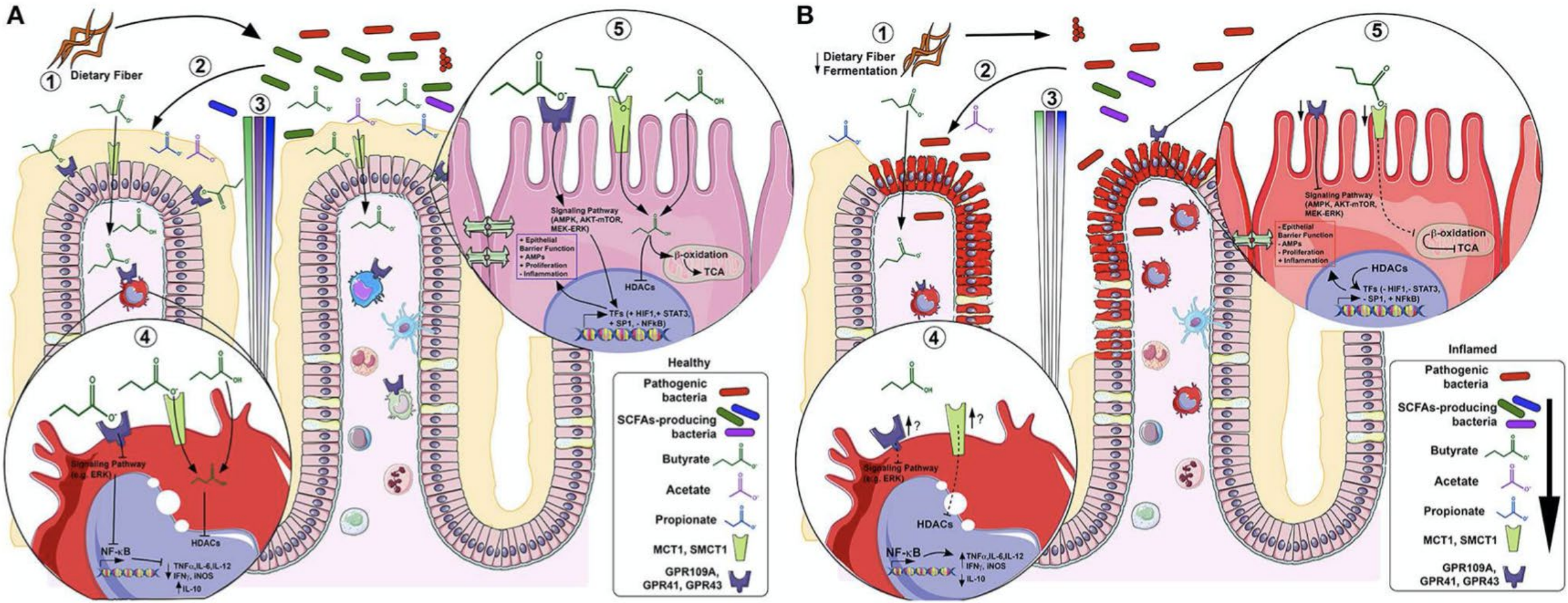
Kimura 2014

GPR109a



Jobin 2014

Zusammengefasst:



Venegas 2019

Das Mikrobiom optimiert das Immunsystem …?

frontiers in Microbiology

REVIEW
published: 09 June 2020
doi: 10.3389/fmicb.2020.01388

Intestinal Flora as a Potential Strategy to Fight SARS-CoV-2 Infection

Li-Hong He[1,2,3†], *Long-Fei Ren*[1,2,3†], *Jun-Feng Li*[4], *Yong-Na Wu*[3], *Xun Li*[1,2,3*] *and Lei Zhang*[1,2,3*]

