63°

CONGRESSO NAZIONALE SIGG

GLI ANZIANI:
LE RADICI DA PRESERVARE

ROMA 28 novembre 01 dicembre 2018 Auditorium della Tecnica, Roma

Microbiota e demenza

Francesco Landi, MD, PhD

Catholic University, Gemelli Hospital, Rome, Italy

Hallmarks of Alzheimer's Disease

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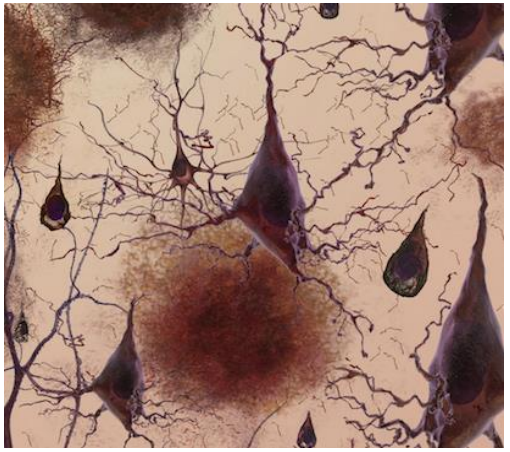
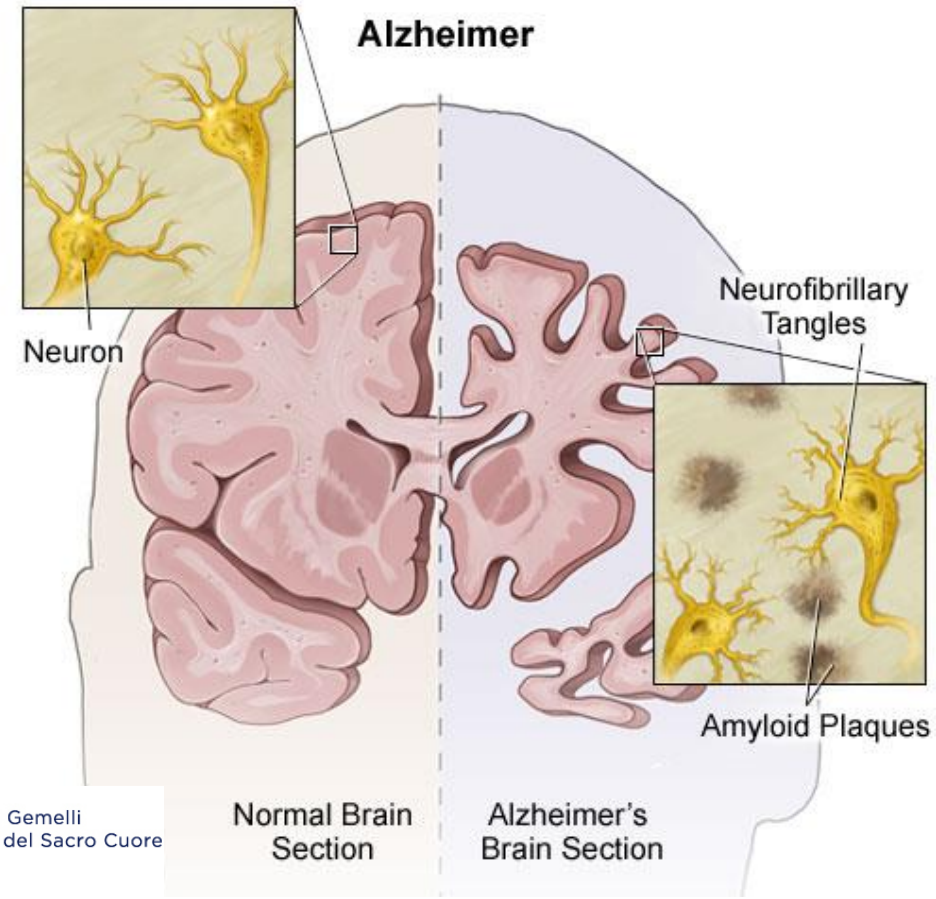
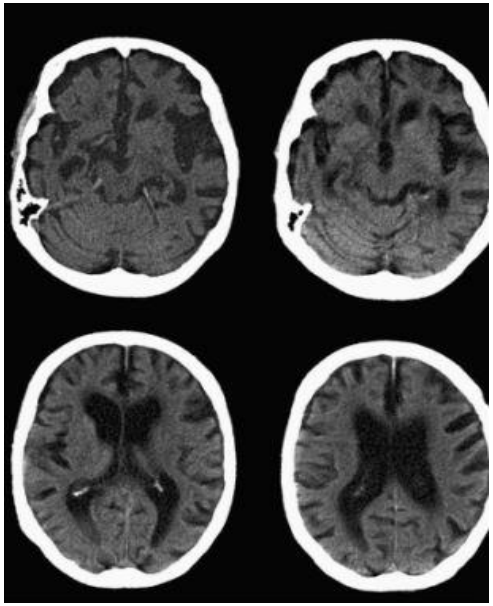
- ✓ β-amyloid containing plaques
- ✓ Neurofibrillar tangles





- ✓ Neurodegeneration



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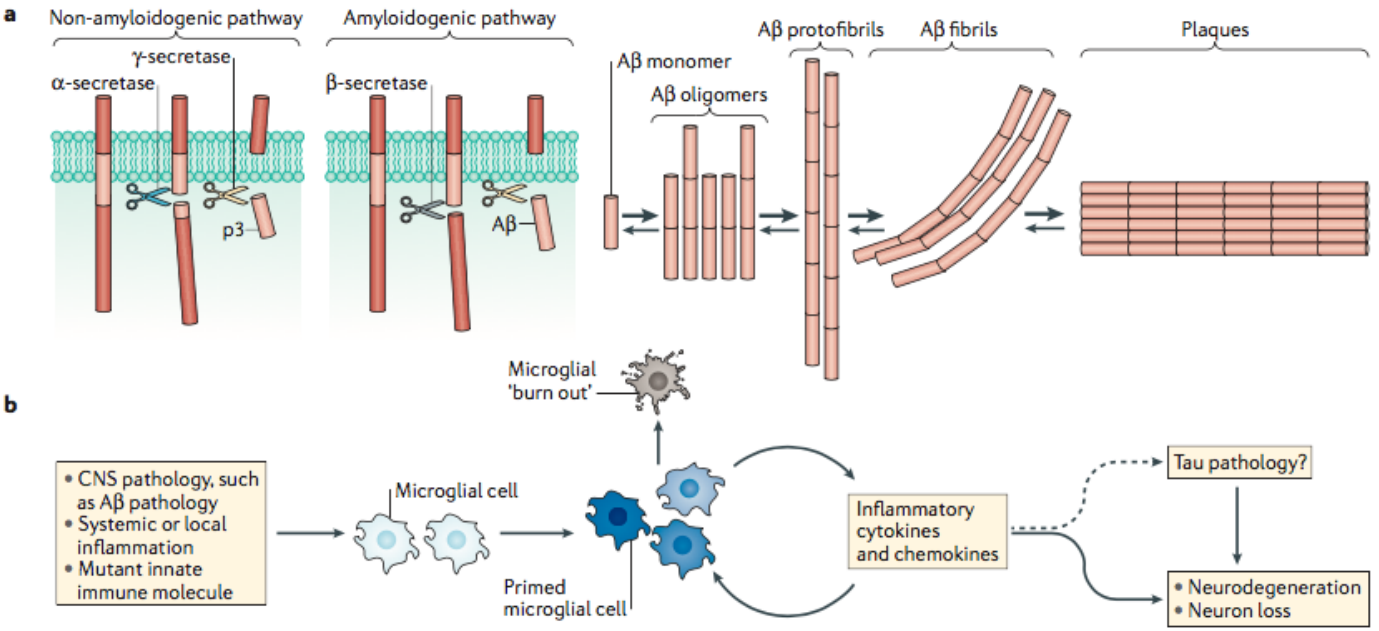
Brain amyloidosis and gut bacteria in humans

Peripheral and Central Inflammation in Alzheimer's Disease

- ✓ **Neuritic amyloid plaques co-localize with reactive microglia and astrocytes**
- ✓ **complement proteins**
- ✓ **Increa**



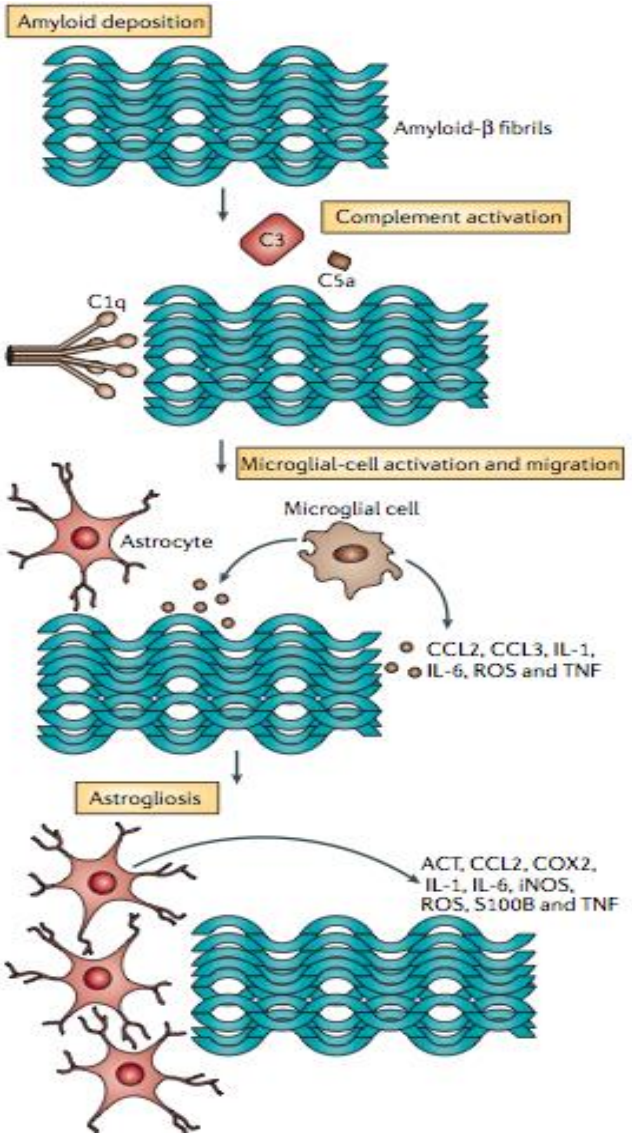
Immune attack: the role of inflammation in Alzheimer disease

Frank L. Heppner[1,2], Richard M. Ransohoff[3] and Burkhard Becher[4]

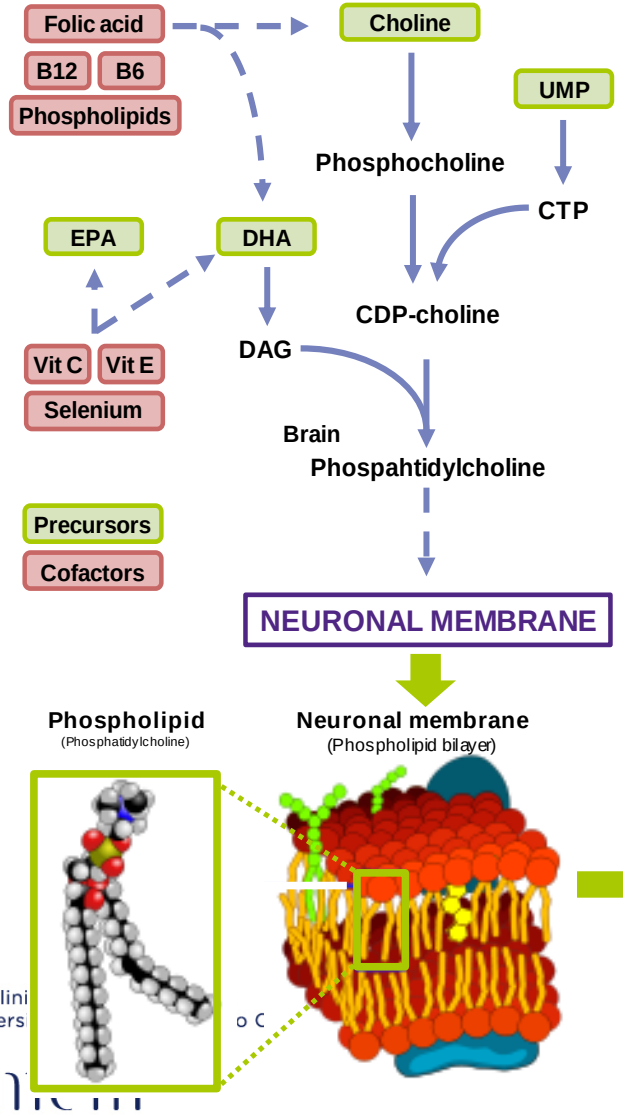
Peripheral and Central Inflammation in Alzheimer's Disease

Pro-inflammatory stimuli →

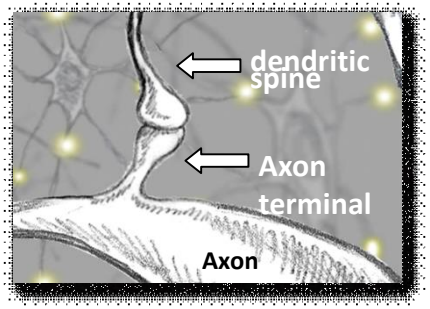
Is amyloid deposition causing inflammation or is inflammation promoting Aβ oligomers aggregation?



