Alterazioni età correlate del microbiota intestinale e fragilità

Francesco Landi, MD, PhD

Catholic University, Gemelli Hospital, Rome, Italy

Aging and muscle

Loss of muscle mass, strength and function

JAMDA 18 (2017) 88.e17–88.e24

JAMDA

journal homepage: www.jamda.com

Original Study

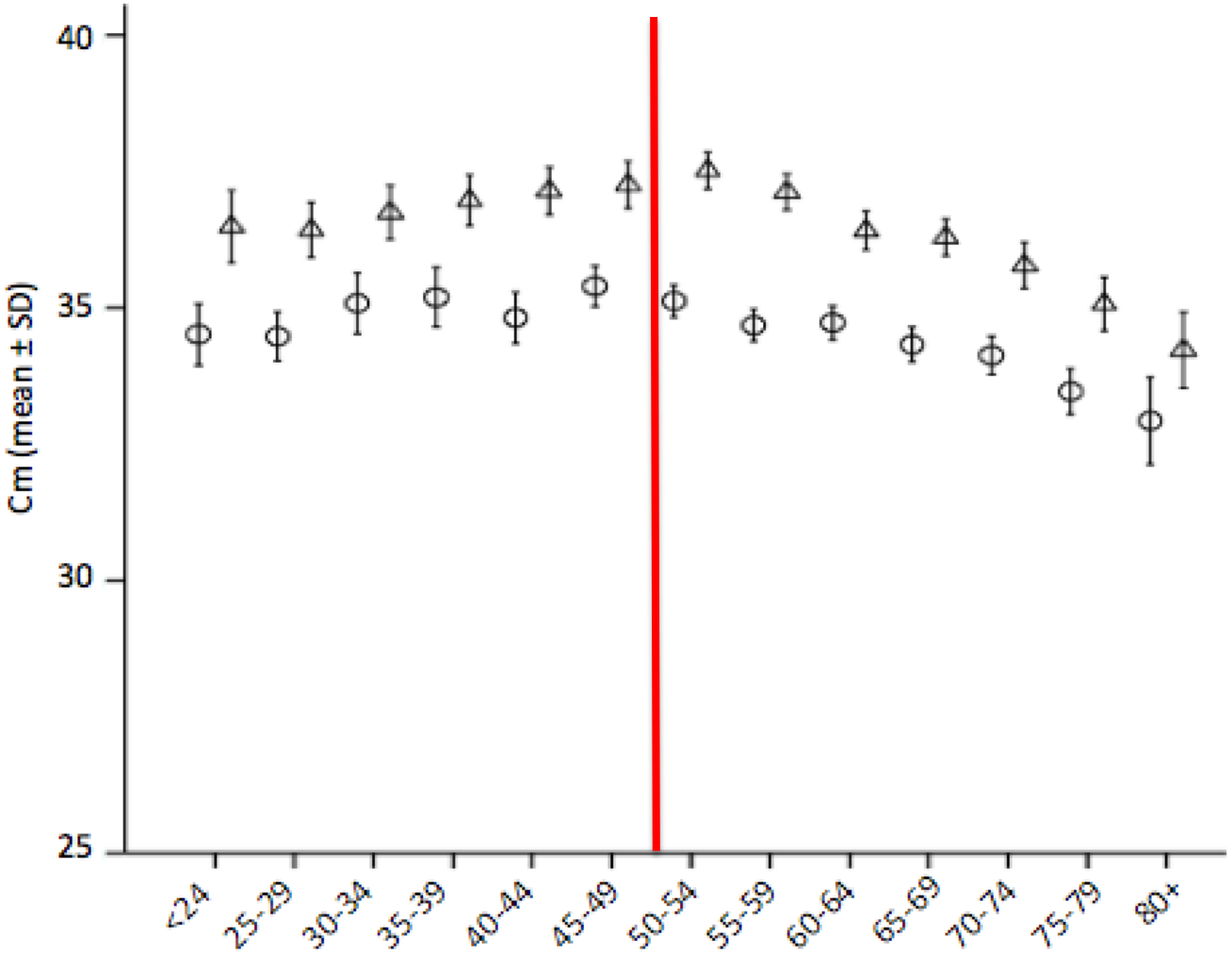
Age-Related Variations of Muscle Mass, Strength, and Physical Performance in Community-Dwellers: Results From the Milan EXPO Survey

Francesco Landi MD, PhD*, Riccardo Calvani PhD, Matteo Tosato MD, PhD, Anna Maria Martone MD, Domenico Fusco MD, PhD, MD, Alex Sisto BA, Elena Ortolani MD, Giulia Savera BS, Sara Salini MD, Emanuele Marzetti MD, PhD

Department of Geriatrics, Neurosciences, and Orthopedics, Catholic University of the Sacred Heart, Rome, Italy

Aging and muscle

Loss of muscle mass, strength and function



Aging and muscle

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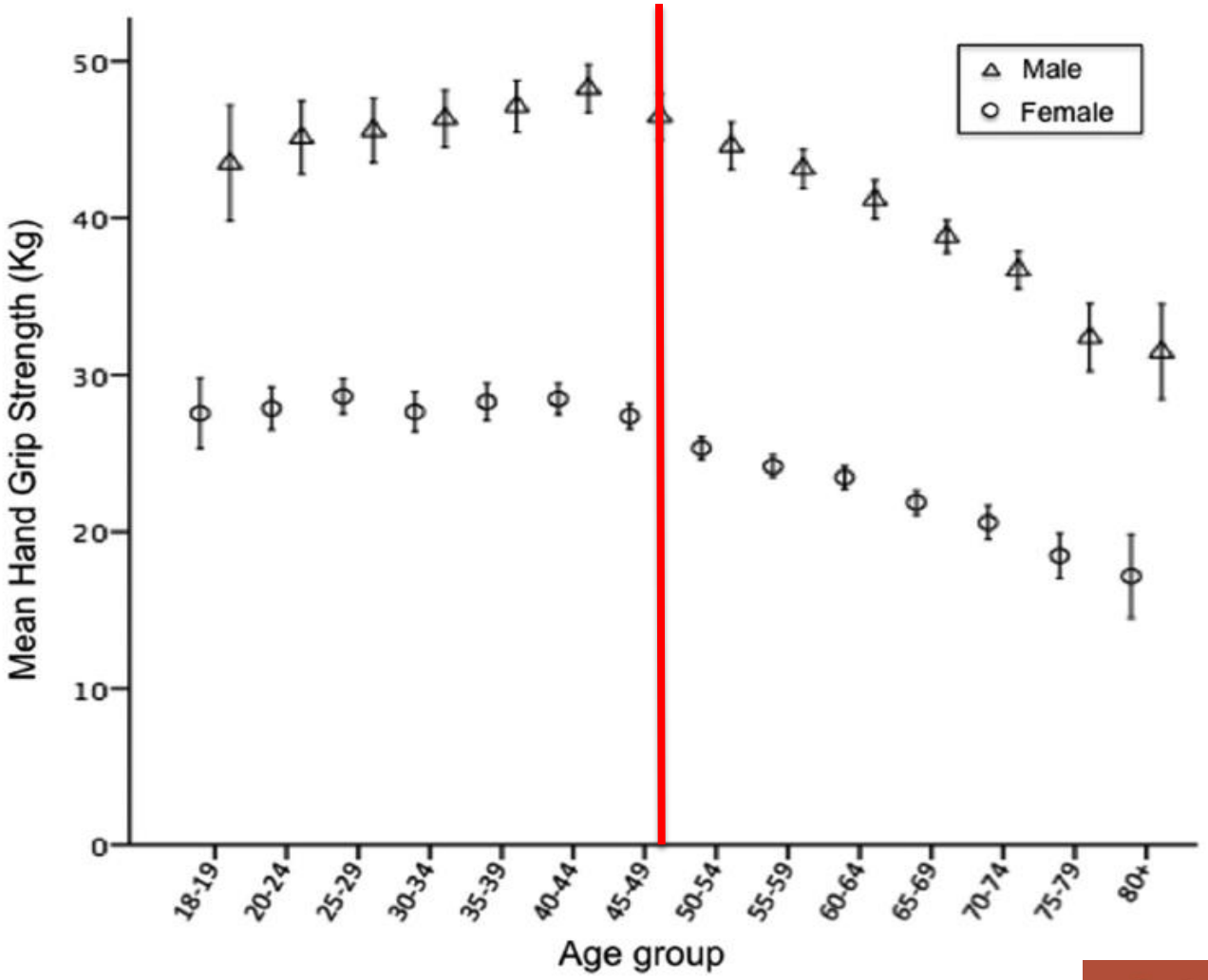

Aging and muscle

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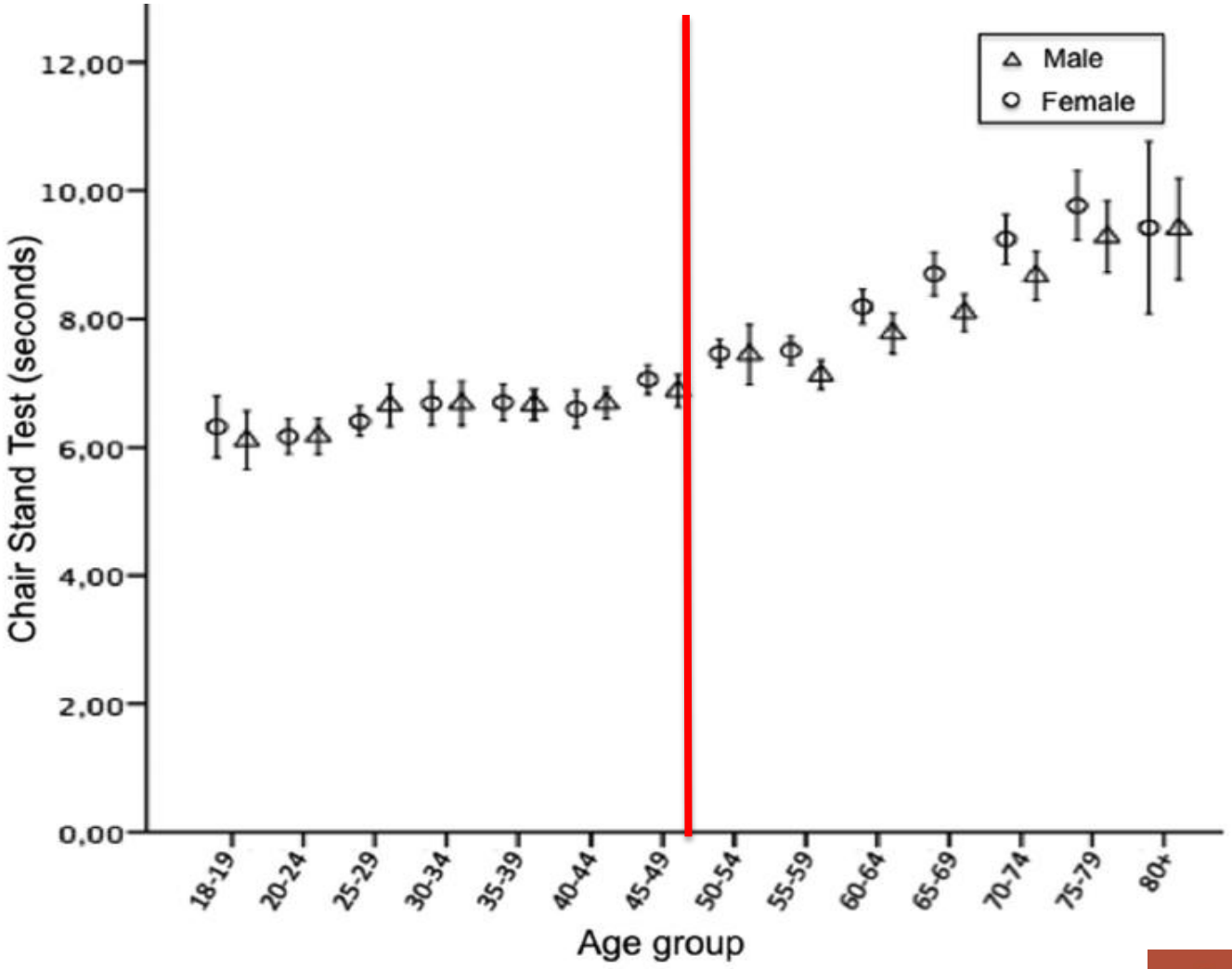