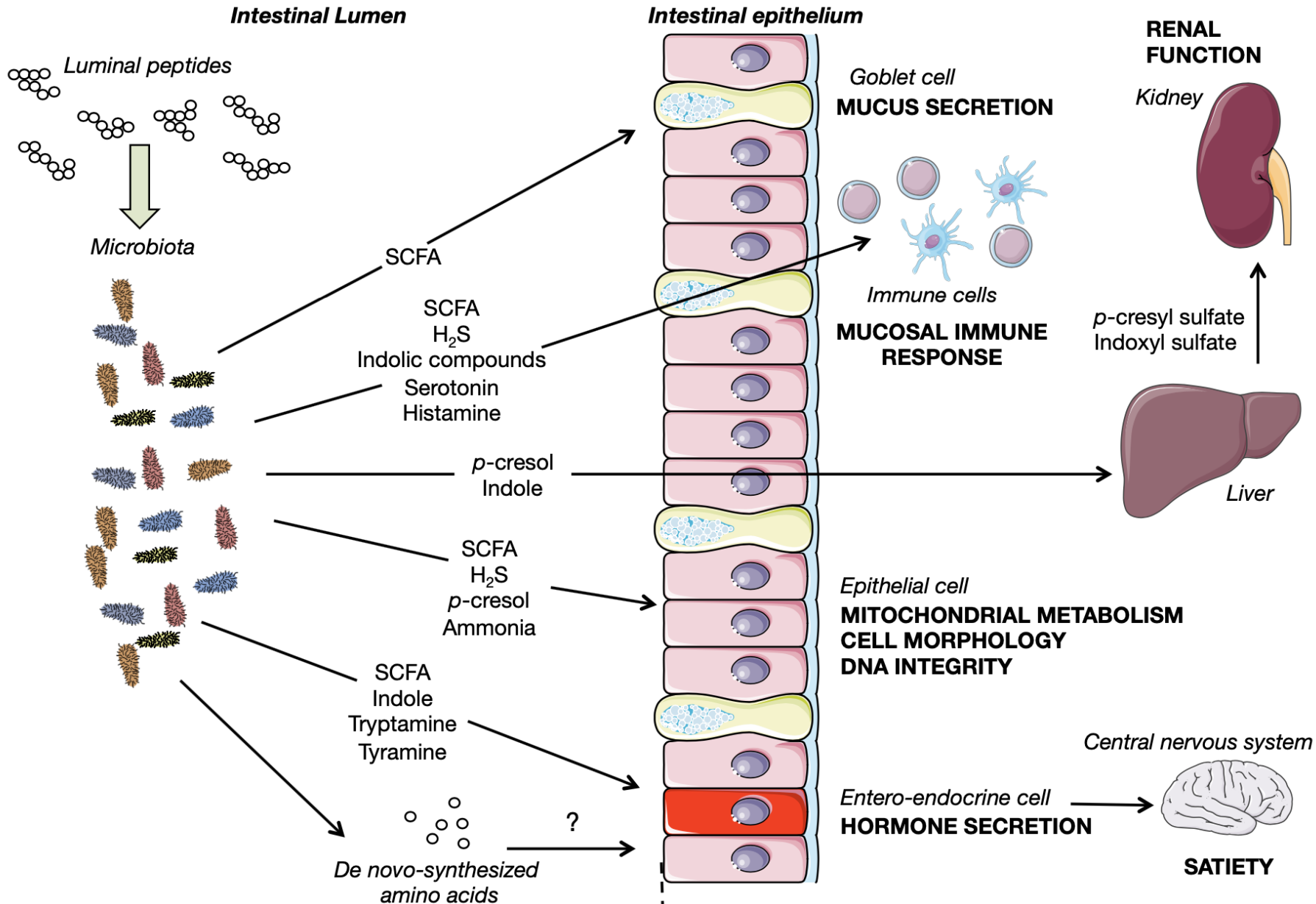
The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread rapidly worldwide, seriously endangering human health. In addition to the typical symptoms of pulmonary infection, patients with COVID-19 have been reported to have gastrointestinal symptoms and/or intestinal flora dysbiosis. It is known that a healthy intestinal flora is closely related to the maintenance of pulmonary and systemic health by regulating the host immune homeostasis. Role of the "gut-lung axis" has also been well-articulated. This review provides a novel suggestion that intestinal flora may be one of the mediators of the gastrointestinal responses and abnormal immune responses in hosts caused by SARS-CoV-2; improving the composition of intestinal flora and the proportion of its metabolites through probiotics, and personalized diet could be a potential strategy to prevent and treat COVID-19. More clinical and evidence-based medical trials may be initiated to determine the strategy.