Synapse formation requires nutritional precursors and cofactors



- Synapses are continuously being remodeled
- Synapses are part of the neuronal membrane
- Membranes consist of phospholipids
- Phospholipid synthesis depends on the presence of uridine, choline and DHA
- Co-factors facilitate phospholipid synthesis by enhancing precursor bioavailability



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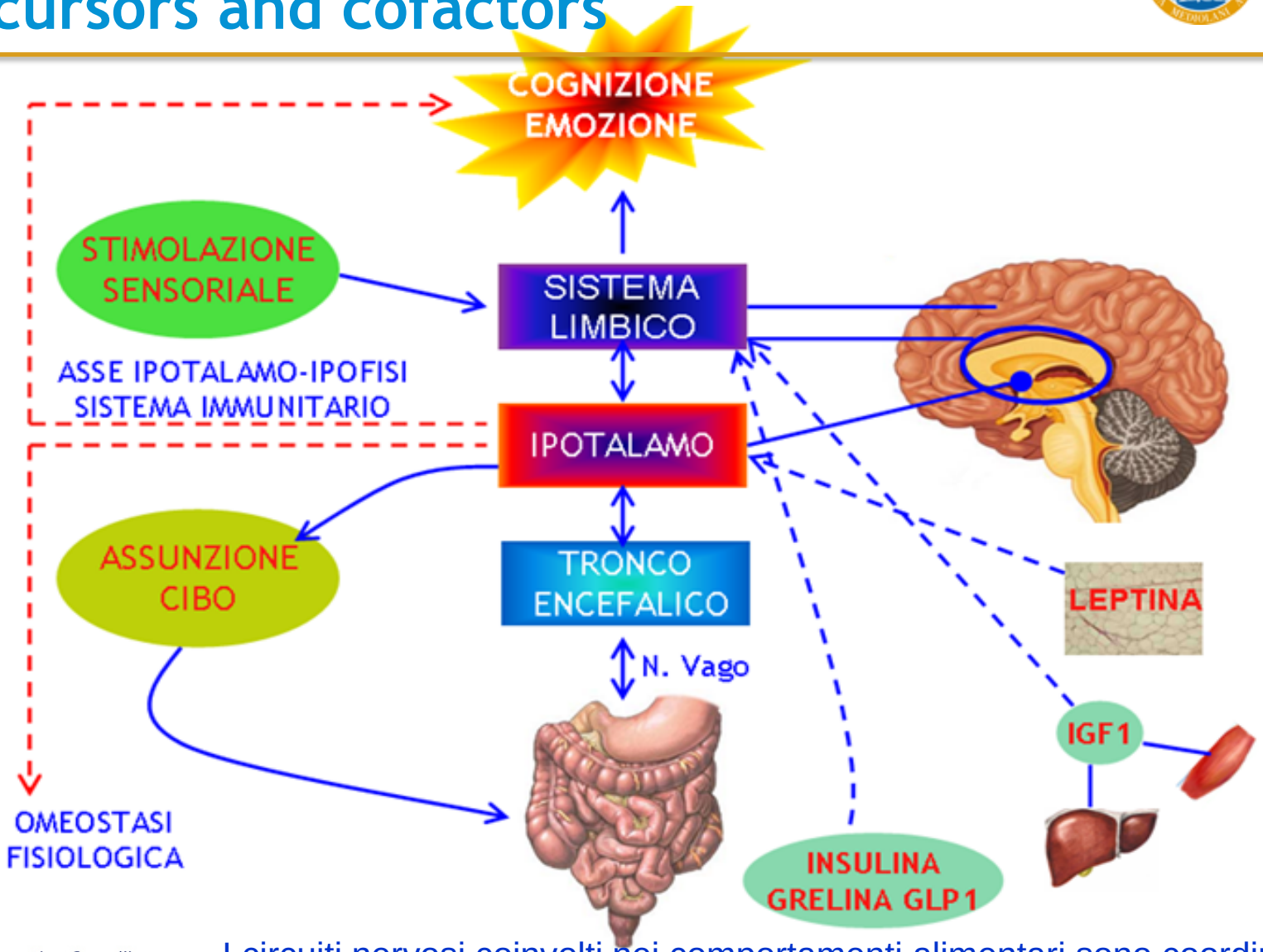
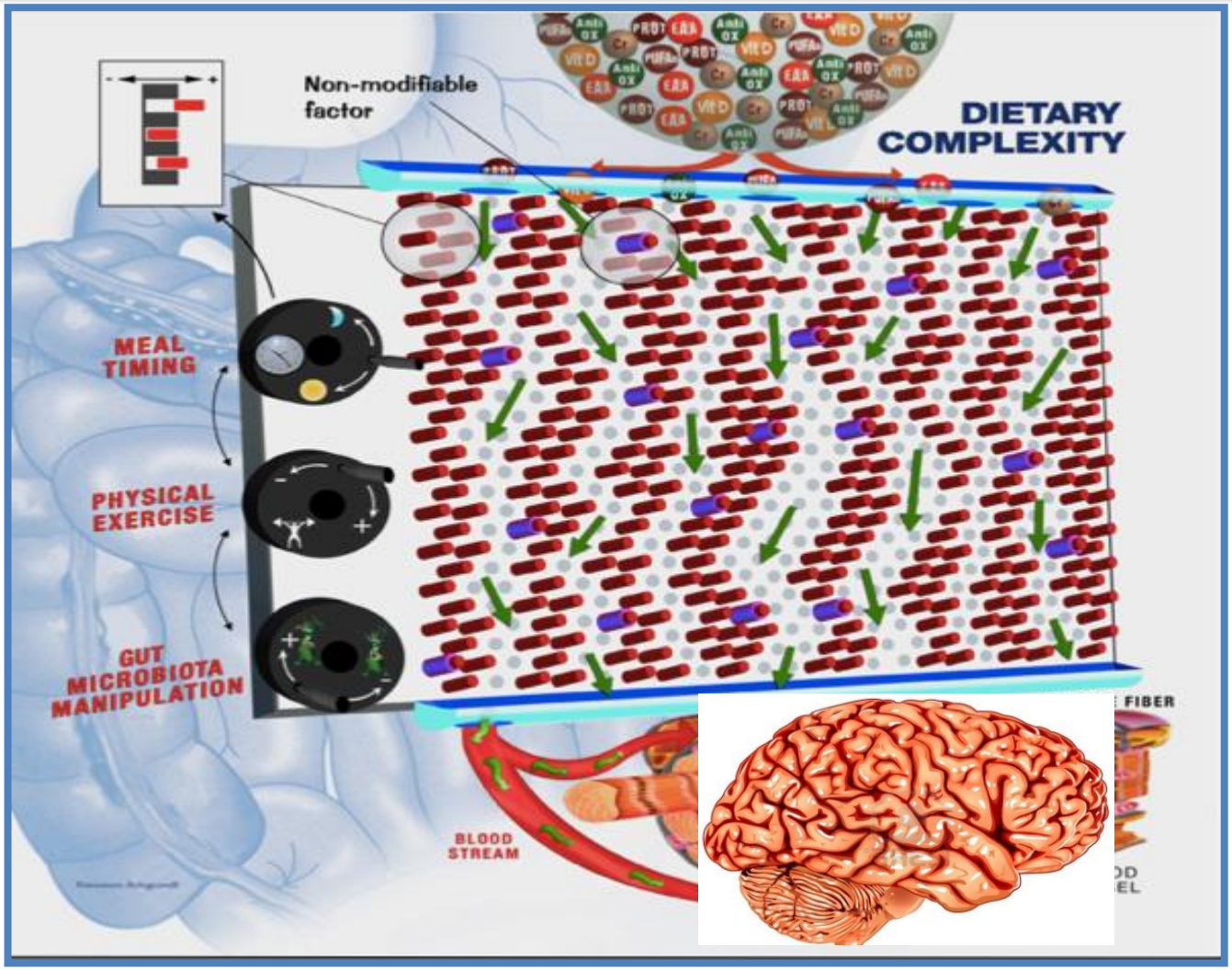


I circuiti nervosi coinvolti nei comportamenti alimentari sono coordinati in modo preciso con i centri cerebrali che regolano l'omeostasi energetica e la funzione cognitiva.

Potential therapeutic strategies

Gut-brain connection The “Pachinko Model”



Calvani R, Landi F et al. 2013

JFA The Journal of Frailty & Aging 2013;2(1):38-53

Gut microbiota as a part of the gut barrier

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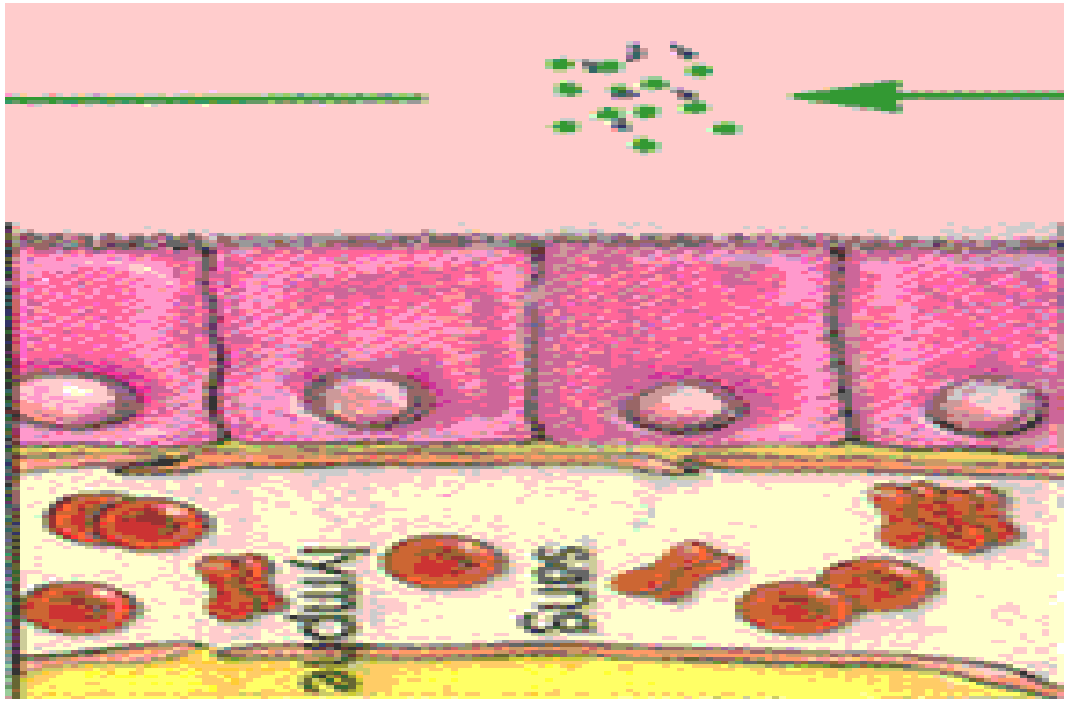
Microbiota