Under-nutrition, Sarcopenia and Frailty

European Geriatric Medicine xxx (2016) xxx–xxx

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ScienceDirect
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EM|consulte
www.em-consulte.com/en

Research paper

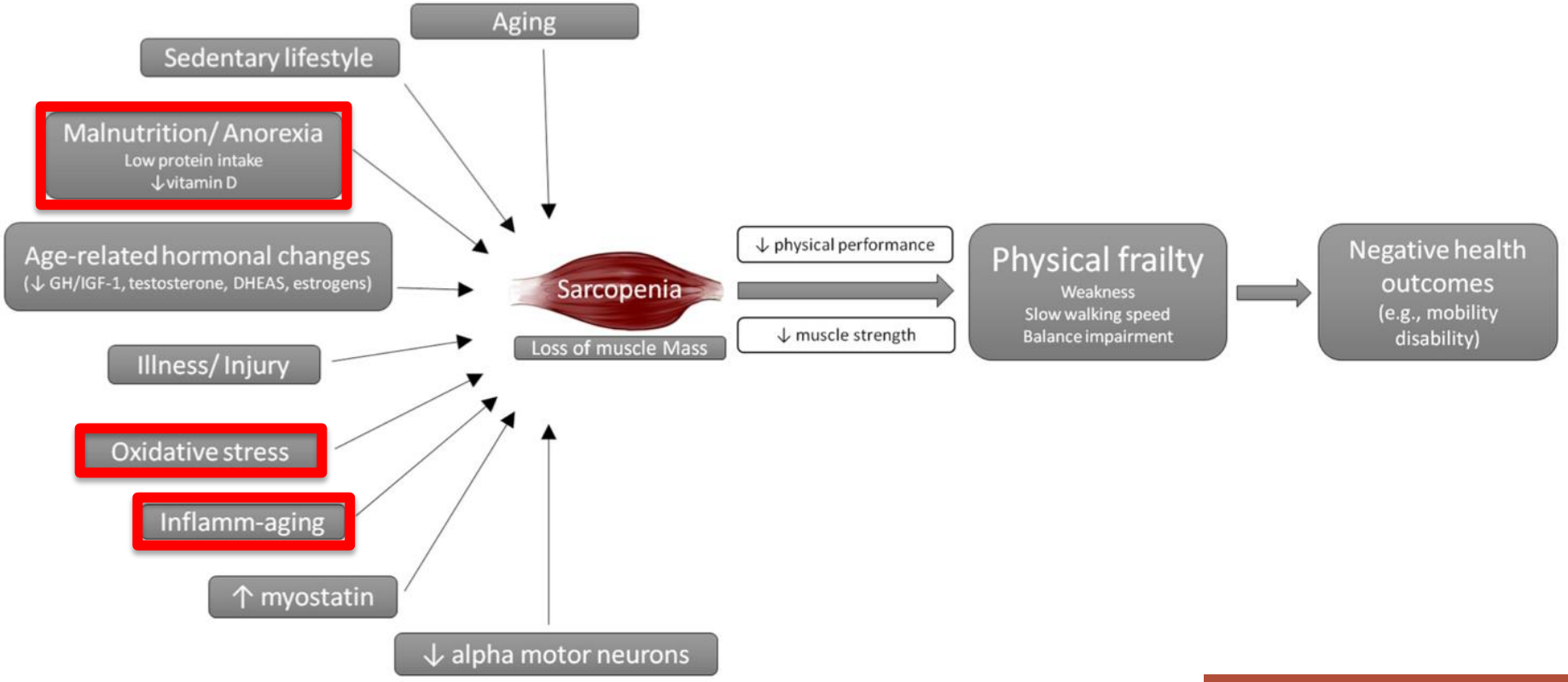
Sarcopenia and frailty: From theoretical approach into clinical practice

F. Landi [a,*], A. Cherubini [b], M. Cesari [c], R. Calvani [a], M. Tosato [a], A. Sisto [a], A.M. Martone [a], R. Bernabei [a], E. Marzetti [a]

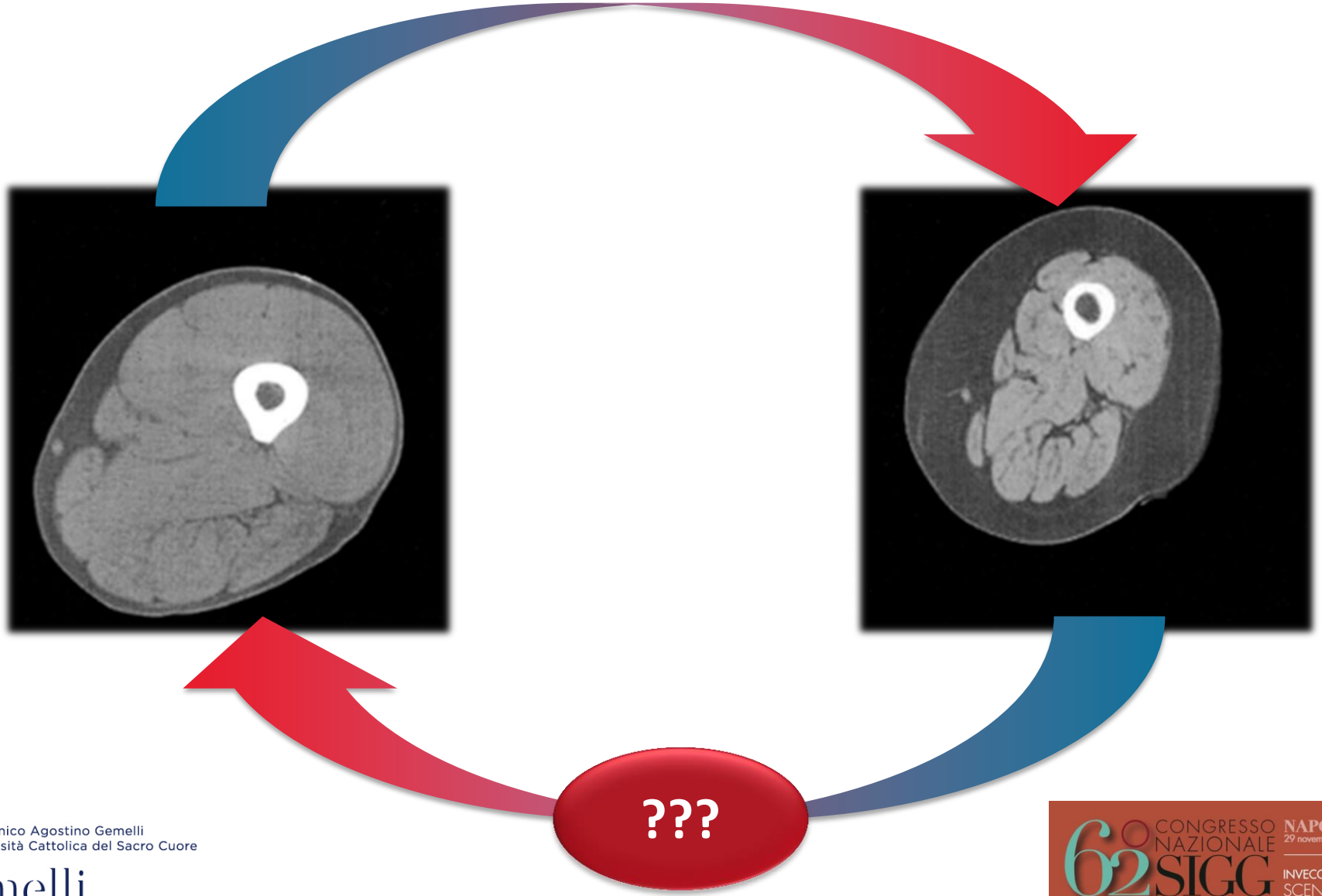
[a] *Department of Geriatrics, Neurosciences and Orthopaedics, Catholic University of the Sacred Heart, Rome, Italy*
[b] *Geriatric Hospital, Italian National Research Center on Aging (INRCA), Ancona, Italy*
[c] *Gérontopôle, centre hospitalier universitaire de Toulouse, Toulouse, France*

Under-nutrition, Sarcopenia and Frailty

- **Physical inactivity and decreased dietary intake**
- **Decreased protein synthesis and increased protein breakdown**
- **Infiltration of fat into muscle**