Effekte ausgewählter Probiotika auf das Immunsystem

Lactobacillus acidophilus:	verstärkte Antivirus-Abwehr
Lactobacillus rhamnosus:	verstärkte Antivirus-Abwehr
	verbesserte Impf-Effizienz
Lactobacillus casei:	verstärkte Phagozytoseaktivität alveolarer Makrophagen sowie mehr sIgA
Bifidobakterien:	verbesserte Impf-Effizienz

He 2020

Unser Mikrobiom produziert nicht nur Fettsäuren



Portune 2016

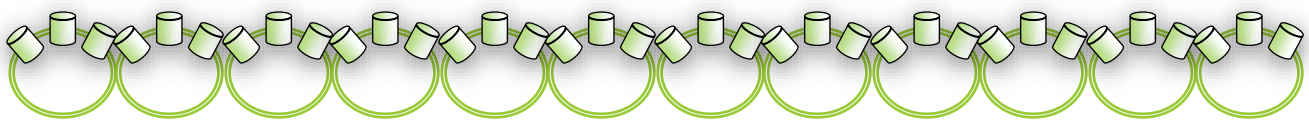
Aminosäurentransporter in Dick- und Dünndarm (>)

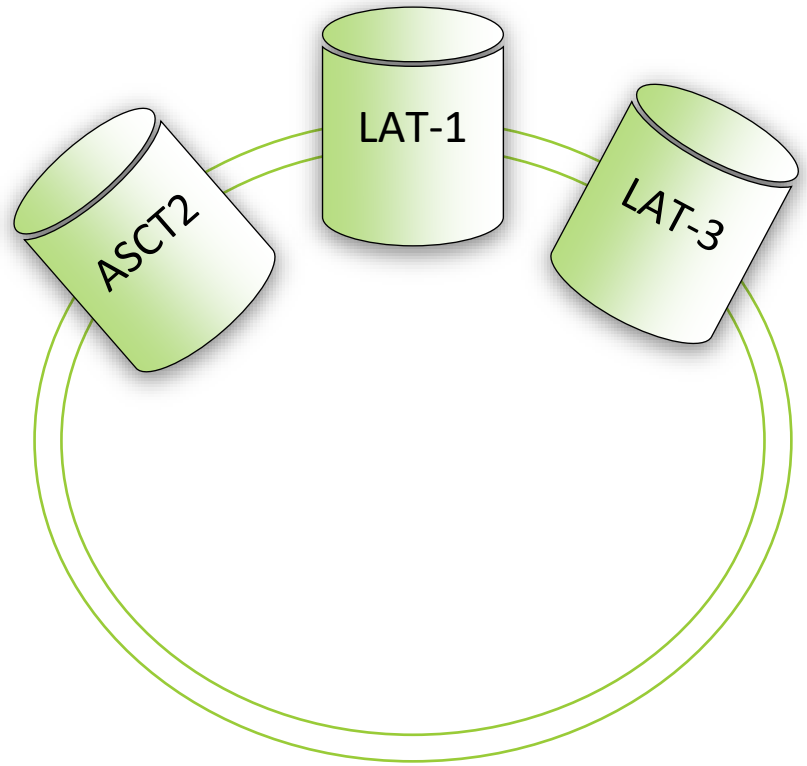
Histidin, Isoleucin, Methionin

Cystein

Valin, Leucin

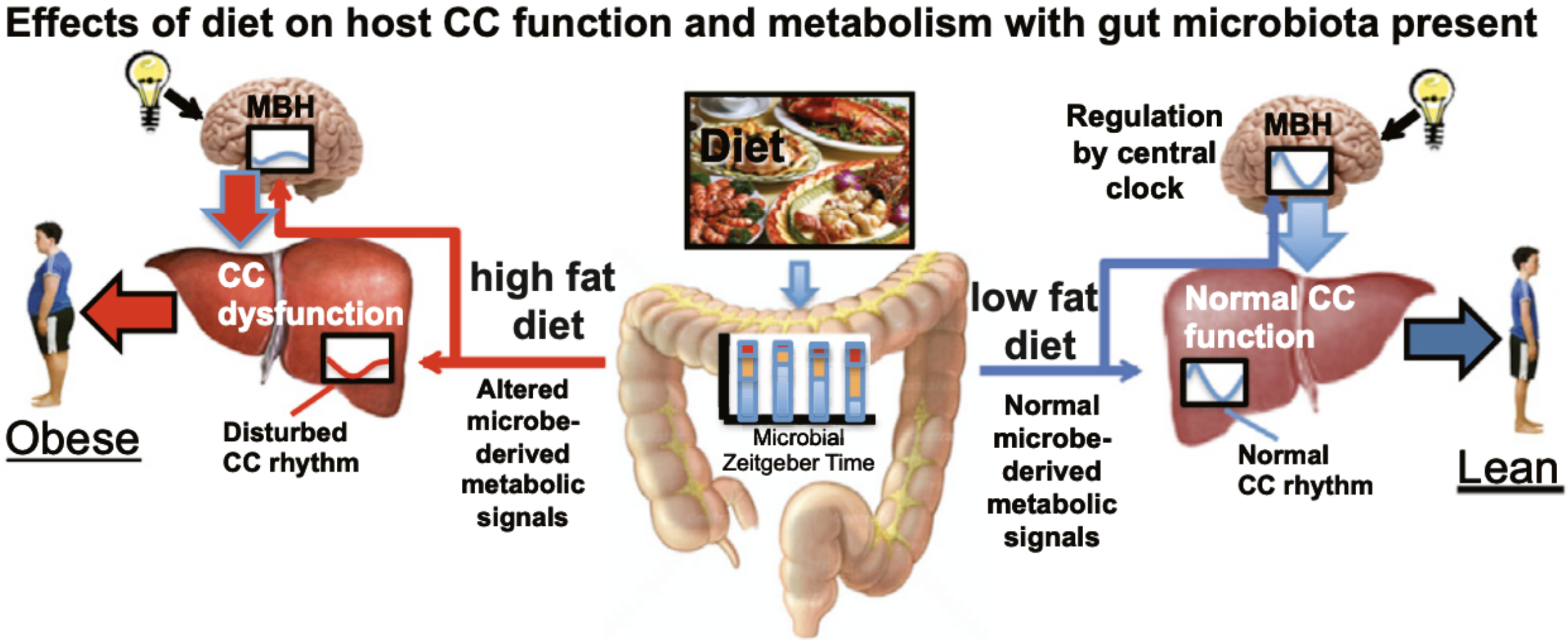
Threonin, Phenylalanin, Tyrosin, Tryptophan





In Anlehnung an: Van der Wielen 2017

Das Mikrobiom bestimmt Biorhythmus und Stoffwechsel



Leone 2015

Epigenetische Einflüsse durch bakterielle Produkte?