Mucosal Barrier

Epithelial barrier

Endocrine system

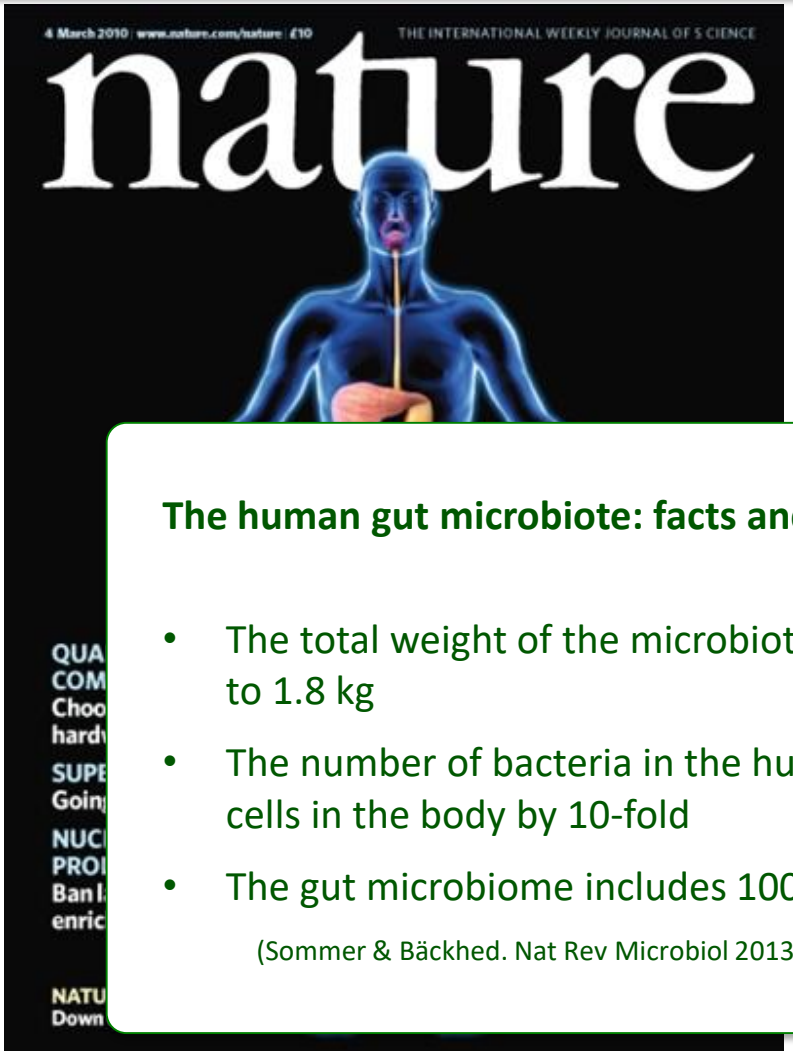


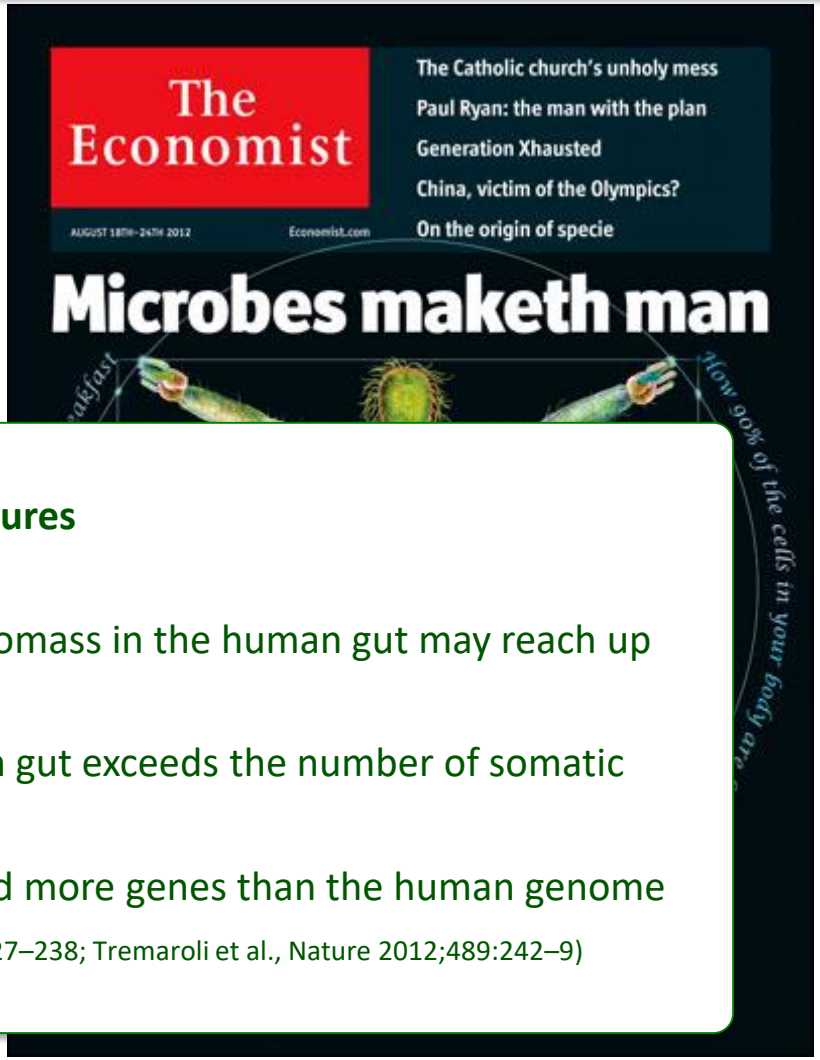
Acquired and Innate immunity

Vascular and lymphatic systems

Digestive enzymes

The gut barrier



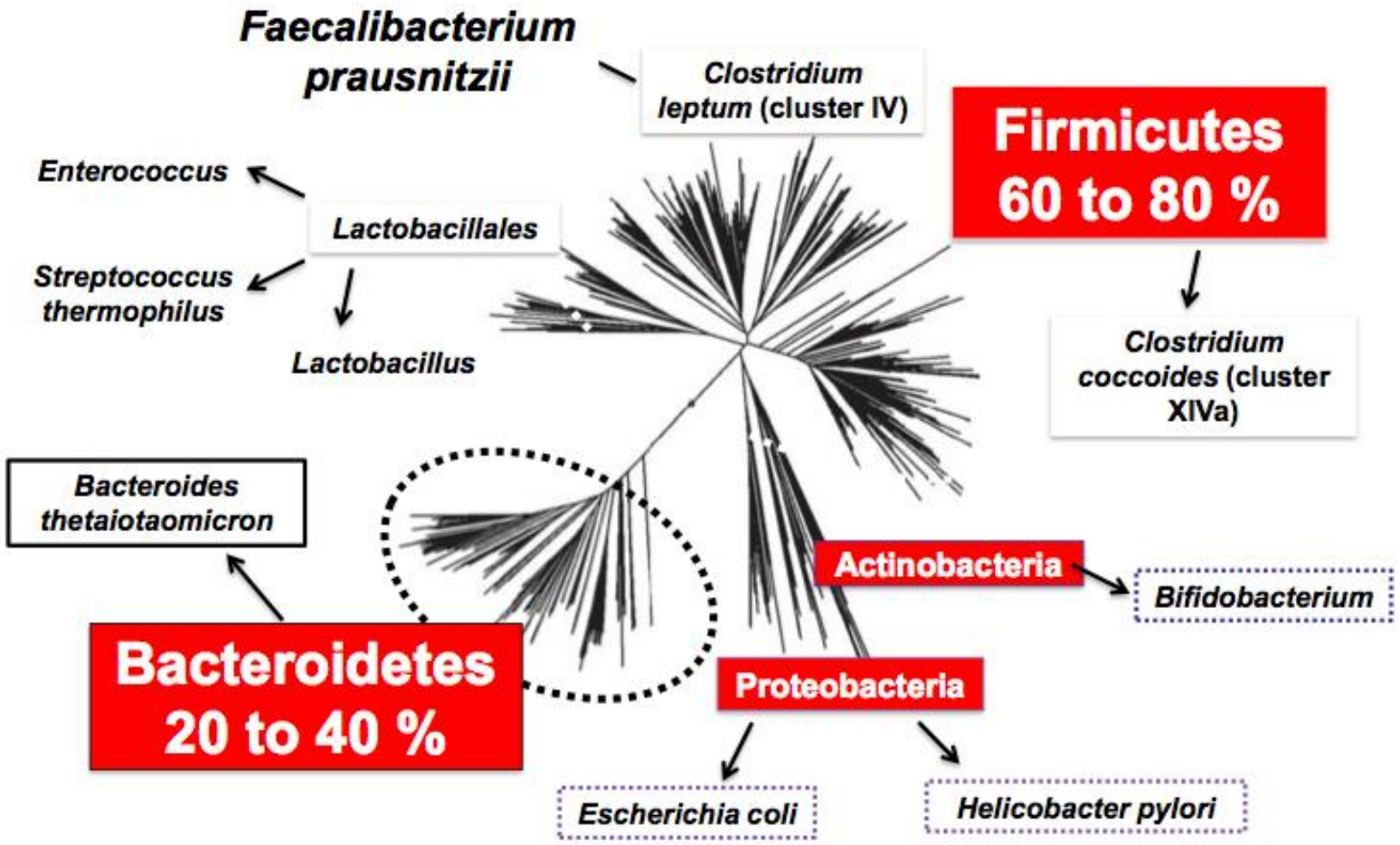


The human gut microbiote: facts and figures

- The total weight of the microbiota biomass in the human gut may reach up to 1.8 kg
- The number of bacteria in the human gut exceeds the number of somatic cells in the body by 10-fold
- The gut microbiome includes 100-fold more genes than the human genome

(Sommer & Bäckhed. Nat Rev Microbiol 2013;11:227–238; Tremaroli et al., Nature 2012;489:242–9)

Phylogenetic diversity of human gut microbiota

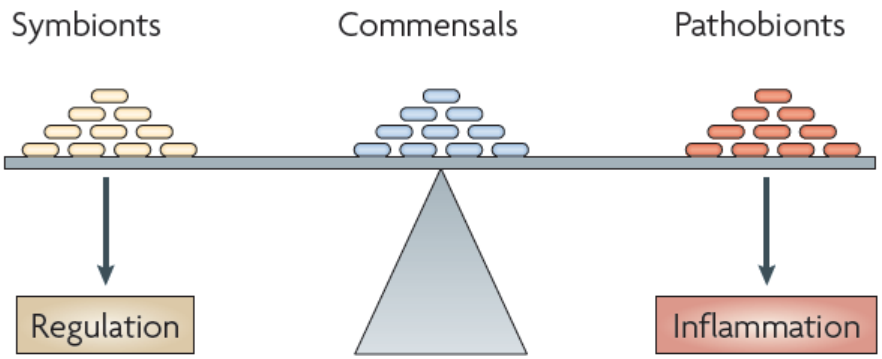


2 major phyla: Firmicutes and Bacteroidetes (>70%)

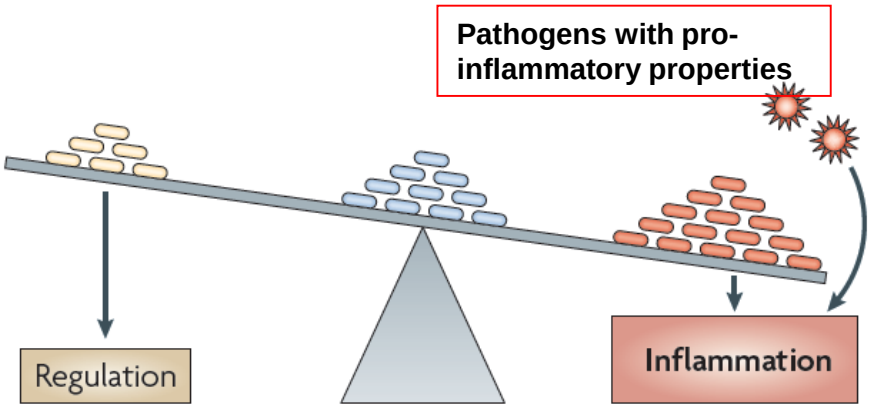
Ley et al., Science, 2008, 20;320(5883):1647-51

Immunological dysregulation associated with dysbiosis of the Gut Microbiota

Immunological equilibrium



Immunological dysequilibrium



Immunological dysregulation associated with dysbiosis of the Gut Microbiota

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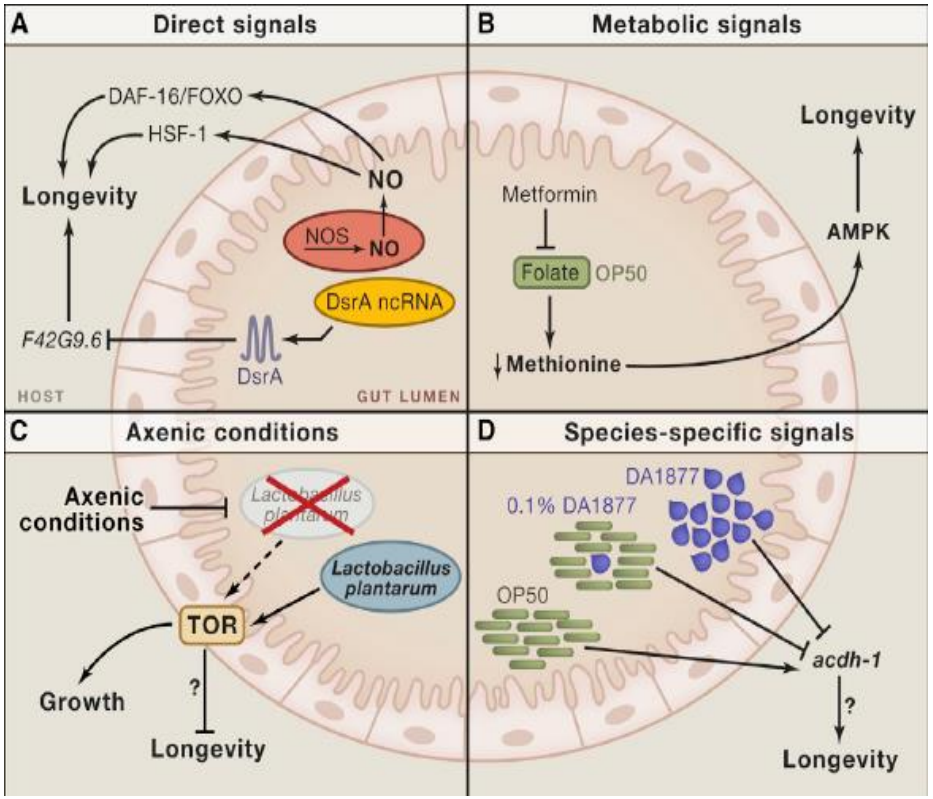
Cell