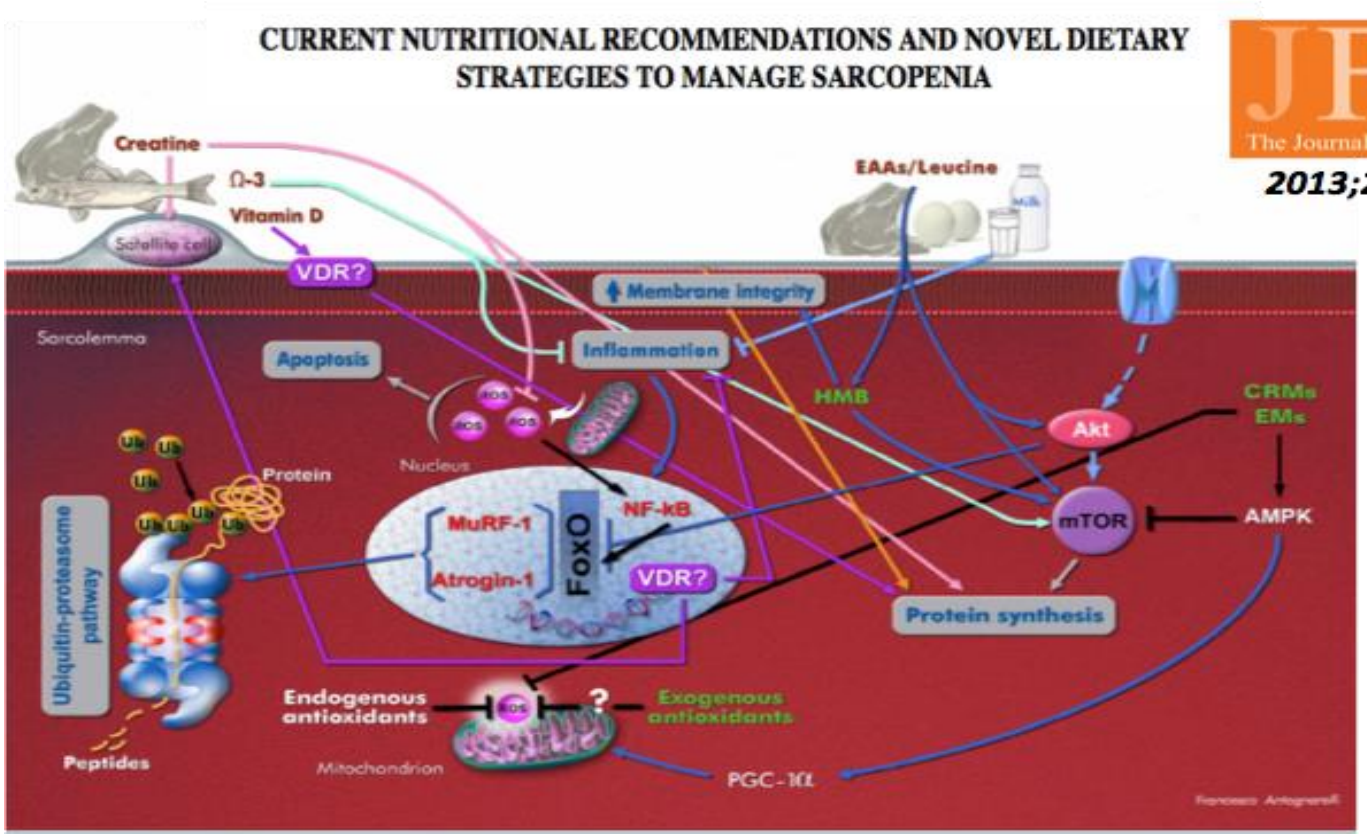
Can sarcopenia/PF be prevented and/or treated?



PUTATIVE MECHANISMS OF PROTEIN ACTION ON MUSCLE CELLS

UNIVERSITÀ CATTOLICA del Sacro Cuore

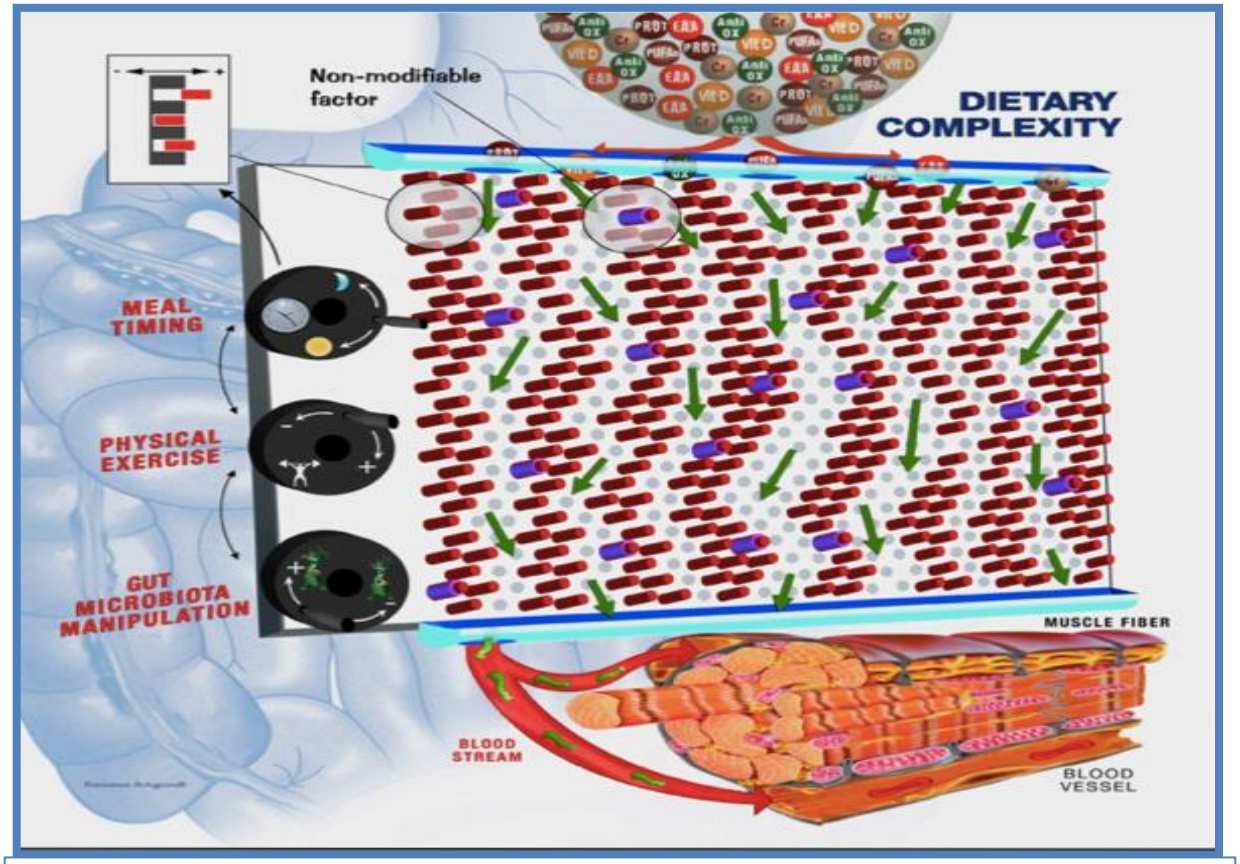
Overview of potential pathways whereby resistance exercise and nutritional interventions may influence cellular events implicated in the regulation of muscle mass



Landi F. et al. The New Metabolic Treatments For Sarcopenia
Aging Clin Exp Res: 2013

Potential therapeutic strategies

Nutrition-muscle connection
The “Pachinko Model”

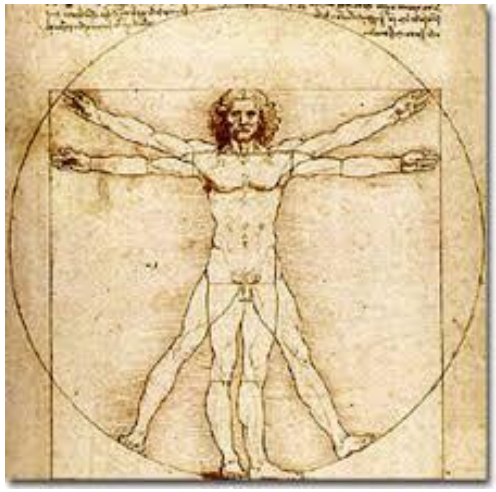


CURRENT NUTRITIONAL RECOMMENDATIONS AND NOVEL DIETARY STRATEGIES TO MANAGE SARCOPENIA

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

Calvani R, Landi F et al. 2013

New perspective



The mammalian holobiont

The result of co-evolution of the eukaryotic and prokaryotic parts of an organism

Gut microbiota as a part of the gut barrier

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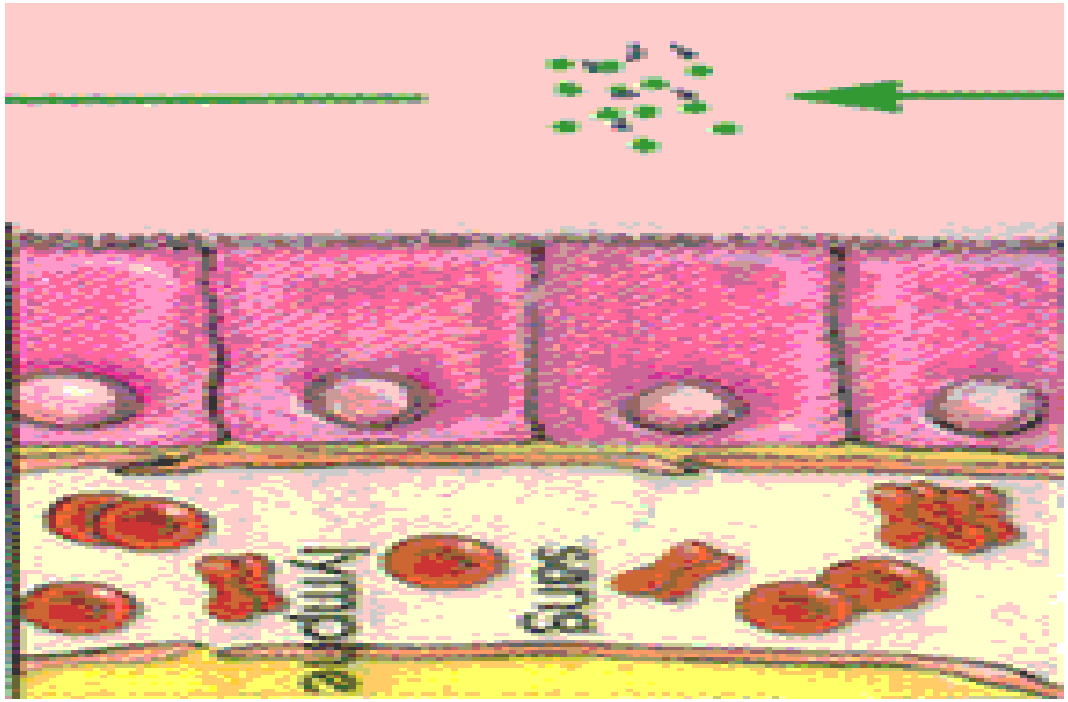
Microbiota