Metabolite	Model	Epigenetic action
Folate (vitamin B9)	In vitro, in vivo, rat	As methyl donor involved in one-carbone metabolism; critical for methylation reaction (Kalhan 2013; Anderson et al. 2012)
		Activity reduction of DNA methyltransferase (Ly et al. 2011)
Cobalamin (vitamin B12)	In vitro, in vivo	As cofactor involved in one-carbone metabolism; critical for methylation reactions (Kalhan 2013; Anderson et al. 2012)
Choline	In vitro, mouse	Methyl donor; loses availability through break-down by human gut microbiota (Dumas et al. 2006)
		DNA methylation and gene expression changes in colitis (Schaible et al. 2011)
		Broken down to TMAO and betaine (Wang et al. 2011)
Betaine	In vitro, in vivo, human	As methyl donor involved in one-carbone metabolism; critical for methylation reaction (Kalhan 2013; Canani et al. 2011)
		Alterations of DNA methylation associated with abnormalities of DNA methyltransferases in human cancers (Kanai and Hirohashi 2007)
Trimethylamin-N-oxid (TMAO)	In vitro, mouse	Break down product of methyl donor choline (Wang et al. 2011)
Equol	In vitro	Ppromoter CpG island hypomethylation of breast cancer susceptibility genes BRCA1 and BRCA2; increase of BRCA1 and BRCA2 proteins (Bosviel et al. 2012)
Ammonium (NH_4)	Human	Inverse association of fecal NH_4 and rectal LINE-1 methylation (Worthley et al. 2011)
α-ketoglutarate	In vitro, human	Effect on histone and DNA (de)methylation; co-factor of HDM and TET protein family memebers (Wang et al. 2013; Hou and Yu 2010)
Conjugated linoleic acids (CLA)	In vitro, in vivo	Increased SIRT1 deacetylation activity by trans-10, cis-12 CLA treatment via reciprocal activation of AMPK (Jiang et al. 2012)
		Decreased histone phosphorylation by CDK2 inhibition (Cho et al. 2006)

Mischke, Plösch 2016

Metabolite	Model	Epigenetic action
Short-chain fatty acids (SCFA), general	In vitro, human	HDAC inhibition (Waldecker et al. 2008)
		Associated to LINE-1 DNA methylation (Worthley et al. 2011)
Acetate (C2:0)	In vitro	HDAC inhibition; histone (H3, H4) hyper-acetylation (Sealy and Chalkley 1978)
Propionate (C3:0)	In vitro	HDAC inhibition; histone (H3, H4) hyper-acetylation (Sealy and Chalkley 1978; Takenaga 1986)
Butyrate (C4:0)	In vitro, in vivo	HDAC inhibition of HDAC class I, IIa, and IV (Davie 2003)
		Regulation of transcription factor availability (Blottiere et al. 2003)
Valerate (C5:0)	In vitro	HDAC inhibition (Ortiz-Caro et al. 1986)
Branched-chain fatty acids (BCFA), general		
Isobutyrate	In vitro	HDAC inhibition (Waldecker et al. 2008)
		Increased histone acetylation, probably via HDAC inhibition (Suzuki-Mizushima et al. 2002)
Isovalerate	In vitro	HDAC inhibition (Waldecker et al. 2008)
		Increased histone acetylation, probably via HDAC inhibition (Suzuki-Mizushima et al. 2002)
Organic acids, general	In vitro, in vivo	HDAC inhibition by low pH (Latham et al. 2012)
Lactate (D-, L-lactate)	In vitro, in vivo	(weak) HDAC inhibition (Latham et al. 2012)