You Are What You Host: Microbiome Modulation of the Aging Process

Leading Edge
Minireview

Caroline Heintz[1] and William Mair[1,*]
[1]Harvard School of Public Health, Boston, MA 02115, USA



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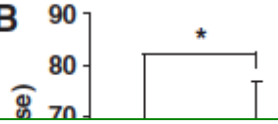
Heinz & Mair, Cell 2014;156:408-11

The human gut microbiote and human diseases

- Rheumatoid arthritis
- A
- O
- N
- F

The Gern
and Joint
Trans

Bacterial DNA



Percent increase in total body fat after

ARTICLE

Inflammasom
regulates prog

Jorge Henao-Mejia[1]*, Eran Elinav[1]*, Chen
Andrew L. Kau[5,6], Stephanie C. Eisenbarth
Hal M. Hoffman[9] & Richard A. Flavell[1,8]

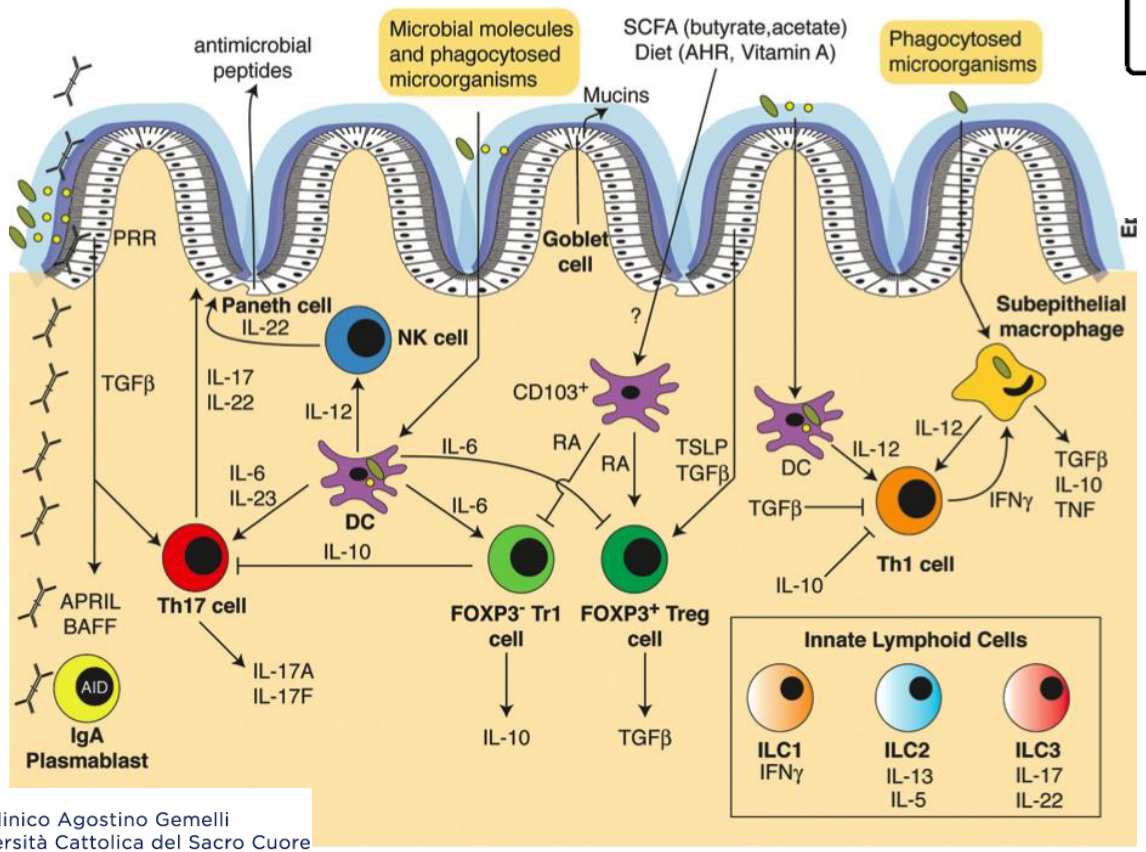
	RC range	RC s.d.	P
Barthel	**–4.8**	**–1.3**	**0.036**
FIM	**–33.3**	**–4.7**	**0.024**
MMSE	**–18.4**	**–4.8**	**0.009**
MNA	**–11.2**	**–3**	**0.004**
BMI	**–5**	**–1.3**	**0.047**
CC	**–6.8**	**–1.77**	**0.0016**
Diastolic blood pressure	**–12.4**	**–3.24**	**0.034**
Systolic blood pressure	–1.57	–0.41	0.83
Weight	**–12.7**	**–3.3**	**0.024**
IL-8	**22.31**	**5.84**	**0.006**
CRP	–3.01	–0.8	0.27

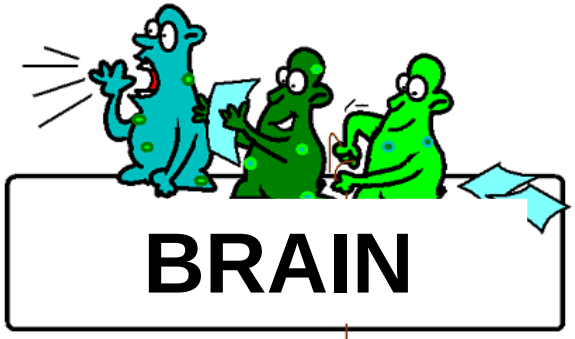
Claesson et al., Nature. 2012;488:178-84


THE GUT MICROBIOTE AND
BRAIN DISEASES

GMB as master Regulator of Immunity and Inflammation

- ✓ **Activation of complement C1q**
- ✓ **Inflammation signals Receptors**





BRAIN

GMB metabolites and inflammation signals into systemic circulation

GUT

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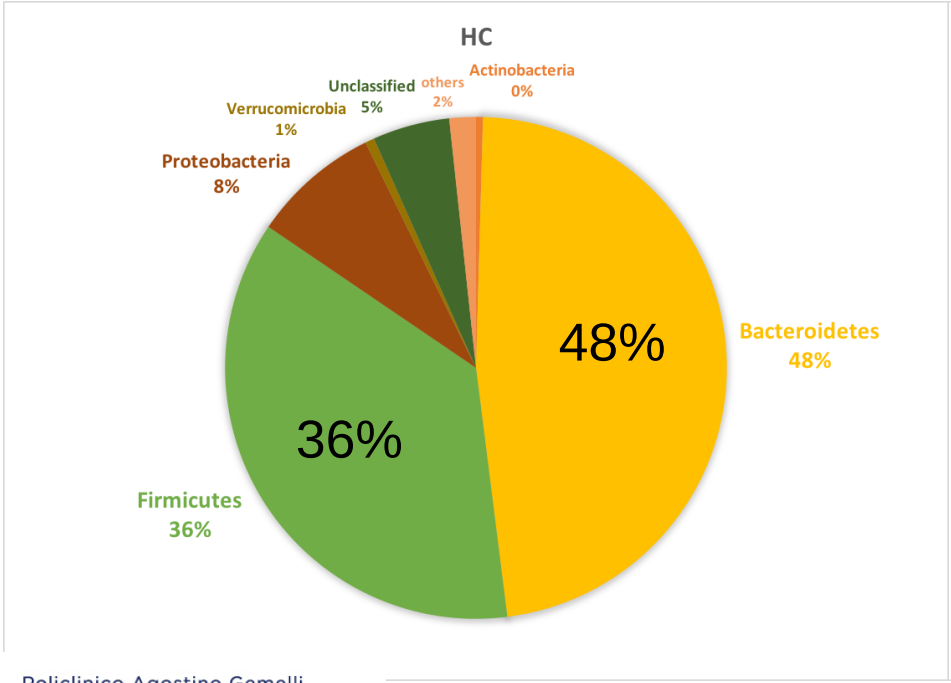
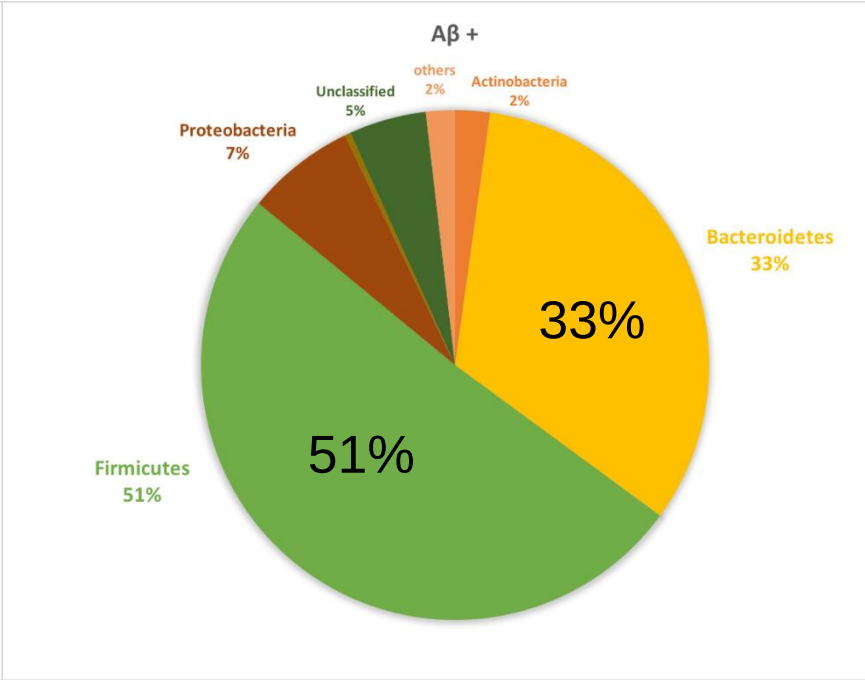
Metagenomic Analyses in AD patients and controls

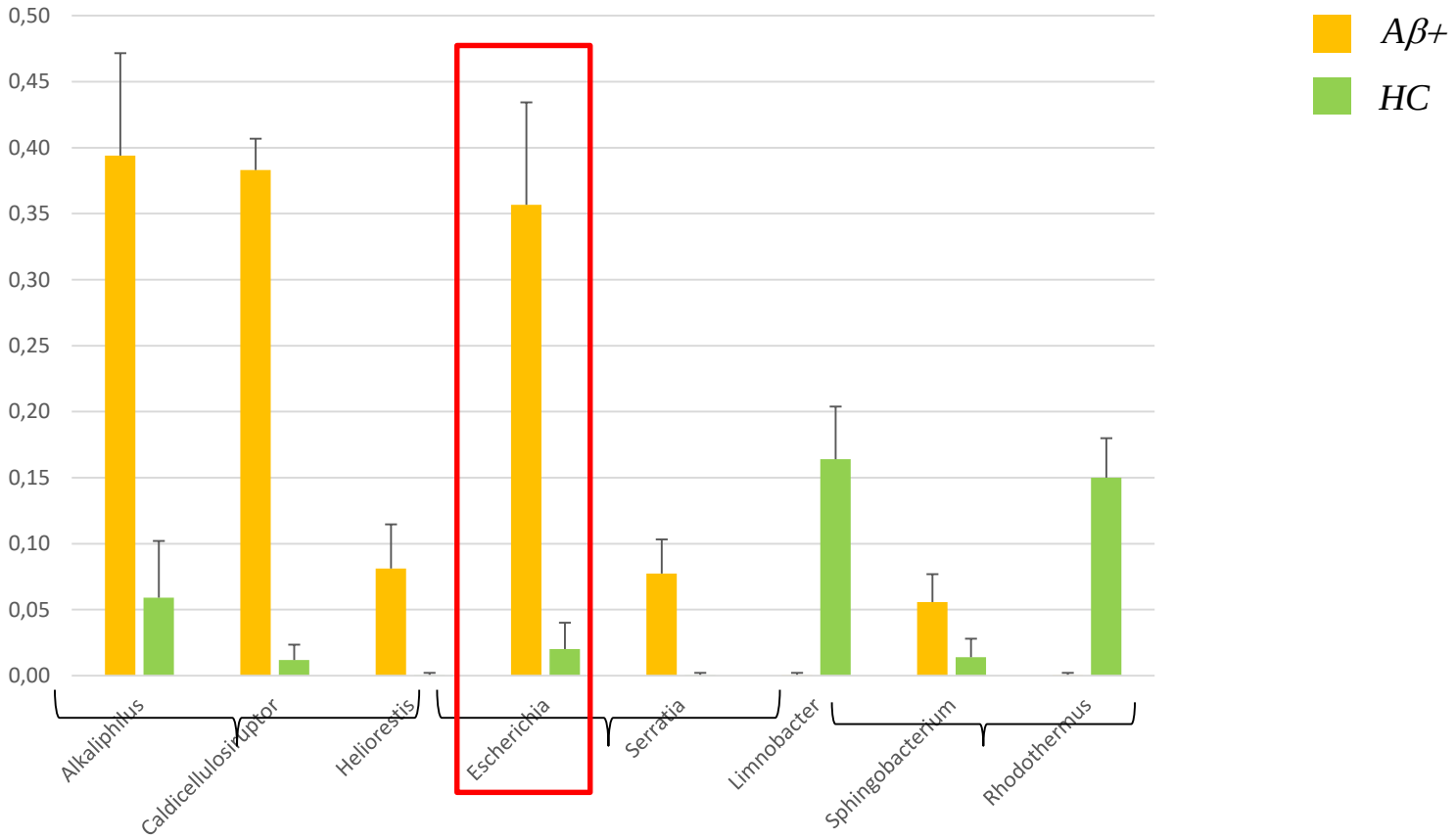
	AD	HC	P-value
Gender (M/F)	20/14	4/5	P>0.05
Age (mean±SD)	71±6.5	69±6.3	P>0.05
MMSE	22±4.5	28±1.1	**P<0.05**