Mucosal Barrier

Epithelial barrier

Endocrine system



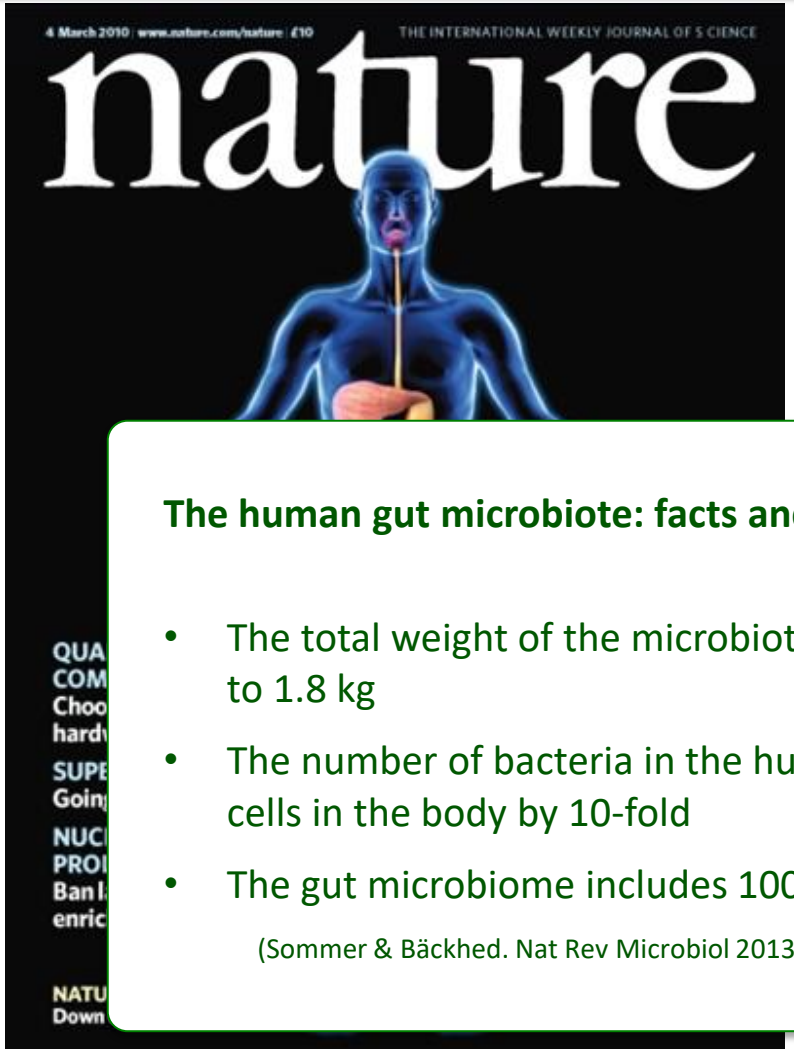
Acquired and Innate immunity

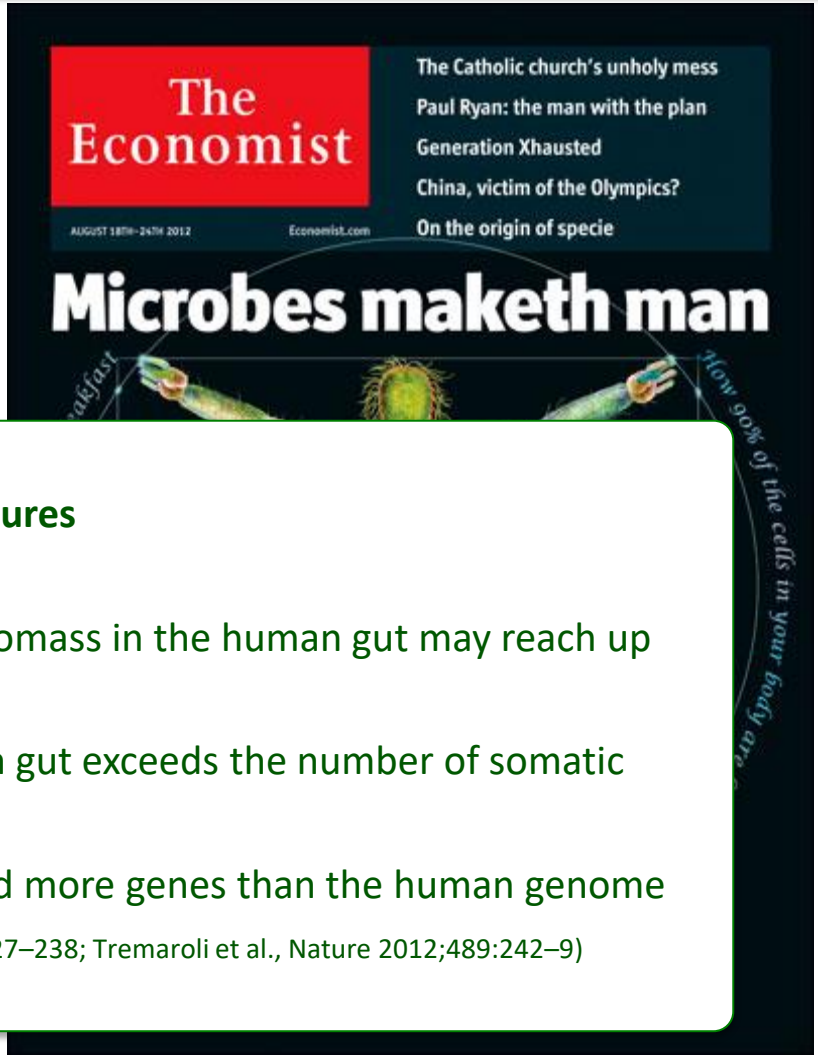
Vascular and lymphatic systems

Digestive enzymes

The gut barrier

The gut barrier



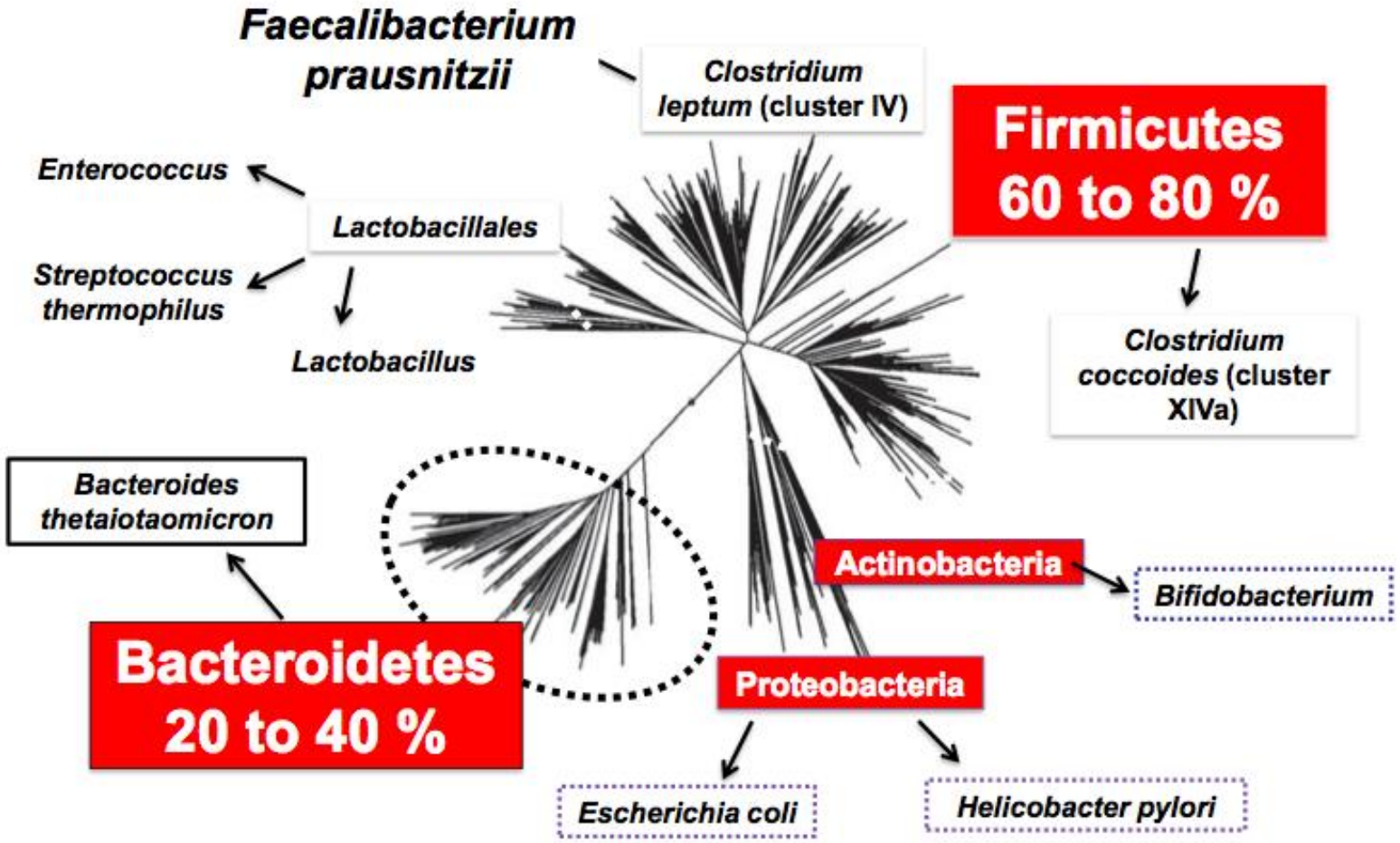


The human gut microbiote: facts and figures

- 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

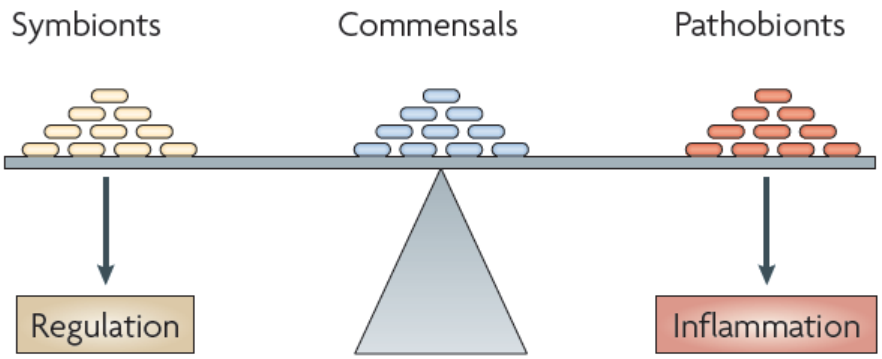


2 major phyla: Firmicutes and Bacteroidetes (>70%)

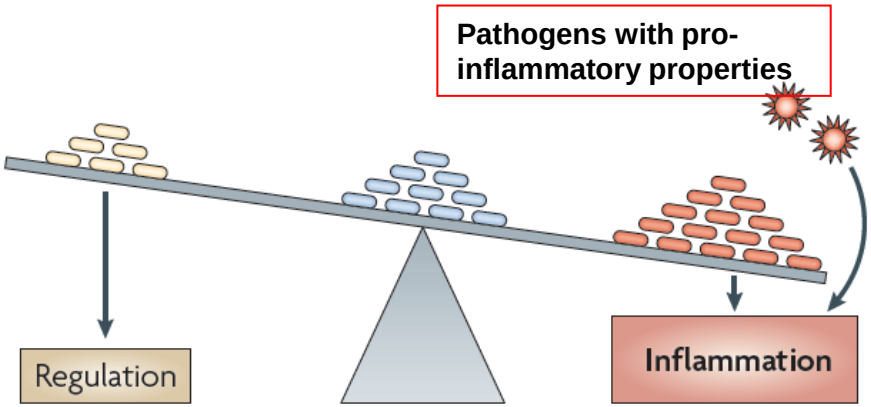
Ley et al., Science, 2008, 20;320(5883):1647-51