Phenolic compounds	In vitro, in vivo	HDAC inhibition (Waldecker et al. 2008)
		Bacterial break down of dietary polyphenols (quercetin, curcumin, catechin) redering them unavailable for affecting HDAC activity (Rajendran et al. 2011)
Phenylbutyrate	In vitro	HDAC inhibition (Lea and Tulsyan 1995; Lea et al. 2004)
Phenylacetate	In vitro	HDAC inhibition (Waldecker et al. 2008; Lea and Tulsyan 1995)
		Reduction of reactive oxygen species, which otherwise affect HAT and HDAC activity and increase DNA methylation (Beloborodova et al. 2012)
4-hydroxyphenylacetate	In vitro	HDAC inhibition (Waldecker et al. 2008)
		Reduction of reactive oxygen species, which otherwise affect HAT and HDAC activity and increase DNA methylation (Beloborodova et al. 2012)
Phenylpropionate	In vitro	HDAC inhibition (Waldecker et al. 2008)
4-hydroxyphenylpropionate	In vitro	HDAC inhibition (Waldecker et al. 2008)
p-cresol	In vitro, mouse	Expression induction of DNA methyltransferases 1, 3a, and 3b (Sun et al. 2012)
		CpG hypermethylation of Klotho gene; decreased Klotho expression (Sun et al. 2012)
Sulfur compounds	In vitro, in vivo	Histone modifications (Canani et al. 2011)
Hydrogen sulfide (H2S)	In vitro, rat	Inhibition of cell proliferation by epigenetic mechanism reducing recruitment of Brg1 to relevant promoter regions (Li et al. 2013)
		Reduction/neutralization of reactive oxygen species, which otherwise affect HAT and HDAC activity and increase DNA methylation (Afanas'ev 2014)
Cell wall components		
Lipopolysaccharide (LPS)	In vitro	Chromatin modification at IL-8 gene, including histone H3 acetylation and methylation; IL-8 activation (Angrisano et al. 2010)
Peptidoglycan (PGN)	In vitro	Modulation of chromatin structure and transcriptional activity at Foxp3 locus (Lal et al. 2011)
Lipoteichoic acid (LTA)	Mouse, in vitro	Potential epigenetic regulation of genes in colorectal cancer (Lightfoot et al. 2013)
Vitamins		
Thiamine (vitamin B1)	In vitro, in vivo	As coenzyme involved in generation of ATP; critical for phosphorylation reactions (Hill 1997)
Riboflavin (vitamin B2)	In vitro, in vivo	As cofactor involved in one-carbone metabolism; critical for methylation reactions (Anderson et al. 2012)
Niacin (vitamin B3)	In vitro, in silico	SIRT (Class III HDAC) inhibitor (Avalos et al. 2005; Denu 2005)
Pantothenate (vitamin B5)	In vitro, in vivo	As coenzyme A substrate for acylation and acetylation reactions; signal transduction, enzyme activity regulation (Marmorstein 2001)
		Histone hypoacetylation and fragile DNA by impaired Coenzyme A synthesis (Cai et al. 2011)
Pyridoxine (vitamin B6)	In vitro, in vivo	As cofactor involved in one-carbone metabolism; critical for methylation reactions (Anderson et al. 2012)
Biotin (vitamin B7)	In vitro, drosophila	Substrate for histone biotinylation; gene activity regulation and transposable element repression (Hassan and Zempleni 2008)
		Decreased histone biotinylation associated with life span and stress resistance in Drosophila (Zempleni et al. 2008)