9 CTRL Amy-
34 AD Amy+





Meta-genomic Analyses in AD patients and controls: Differences in genus abundances



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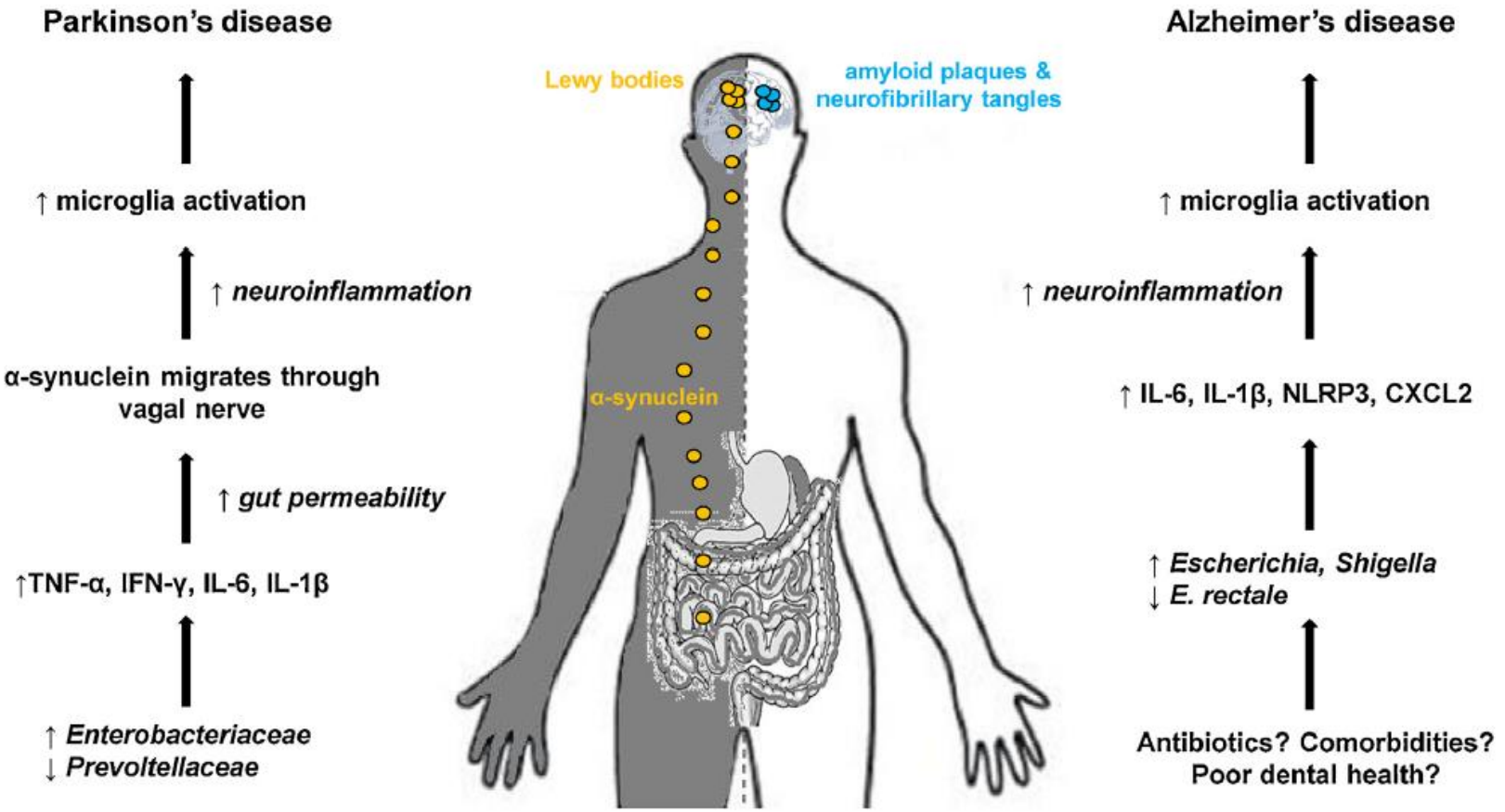
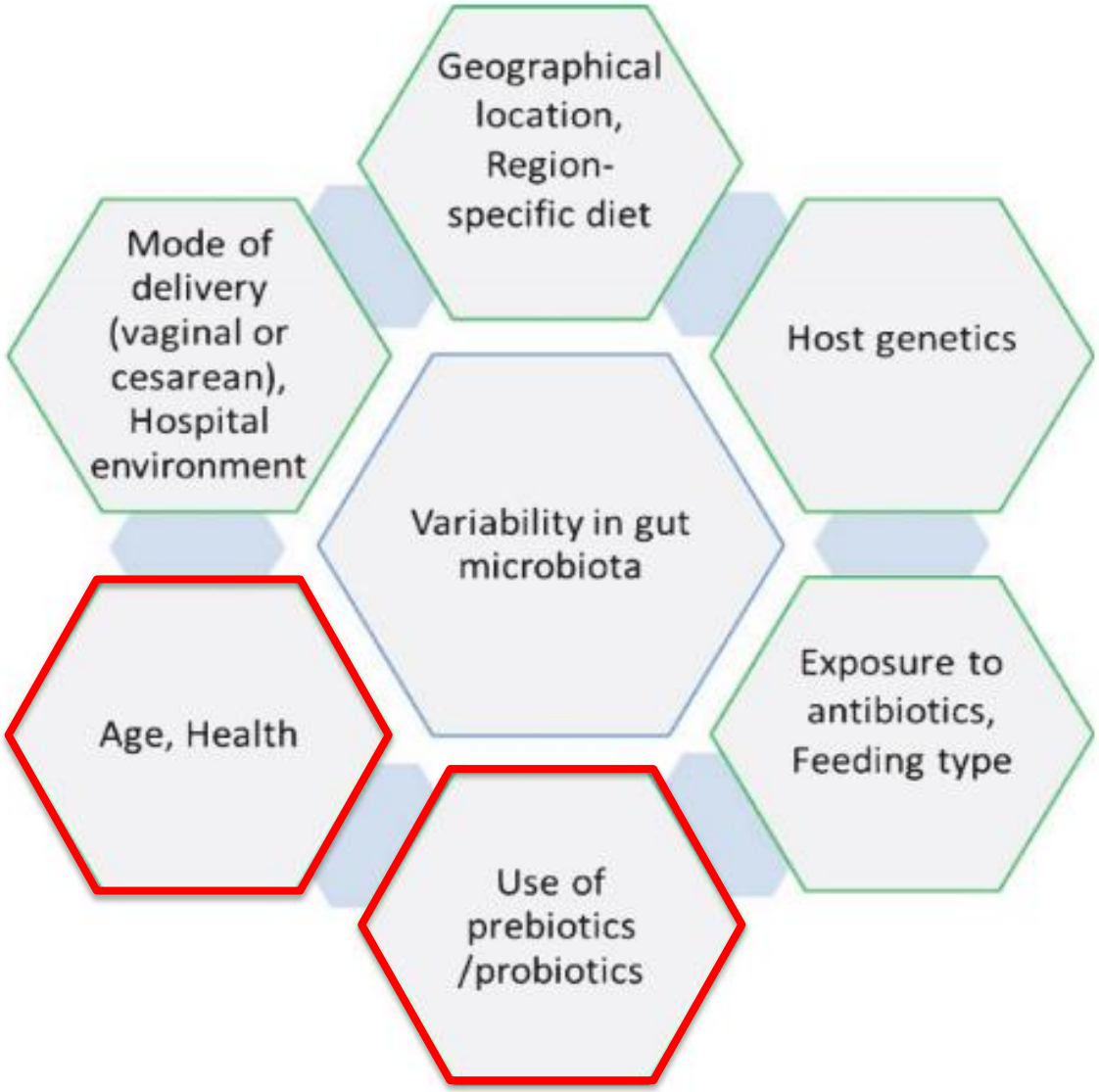
Meta-genomic Analyses in AD patients and controls: Differences in genus abundances