Immunological dysregulation associated with dysbiosis of the Gut Microbiota

Immunological equilibrium



Immunological dysequilibrium

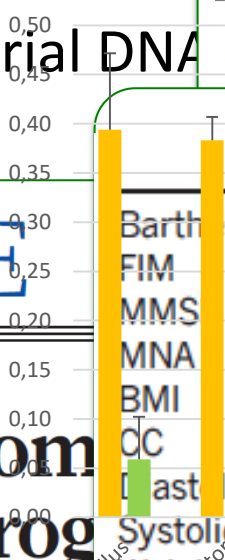


The human gut microbiote and human diseases

- Rheumatoid arthritis
- A
- O
- N
- F
- A

The Gern
and Joint
Transcri

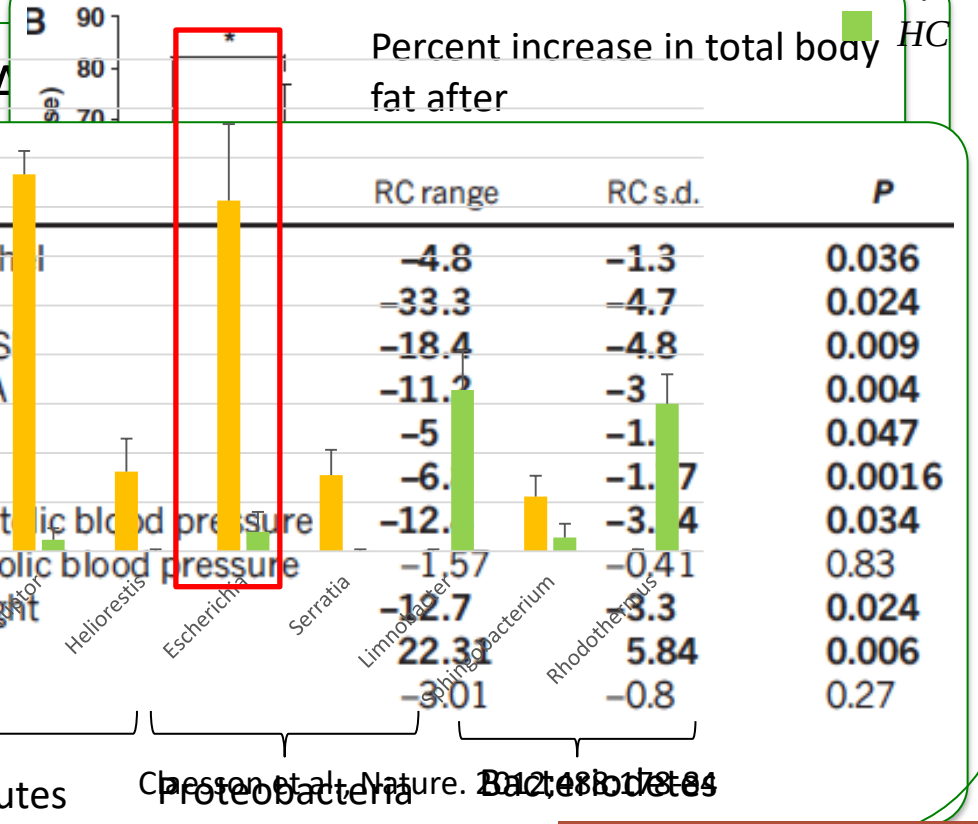
Bacterial DNA



ARTICLE

Inflammasom
regulates prog

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



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

GMB as master Regulator of Immunity and Inflammation

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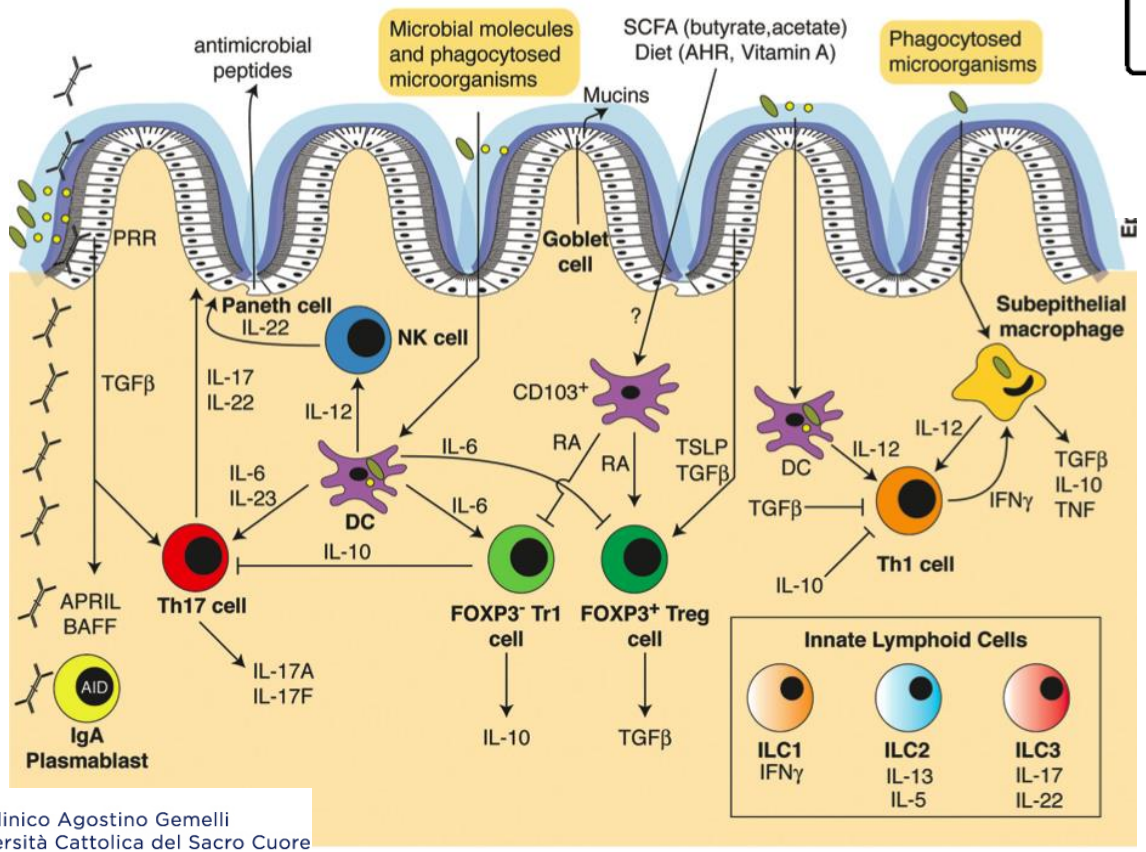
- ✓ Activation of complement C1q
- ✓ Inflammation signals Receptors



MUSCLE

GMB metabolites and inflammation signals into systemic circulation

GUT

Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore

Gemelli

62° CONGRESSO NAZIONALE SIGG NAPOLI2017 29 novembre - 2 dicembre
INVECCHIAMENTO: SCENARIO 2.0

Concepts on the pathophysiology of obesity and metabolic diseases related to the gut

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Western-style diet
Rich in fat (in particular saturated fatty acids)
Rich in sugars (in particular fructose)
Poor in fibers

↓

Energy-dense food uptake
Inadequate energy balance

↓

Change in microbiota composition in the intestine
(e.g. Induction of firmicutes)