Mischke, Plösch 2016

Darmbakterien und Verhalten

Genus	Change in abundance	Behavioural trait/psychiatric condition	Study subject	References
Akkermansia	↓	Autism	Children	[52]
	[↑]	Autism	Children	[53]
	↓	Stress	Mice	[54,55]
	↑	Sociability	Adults	This study
Corynebacterium	[↑]	Autism	Children	[56]
	↓	Stress	Rats	[83]
	↓	Neurotic tendencies	Adults	This study
Desulfovibrio	↑	Autism	Children	[60,80]
	↓	Sociability	Adults	This study
Lactococcus	↓	Autism	Children	[53,60]
	↑	Sociability	Adults	This study
Oscillospira	↓	Autism	Children	[53]
	↑	Sociability	Mice	[94]
	↓	Stress	Mice	[55,94,95]
	↑	Sociability	Adults	This study
Streptococcus	↓	Autism	Children	[53,60]
	[↑]	Depression	Adults	[82]
	↓	Neurotic tendencies	Adults	This study
Sutterella	↑	Autism	Children	[52,65,96,97]
	[↓]	Autism	Children	[75]
	↑	Stress	Mice	[55]
	↓	Sociability	Adults	This study

Johnson 2020

Offene Fragen:

- Ist mein Lebensstil gesund?
- Was muss ich tun, um ein optimales Mikrobiom zu erhalten?
- Wenn mein Mikrobiom nicht „ok“ ist, was tun? Gibt es Protokolle?
- Kann ich mit einer Mikrobiomveränderung Krankheiten beeinflussen?

Wir sehen uns am 08.10.21

Vielen Dank

kontakt@energeticanatura.com
www.energeticanatura.com