Factors responsible for inducing the variability in the human gut microbiota



Aging and variability in the human gut microbiota

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EUBIOSIS

↓

Modification of MICROBIOTA-HOST equilibrium during lifetime

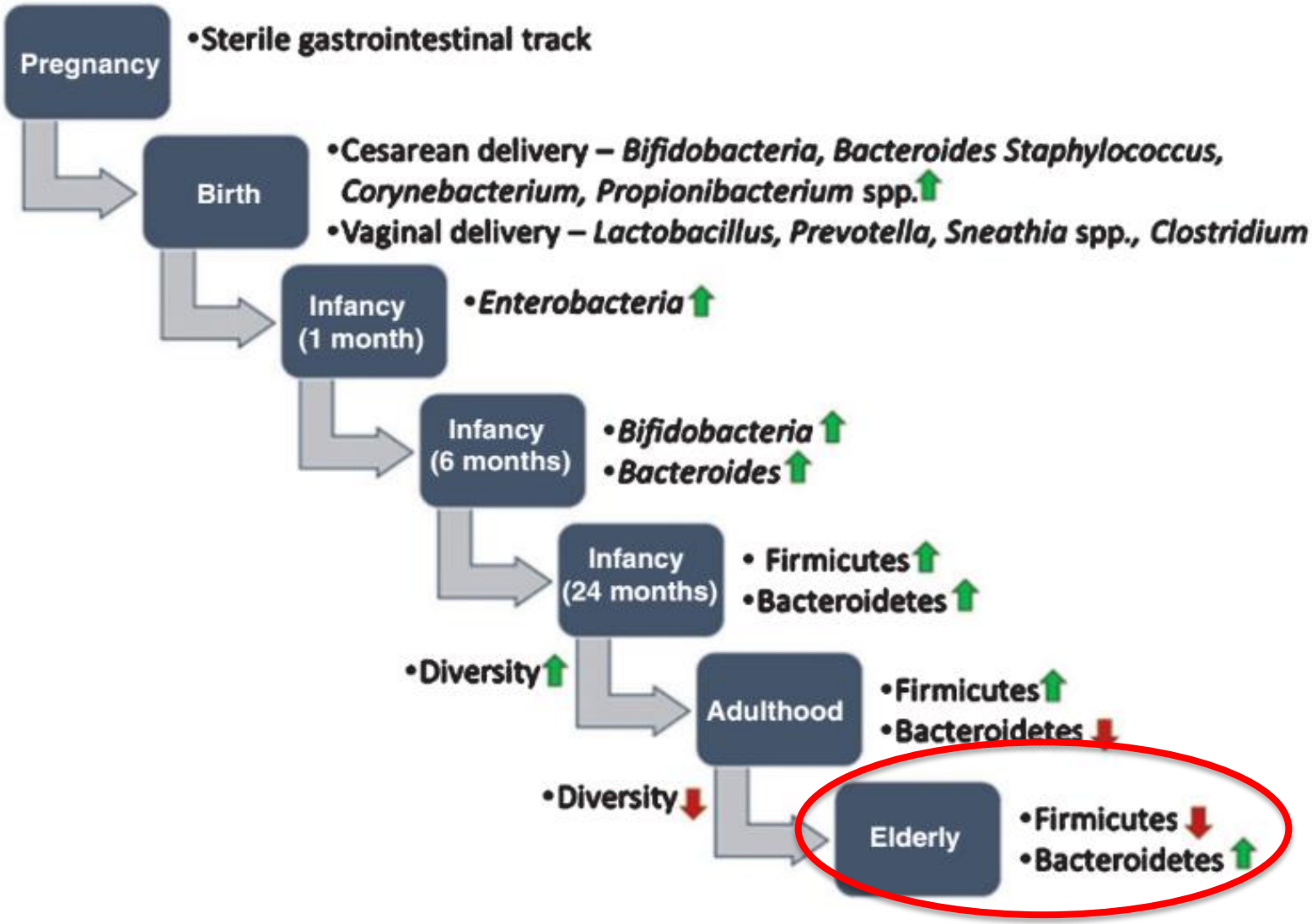
↓

Quali-quantitative alteration of gut microbiota and its functions

↓

"AGED" GUT MICROBIOTA

Development of human gut microbiota from prenatal to elderly



Aging compromise the homeostatic equilibrium between microbiota and host

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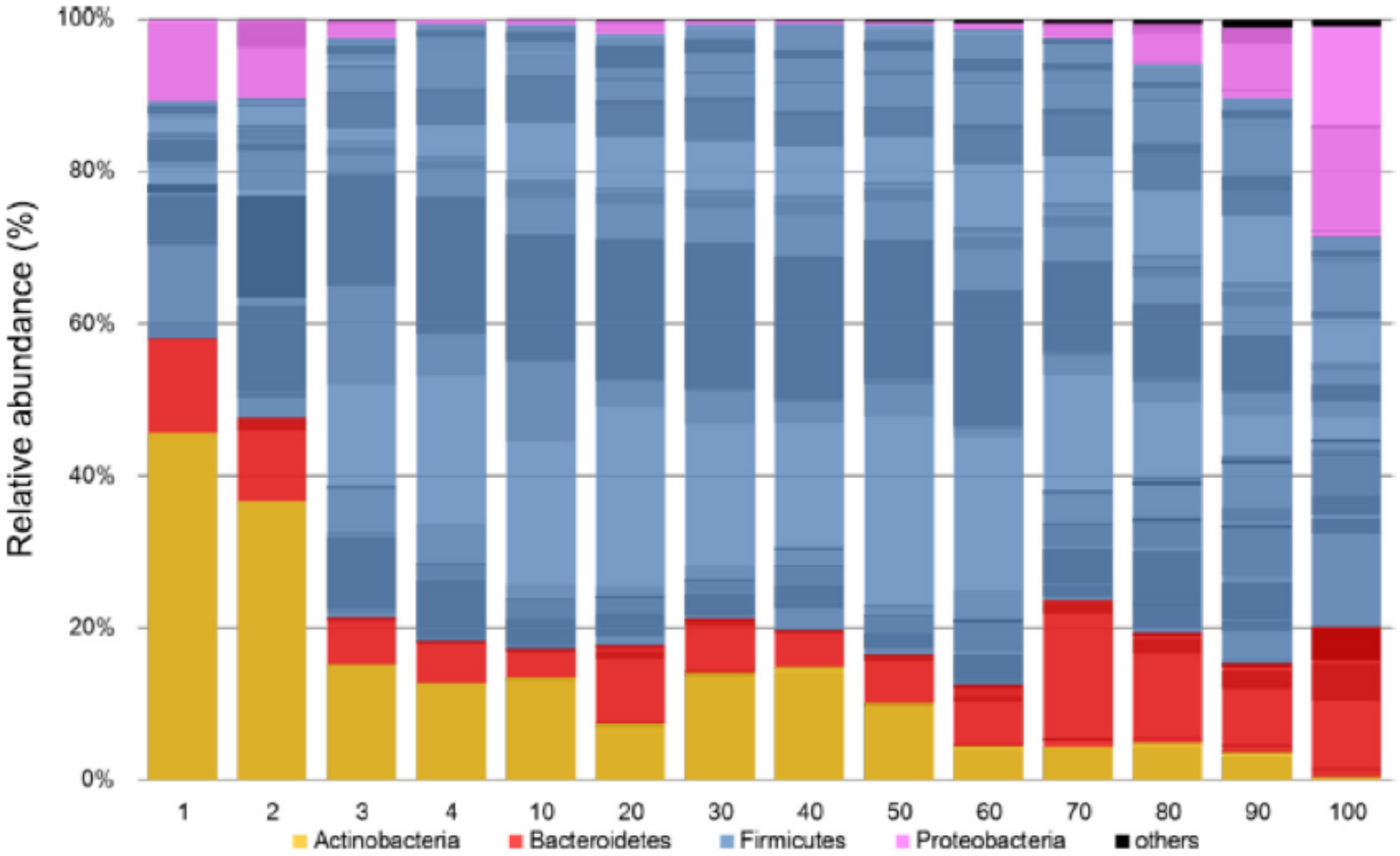
367 Japanese individuals: 6 centenarians (100-104 years old) and 7 individuals >95 years



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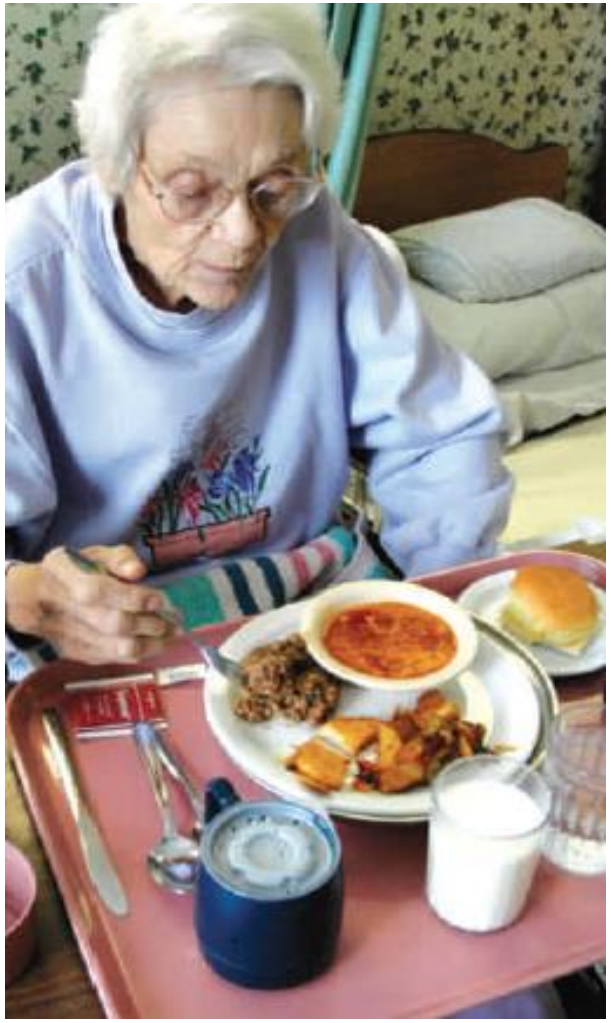
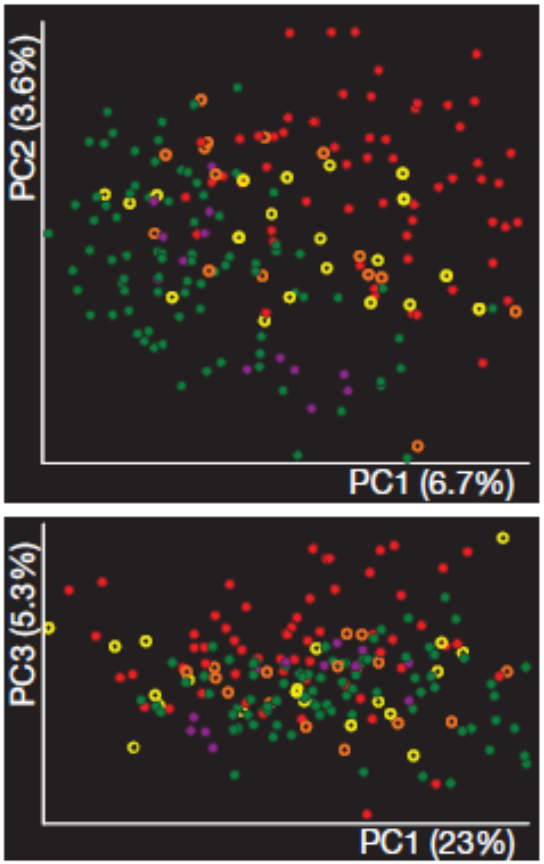
Odamaki et al. BMC Microbiology, 2016

Microbiota correlated with residence location



(1) community-dwelling
(2) attending an out-patient day hospital
(3) in short-term (<6 weeks) rehabilitation hospital care
(4) in long-term residential care (long-stay)



Microbiota composition in elderly people living in long-stay residential care facilities was different from that of the free living elderly, within the same ethno-geographic region.

Long-stay microbiota had a **higher proportion of phylum Bacteroidetes**, compared to the proportion of phylum Firmicutes and unclassified reads in community-dwelling subjects

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Claesson et al, Nature 2012

The composition of the microbiota is determined by the composition and diversity of the diet

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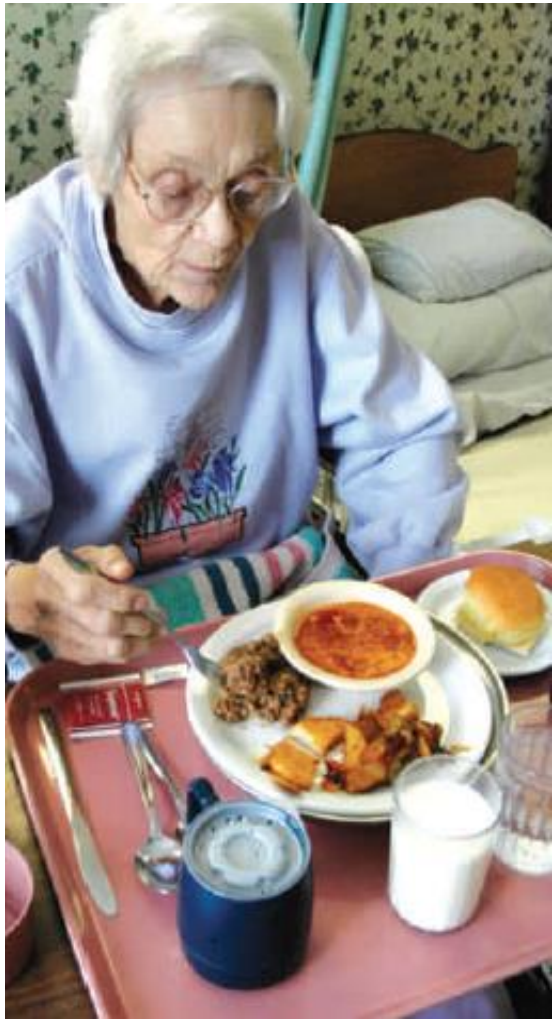