↓

Enhancement of energy harvest
High energy load

↓

Obesity
Joint disease
Depression

↓

Translocation of bacteria and bacterial products in the intestine

↓

Enhanced endotoxin in the portal vein

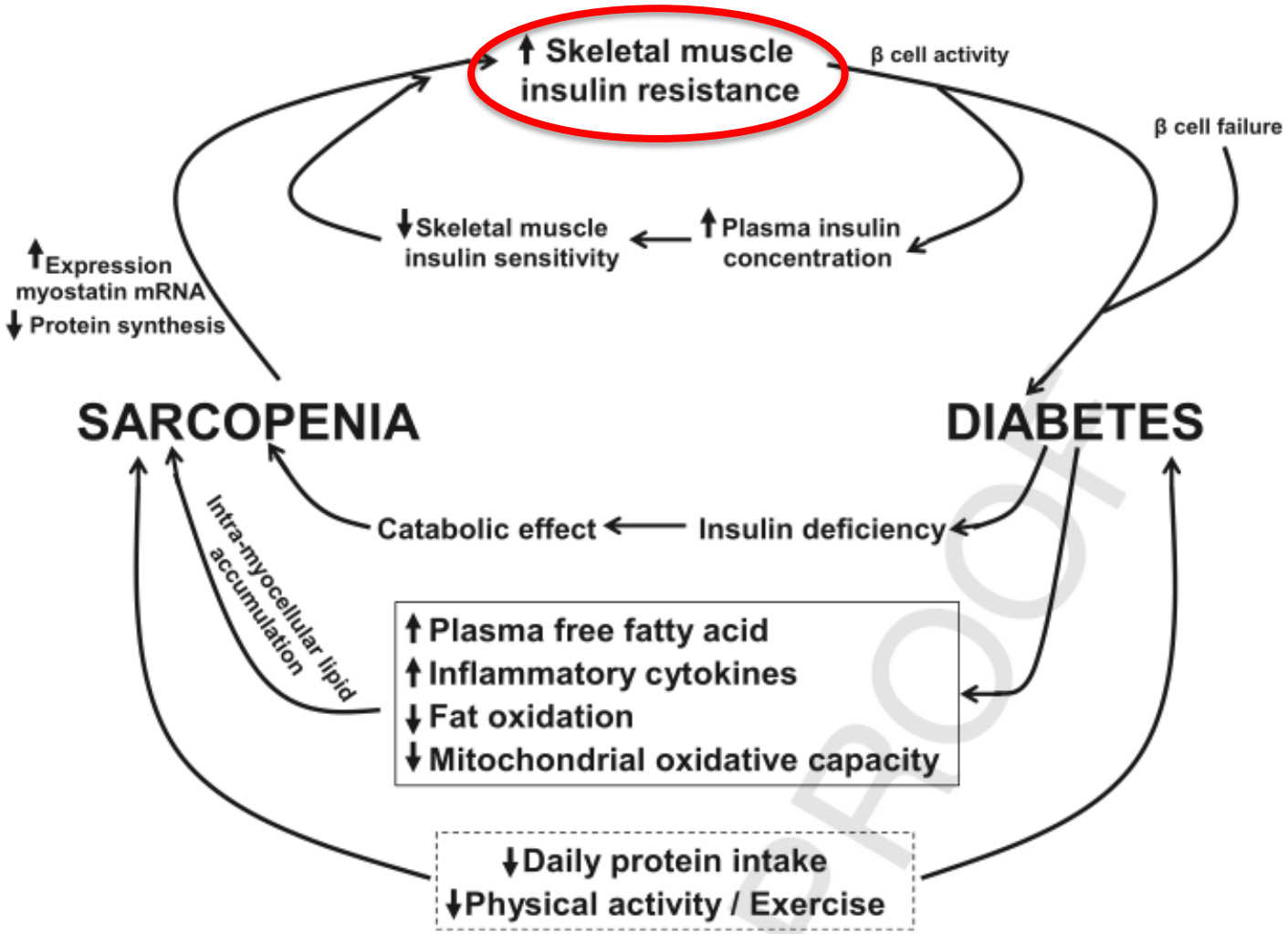
↓

Low-grade liver Inflammation

↓

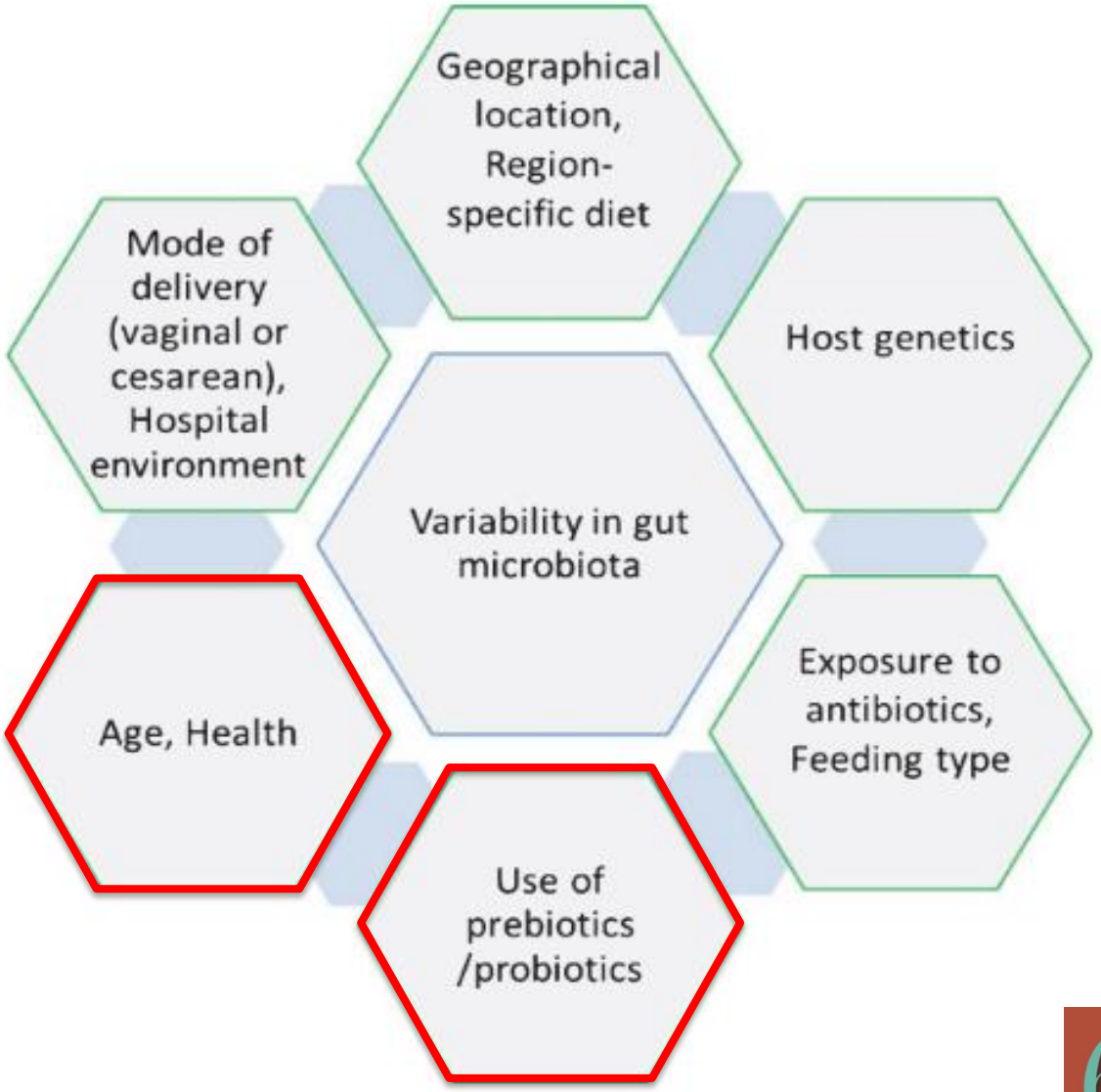
NAFLD / NASH
Insulin resistance
Metabolic disease

The interaction between sarcopenia and diabetes



Landi F et al. JAMDA, 2013

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

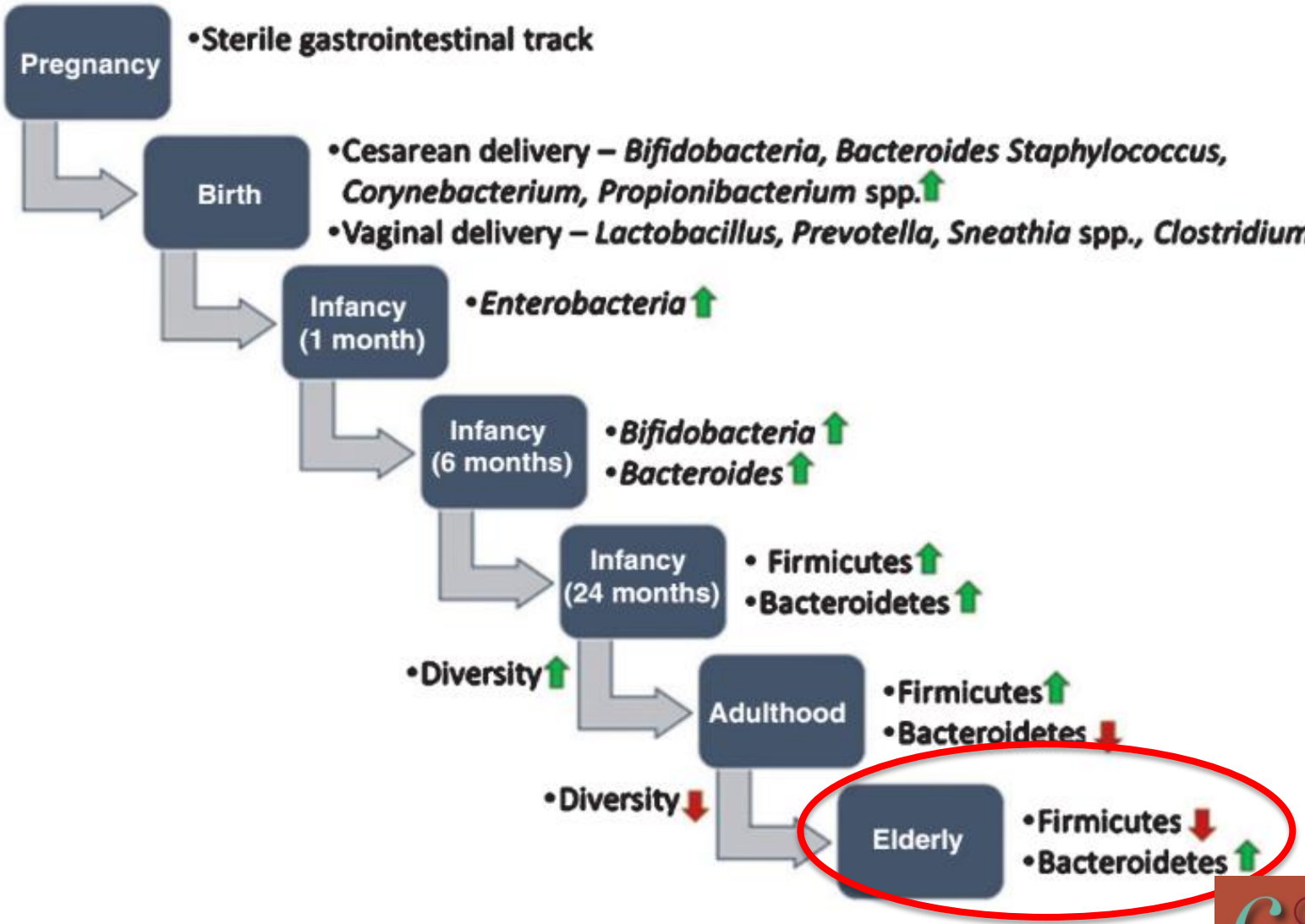
↓

Quali-quantitative alteration of gut microbiota and its functions

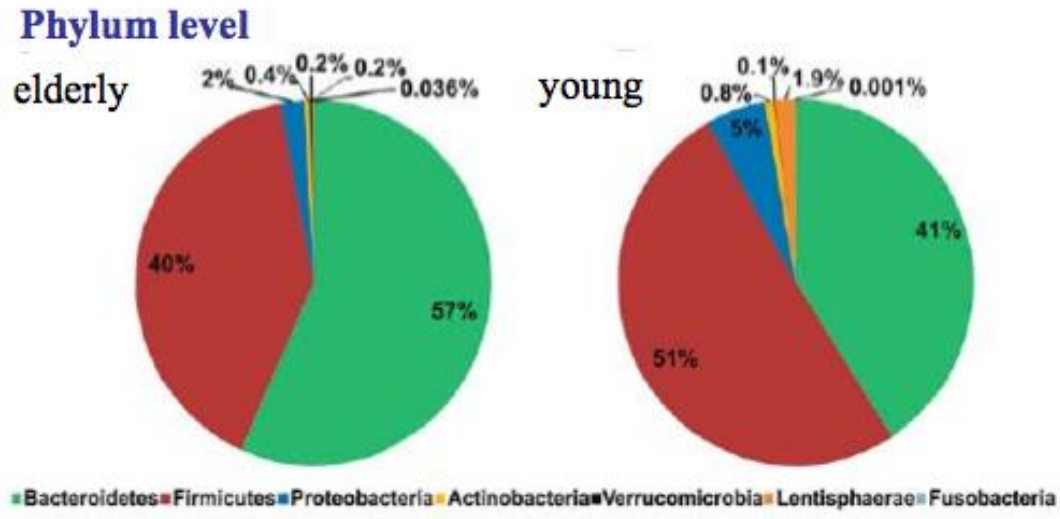
↓

"AGED" GUT MICROBIOTA

Development of human gut microbiota from prenatal to elderly



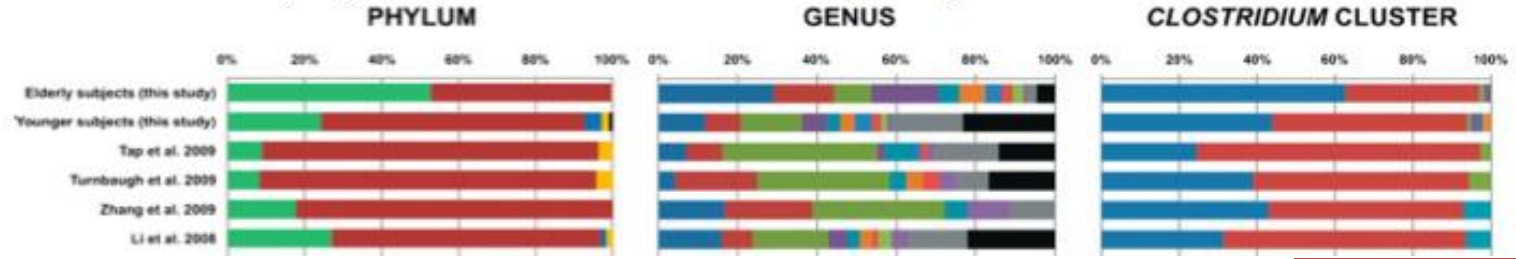
Aging compromise the homeostatic equilibrium between microbiota and host



161 ELDERLY IRISH SUBJECTS:

The individual composition datasets showed extraordinary variation, with the proportion of the Bacteroidetes ranging from 3% to 92% and the proportion of the phylum Firmicutes ranging from 7% to 94%

More than one-half of the core microbiota (53%) in the elderly subjects-comprised Bacteroidetes were made up by the genera Bacteroides (29%), Alistipes (17%), and Parabacteroides (7%) compared with 8–27% in the younger adults.