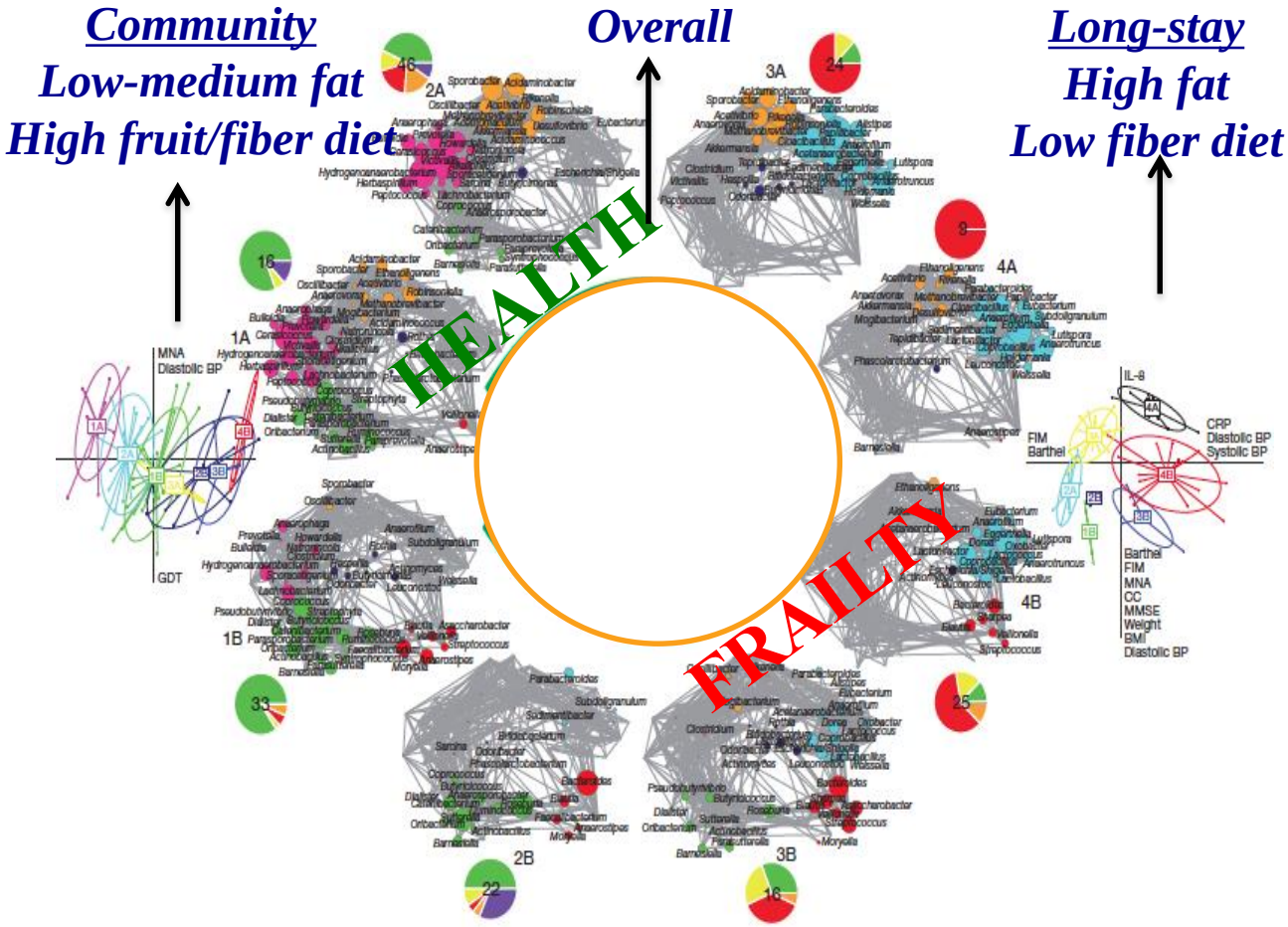

The most discriminating food types were vegetables, fruit and meat

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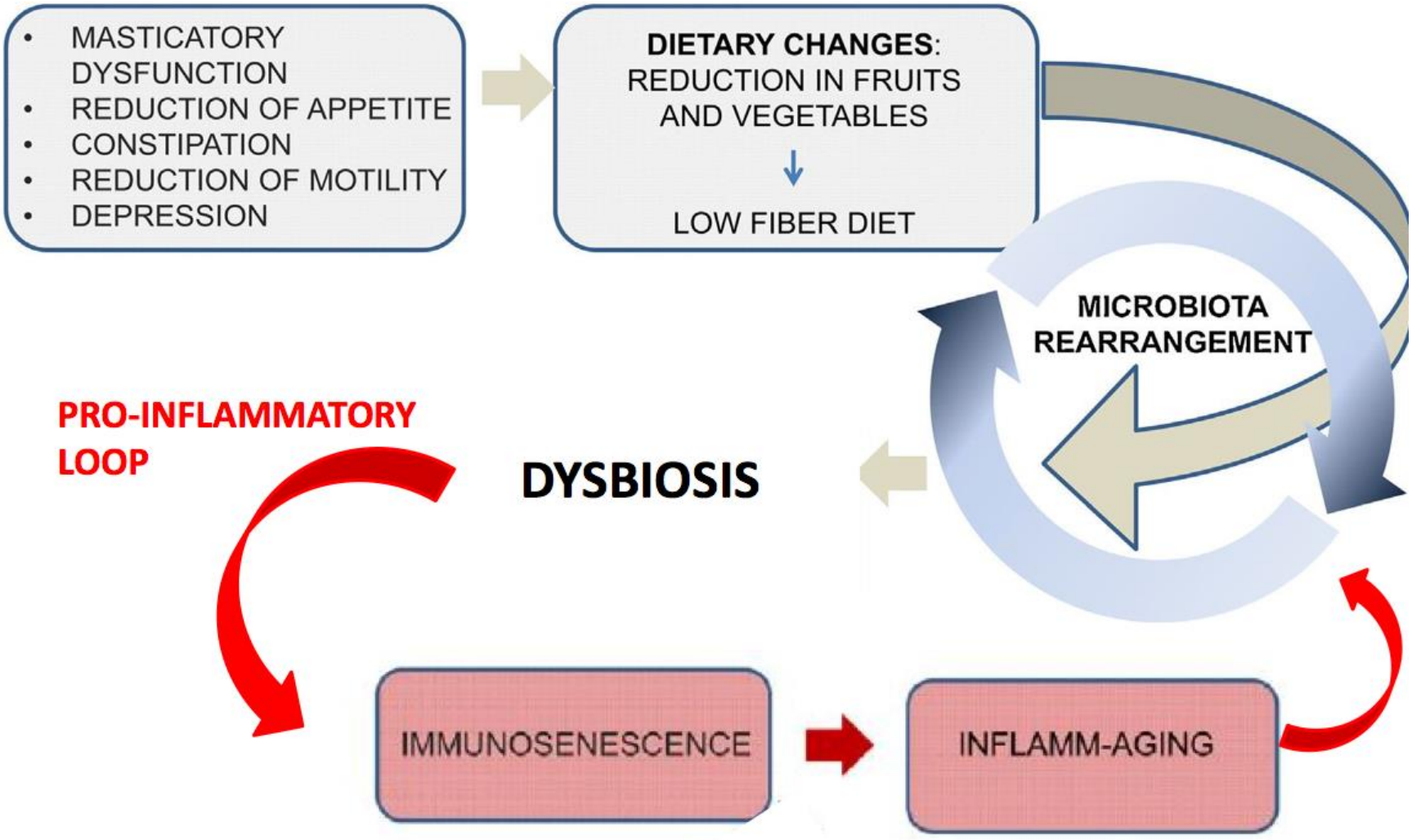
Claesson et al, Nature 2012

Ageing inevitably affects gut microbiota



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Candela M et al. Mech Ageing Dev 2013

Factors proposed to support the gut barrier

Dietetic approach	Avoidance of high amounts of sugar and fat
	Avoidance of energy-dense Western-style diet
	FODMAP diet
	Prebiotics/fibers
	Glutamine
	Other immune-modulating formula
Probiotic approach	Selected probiotics
	Probiotic cocktails (multispecies concept)
	Synbiotics (combination of probiotics and prebiotics)
Drugs/others	Short-chain fatty acids (SCFA)
	Metformin
	Quercetin and other flavonoids

Bischoff et al. BMC Gastroenterology 2014, 14:189

Probiotics as New therapies ?

- PROBIOTICS (“living organisms that can provide benefit to the Host”)

- PREBIOTICS (“substances that are present in the food that is not absorbed by the Host but that it is used by the gut bacteria”)

Potential therapeutic strategies

- Lactobacillus Plantarum LP01: modulazione della flogosi per positivo rapporto tra citochine antinfiammatorie e pro-infiammatorie

- Lactobacillus Buchneri LB26: probiotico inattivato che internalizza Selenio e Zinco per aumentarne la biodisponibilità

- Bifidobacterium Animalis specie lactis BS05: effetto antiossidante per produzione GSH e SOD

Lactobacillus and Bifidobacterium are the most commonly used probiotic bacteria

Lactobacillus Plantarum LP01

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Siezen and van Hylckama Vlieg *Microbial Cell Factories* 2011, **10**(Suppl 1):S3
http://www.microbialcellfactories.com/content/10/S1/S3

MICROBIAL CELL FACTORIES

PROCEEDINGS **Open Access**

Genomic diversity and versatility of *Lactobacillus plantarum*, a natural metabolic engineer

Roland J Siezen[1,2,3,4*], Johan ET van Hylckama Vlieg[1,3,5]

From 10th Symposium on Lactic Acid Bacterium
Egmond aan Zee, the Netherlands. 28 August - 1 September 2011

Abstract

In the past decade it has become clear that the lactic acid bacterium *Lactobacillus plantarum* occupies a diverse range of environmental niches and has an enormous diversity in phenotypic properties, metabolic capacity and industrial applications. In this review, we describe how genome sequencing, comparative genome hybridization and comparative genomics has provided insight into the underlying genomic diversity and versatility of *L. plantarum*. One of the main features appears to be genomic life-style islands consisting of numerous functional gene cassettes, in particular for carbohydrates utilization, which can be acquired, shuffled, substituted or deleted in response to niche requirements. In this sense, *L. plantarum* can be considered a "natural metabolic engineer".

Lactobacillus Buchneri LB26

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Selenium and Zinc Internalized by *Lactobacillus buchneri* Lb26 (DSM 16341) and *Bifidobacterium lactis* Bb1 (DSM 17850)

Improved Bioavailability Using a New Biological Approach

Luca Mogna, BS, Stefania Nicola, PhD,* Marco Pane, BS,* Paola Lorenzini, BS,* Gianpaolo Strozzi, BS,† and Giovanni Mogna, BS†*

Background: Minerals, often referred to as micronutrients, are one of the 5 fundamental groups of nutrients needed to sustain life. Micronutrient malnutrition affects >50% of the worldwide population. In particular, zinc (Zn) deficiency is considered an emerging public health problem in India and in other developing countries. Selenium (Se) is another trace mineral essential for humans and animals. Dietary Se exists primarily as selenomethionine and selenocysteine. In addition, Se may be present in its inorganic form (selenite) in some vegetables. To increase the daily intake of these minerals, numerous food supplements containing different inorganic and organic forms of Zn or Se are commercially available. At any rate, it is quite well known that inorganic salts have a very low bioavailability. Organic salts, commonly based on gluconate, orotate, citrate, or other molecules, are characterized by a higher systemic effect. The innovative opportunity of using certain species of probiotics enriched with the 2 minerals could represent an interesting alternative to these preparations. Diet integration with bacteria able to internalize Zn and Se may embody a new application of probiotics.

were predominantly found in the apical compartment, thus demonstrating their poor ability to diffuse into the cell and become bioavailable in all subcellular areas.

Conclusions: The opportunity of delivering minerals in a highly bioavailable form by means of a probiotic bacterium has not been deeply investigated to date. This is the first study reporting quantitative data on the bioavailability and percentage of absorption of minerals internalized by specific probiotics. The most noticeable aspect is the significantly higher absorption of both probiotic Se and Zn compared with their organic forms, with particular reference to seleno-L–methionine, seleno-L-cysteine, and zinc gluconate.

Key Words: probiotic strain, selenium and zinc, organic form, Transwell system, bioavailability

(*J Clin Gastroenterol* 2012;46:S41–S45)

Bifidobacterium Animalis (lactis BS05)

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Appl Microbiol Biotechnol (2013) 97:809–817
DOI 10.1007/s00253-012-4241-7

APPLIED MICROBIAL AND CELL PHYSIOLOGY

Antioxidant properties of potentially probiotic bacteria: in vitro and in vivo activities

Alberto Amaretti · Mattia di Nunzio · Anna Pompei · Stefano Raimondi · Maddalena Rossi · Alessandra Bordoni

Received: 7 May 2012 / Revised: 11 June 2012 / Accepted: 13 June 2012 / Published online: 12 July 2012

Abstract Thirty-four strains of lactic acid bacteria (seven *Bifidobacterium*, 11 *Lactobacillus*, six *Lactococcus*, and 10 *Streptococcus thermophilus*) were assayed in vitro for antioxidant activity against ascorbic and linolenic acid oxidation (TAA_{AA} and TAA_{LA}), trolox-equivalent antioxidant capacity (TEAC), intracellular glutathione (TGSH), and superoxide dismutase (SOD). Wide dispersion of each of TAA_{AA}, TAA_{LA}, TEAC, TGSH, and SOD occurred within bacterial groups, indicating that antioxidative properties are strain specific. The strains *Bifidobacterium animalis* subsp. *lactis* DSMZ 23032, *Lactobacillus acidophilus* DSMZ 23033, and *Lactobacillus brevis* DSMZ 23034 exhibited among the highest TAA_{AA}, TAA_{LA}, TEAC, and TGSH values within the lactobacilli and bifidobacteria. mixture effectively reduced doxorubicin-induced oxidative stress. Probiotic strains which are capable to limit excessive amounts of reactive radicals in vivo may contribute to prevent and control several diseases associated with oxidative stress.

Keywords *Bifidobacterium* · *Lactobacillus* · Probiotic · Antioxidant · In vivo · In vitro

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PROBIOTICS & malattie psichiatriche

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	sample	probiotic	effects	Pathology/physiology	reference
animal	BALB/c mice	*Lactobacillus rhamnosus*	↓ depressive-anxious behaviour	Depression, anxiety	Bravo 2011
	BALB/c mice	*Mycobacterium caccae*	↓ anxiety	anxiety	Matthews 2013
	BALB/c mice	*Lactobacillus rhamnosus*	In vivo Magnetic Resonance Spectroscopy (MRS) ↑ Glu, Gln, GABA, N-acetyl aspartate + N-acetyl aspartyl glutamic acid long term effect (not for GABA)	neurotransmission	Janik 2016
	Sprague-Dawley rats Maternal separation model	*Lactobacillus rhamnosus* + *L. helveticus*	↓ HPA	Anxiety, depression	Gareau 2007
	Sprague-Dawley rats	*Bifidobacterium infantis*	No behavioural changes ↑ Trp in plasma ↓ pro-inflammatory cytokines	depression	Desbonnet 2008
	Sprague-Dawley rats Maternal separation model	*Bifidobacterium infantis*	probiotic ≅ citalopram	depression	Desbonnet 2010
	Sprague-Dawley rats	*Lactobacillus helveticus*	↓ corticosterone ↓ ACTH ↑ IL-10, BDNF, NA, 5-HT probiotic ≅ citalopram	Depression	Liang 2015
human	Healthy subjects	*Lactobacillus casei Shirota (yakult)*	Amelioration of mood (only subjects whose baseline mood scores fell in the lowest 3rd of the total range)	depression	Benton 2007
	Healthy subjects	*Lactobacillus helveticus and Bifidobacterium longum*	↓ negative mood ↓ urinary cortisol	depression	Messaoudi 2011
	Healthy subjects		↓ reactivity to sad mood	depression	Steenberg 2015
	Healthy students (examination time)	*Lactobacillus casei Shirota (yakult)*	↓ plasma cortisol (the day before the examination) ↑ higher fecal 5-HT	anxiety	Kato-Kataoka 2016

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frontiers in Aging Neuroscience

CLINICAL TRIAL
published: 10 November 2016
doi: 10.3389/fnagi.2016.00256

Effect of Probiotic Supplementation on Cognitive Function and Metabolic Status in Alzheimer's Disease: A Randomized, Double-Blind and Controlled Trial

Elmira Akbari[1], Zatollah Asemi[2], Reza Daneshvar Kakhaki[3], Fereshteh Bahmani[2], Ebrahim Kouchaki[3], Omid Reza Tamtaji[1], Gholam Ali Hamidi[1] and Mahmoud Salami[1]**

[1] Physiology Research Center, Kashan University of Medical Sciences, Kashan, Iran, [2] Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, Iran, [3] Department of Neurology, School of Medicine, Kashan University of Medical Sciences, Kashan, Iran

Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore

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TABLE 2 | Mean values of the behavioral test and the biomarkers measurements in the probiotic and control groups.

	Control group		Probiotic group		Difference between the two groups
	Baseline	End-of-trial	Baseline	End-of-trial	*P*-value[a]
MMSE (score out of 30)	8.47 ± 1.10	8.00 ± 1.08	8.67 ± 1.44	10.57 ± 1.64	<0.001
TAC (mmol/L)	895.66 ± 25.96	915.35 ± 26.60	876.13 ± 26.48	922.42 ± 28.53	0.25
GSH (μmol/L)	390.78 ± 17.46	386.76 ± 20.33	377.26 ± 14.82	401.25 ± 16.68	0.19
MDA (μmol/L)	4.26 ± 0.30	4.32 ± 0.31	4.31 ± 0.26	3.21 ± 0.23	<0.001
hs-CRP (μg/ml)	4.54 ± 1.30	6.59 ± 1.14	6.61 ± 1.24	5.44 ± 0.85	<0.001
NO (imol/L)	44.76 ± 0.53	45.56 ± 0.82	43.68 ± 0.64	44.37 ± 1.14	0.93
FPG (mg/dl)	83.40 ± 2.36	86.77 ± 4.07	92.00 ± 7.92	94.13 ± 7.72	0.98
HOMA-IR	1.43 ± 0.24	2.08 ± 0.27	1.30 ± 0.13	1.60 ± 0.19	0.002
HOMA-B	25.04 ± 3.21	37.86 ± 4.64	27.36 ± 3.50	22.06 ± 2.43	0.001
QUICKI	0.38 ± 0.01	0.36 ± 0.01	0.38 ± 0.01	0.37 ± 0.01	0.006
Triglycerides (mg/dl)	84.32 ± 4.65	81.74 ± 4.76	119.60 ± 10.25	94.33 ± 10.04	0.003
VLDL (mg/dL)	16.86 ± 0.93	16.35 ± 0.95	23.92 ± 2.05	18.87 ± 2.01	0.003
LDL (mg/dl)	90.44 ± 4.58	94.34 ± 4.39	85.16 ± 4.14	90.64 ± 5.29	0.76
HDL (mg/dl)	51.27 ± 1.75	44.49 ± 1.97	45.81 ± 1.45	38.82 ± 1.35	0.93
Total cholesterol (mg/dl)	158.57 ± 5.75	155.17 ± 5.59	154.88 ± 4.91	148.32 ± 5.43	0.63
Total/ HDL-cholesterol	3.15 ± 0.12	3.62 ± 0.16	3.43 ± 0.12	3.95 ± 0.2	0.81

Data are mean ± SEM.[a] represents P-values obtained from the time × group interaction analysis. FPG, fasting plasma glucose; GSH, total glutathione; HOMA-IR, homeostasis model of assessment-estimated insulin resistance; HOMA-B, homeostasis model of assessment-estimated B cell function; hs-CRP, high-sensitivity C-reactive protein; MMSE, mini-mental state examination; MDA, malondialdehyde; NO, nitric oxide; QUICKI, quantitative insulin sensitivity check index; TAC, total antioxidant capacity.

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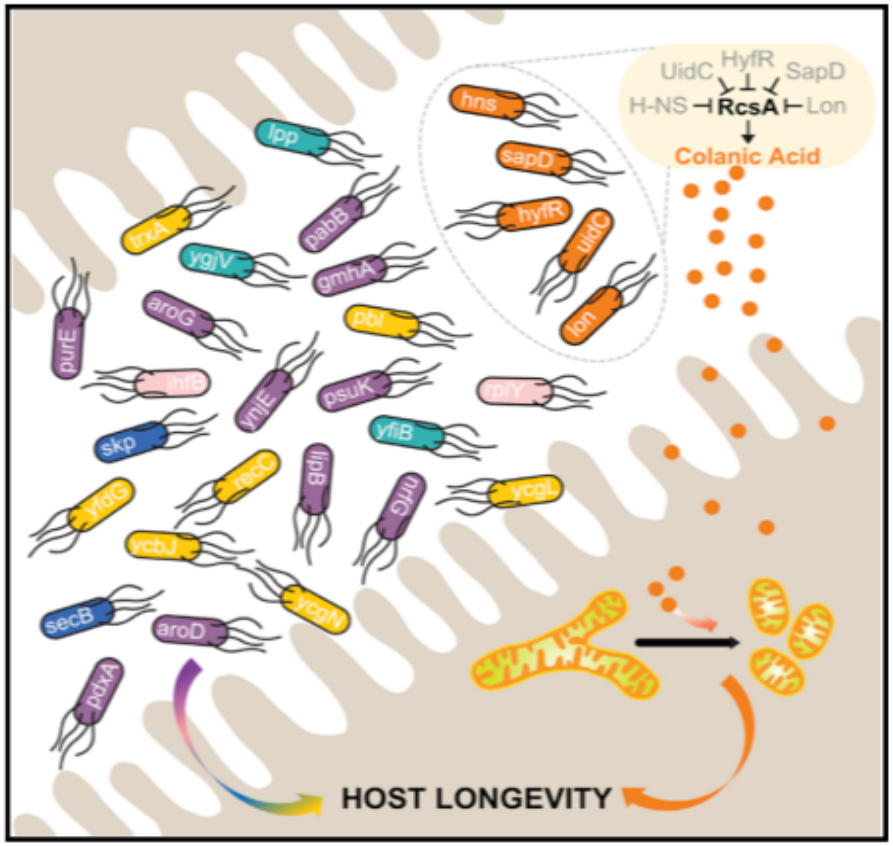
Microbial Genetic Composition Tunes Host Longevity

Graphical Abstract



Authors

Bing Han, Priya Sivaramakrishnan, Chih-Chun J. Lin, ..., Jin Wang, Christophe Herman, Meng C. Wang

Correspondence

wmeng@bcm.edu

In Brief

The genetic composition of gut microbes controls the production of metabolites that impact host longevity.

Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore

Gemelli

Cell 169, 1249–1262, June 15, 2017

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Microbial Genetic Composi
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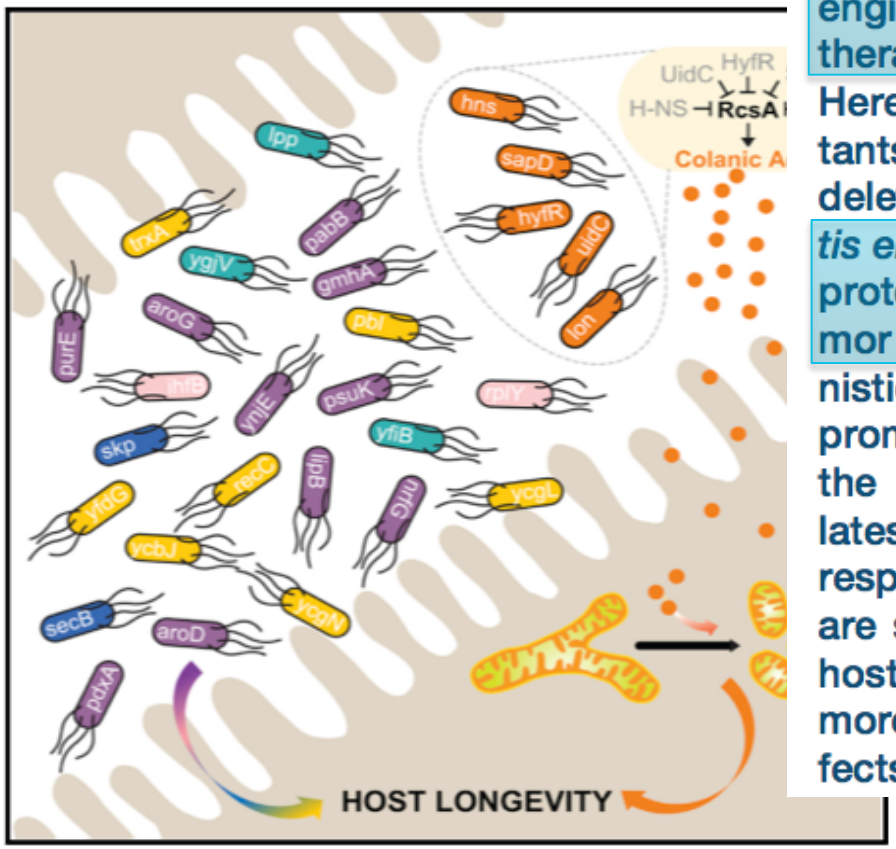

SUMMARY

Homeostasis of the gut microbiota critically influences host health and aging. Developing genetically engineered probiotics holds great promise as a new therapeutic paradigm to promote healthy aging. Here, through screening 3,983 *Escherichia coli* mutants, we discovered that 29 bacterial genes, when deleted, increase longevity in the host *Caenorhabditis elegans*. A dozen of these bacterial mutants also protect the host from age-related progression of tumor growth and amyloid-beta accumulation. Mechanistically, we discovered that five bacterial mutants promote longevity through increased secretion of the polysaccharide colanic acid (CA), which regulates mitochondrial dynamics and unfolded protein response (UPR^{mt}) in the host. Purified CA polymers are sufficient to promote longevity via ATFS-1, the host UPR^{mt}-responsive transcription factor. Furthermore, the mitochondrial changes and longevity effects induced by CA are conserved across different

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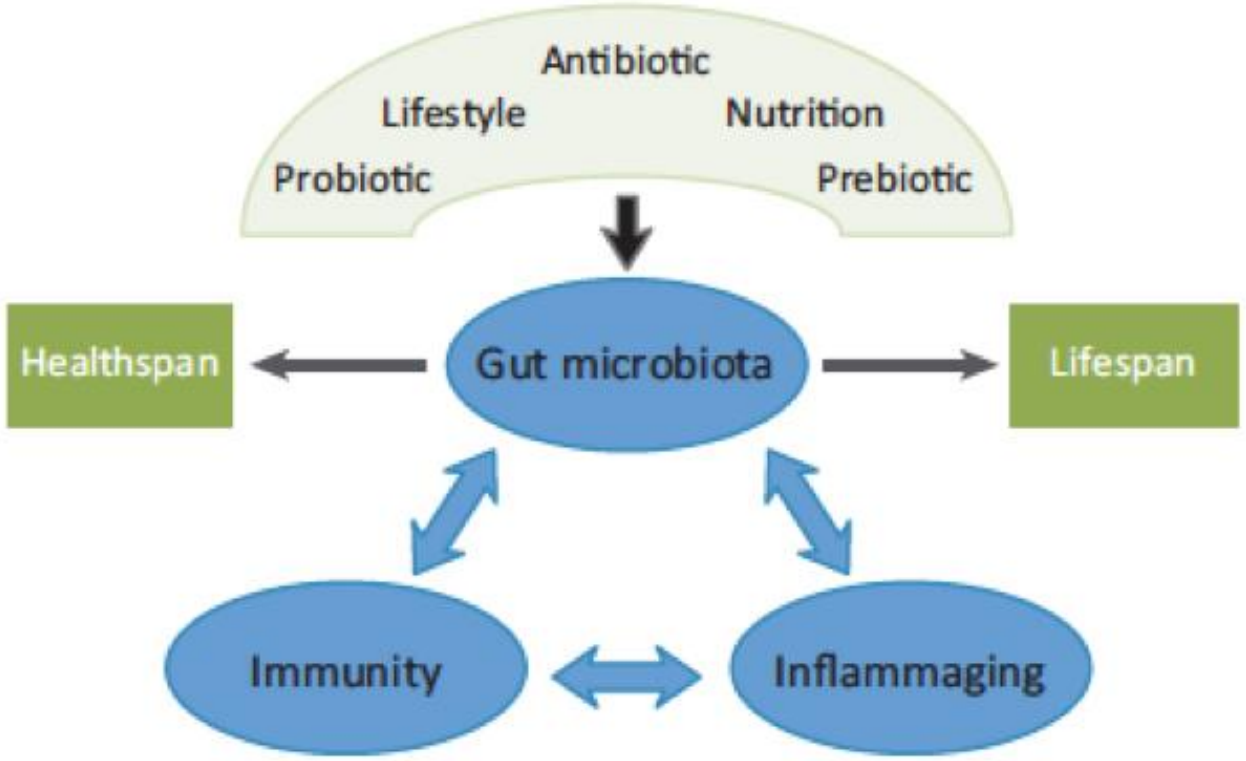
The age-tailored and personalized modulation of the gut microbiota will be aimed at maintaining the microbial profile **with the highest probability to help the host in preventing diseases and promoting (brain) health**



Nikoletopoulou V et al.
Trend in Endocrinology and Metabolism 2014

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