Claesson et al, PNAS 2011

Aging compromise the homeostatic equilibrium between microbiota and host

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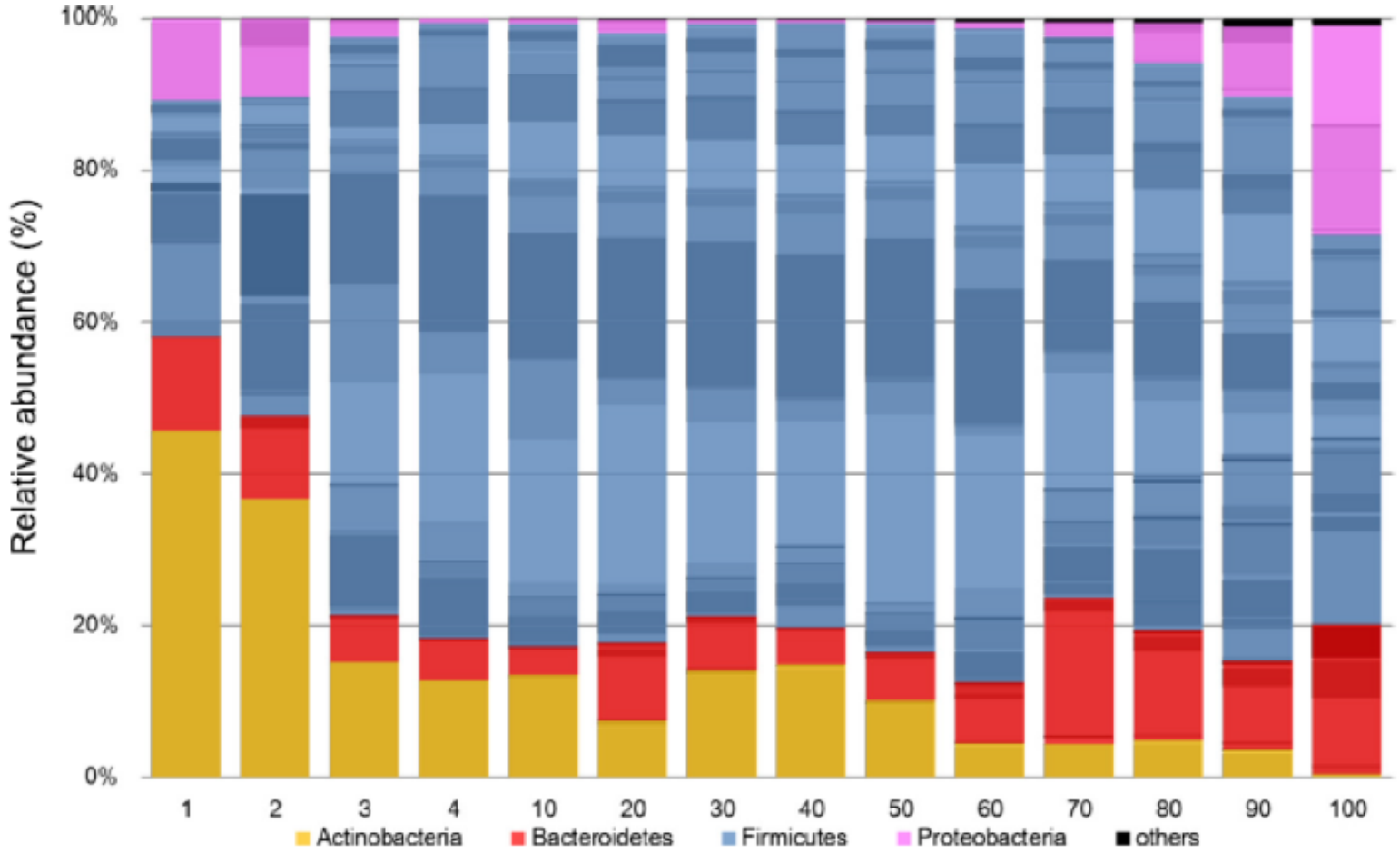
367 Japanese individuals: 6 centenarians (100-104 years old) and 7 individuals >95 years



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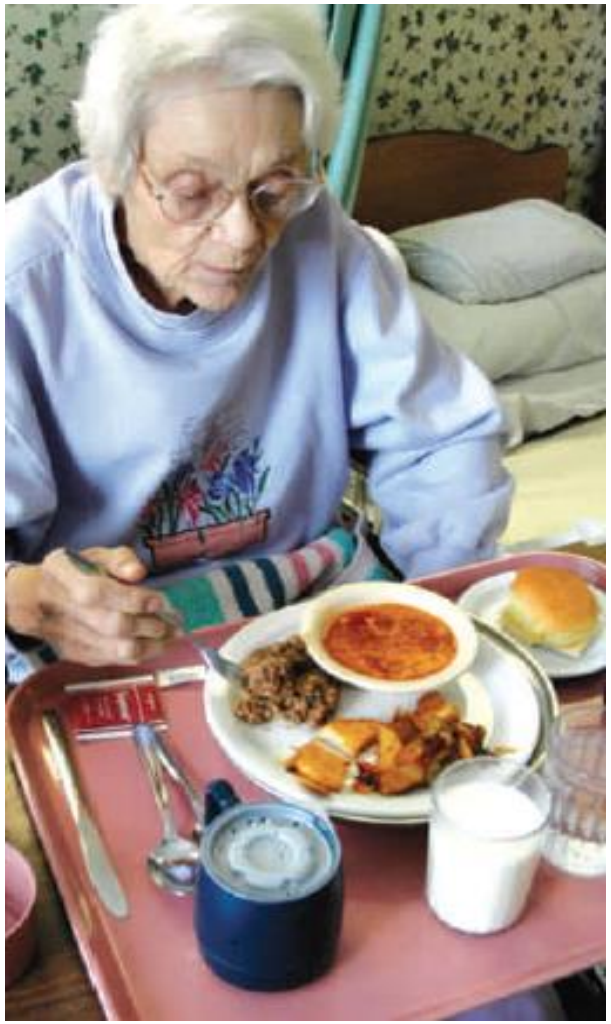
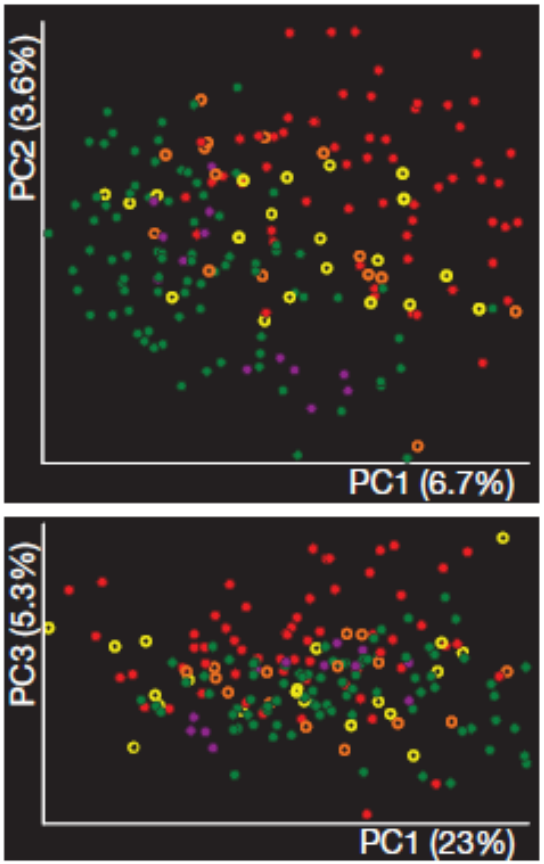
Odamaki et al. BMC Microbiology, 2016

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)

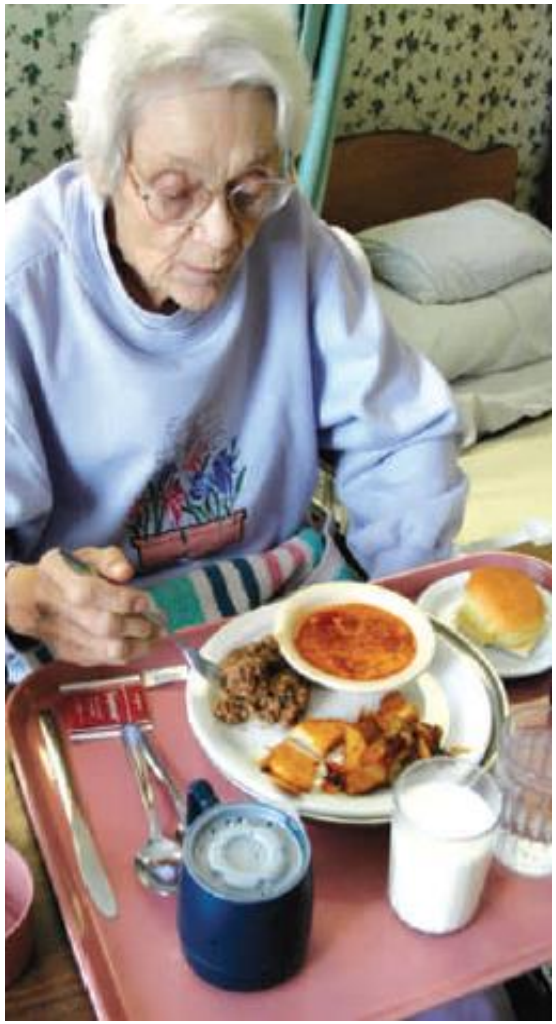


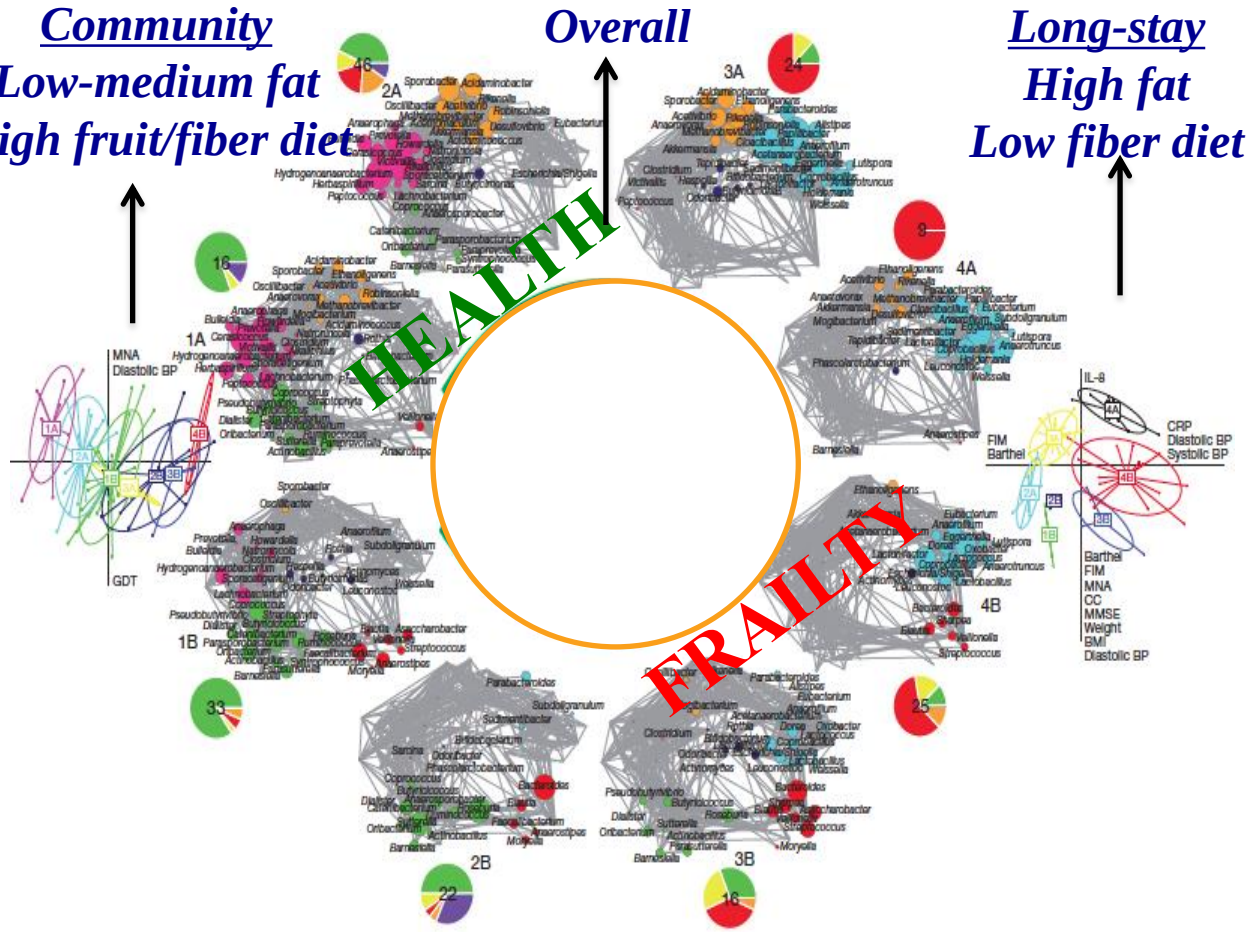
Microbiota composition in elderly people living in long-stay residential care facilities was different from that of the free living elderly, within the same ethno-geographic region.

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

Claesson et al, Nature 2012

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

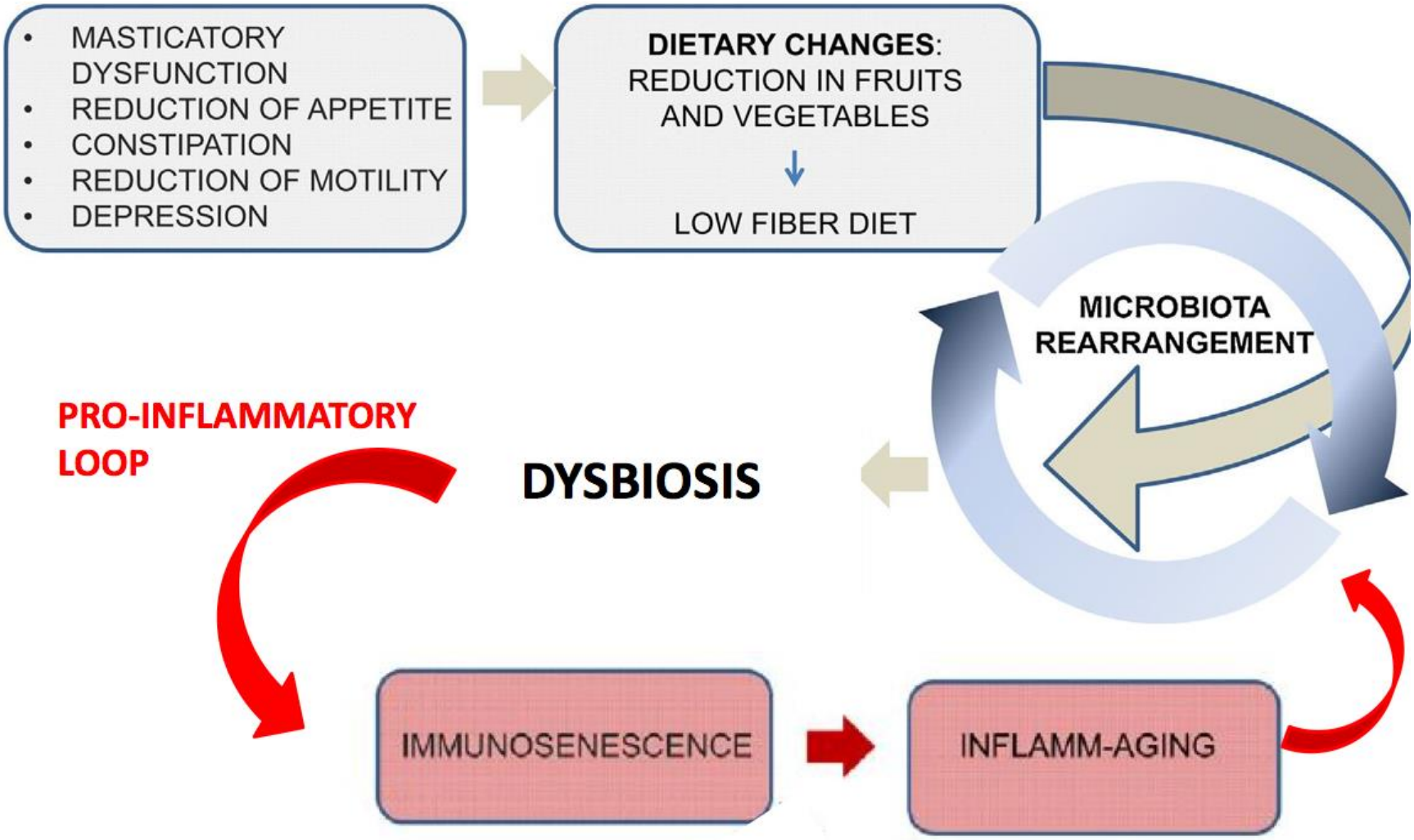




The most discriminating food types were vegetables, fruit and meat

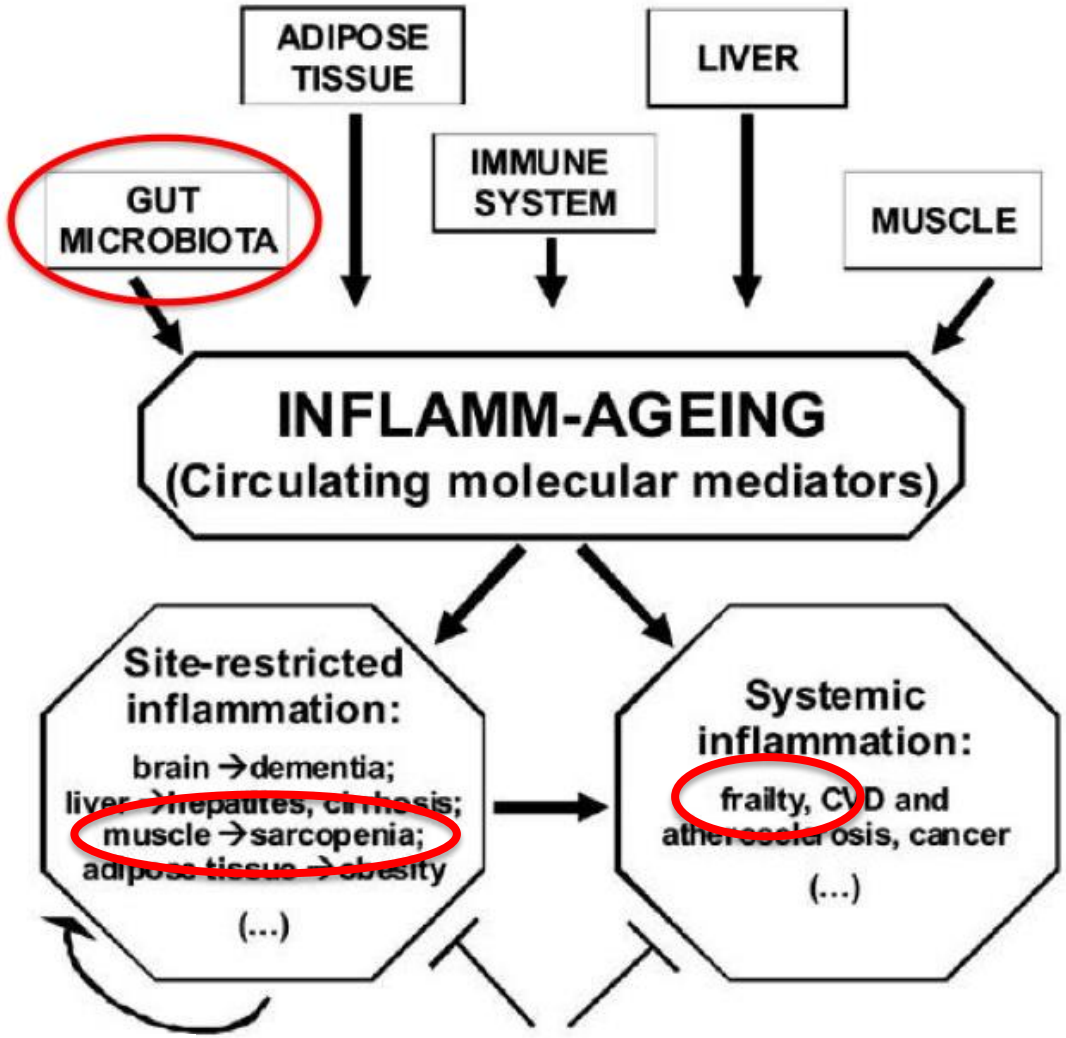
Claesson et al, Nature 2012

Ageing inevitably affects gut microbiota



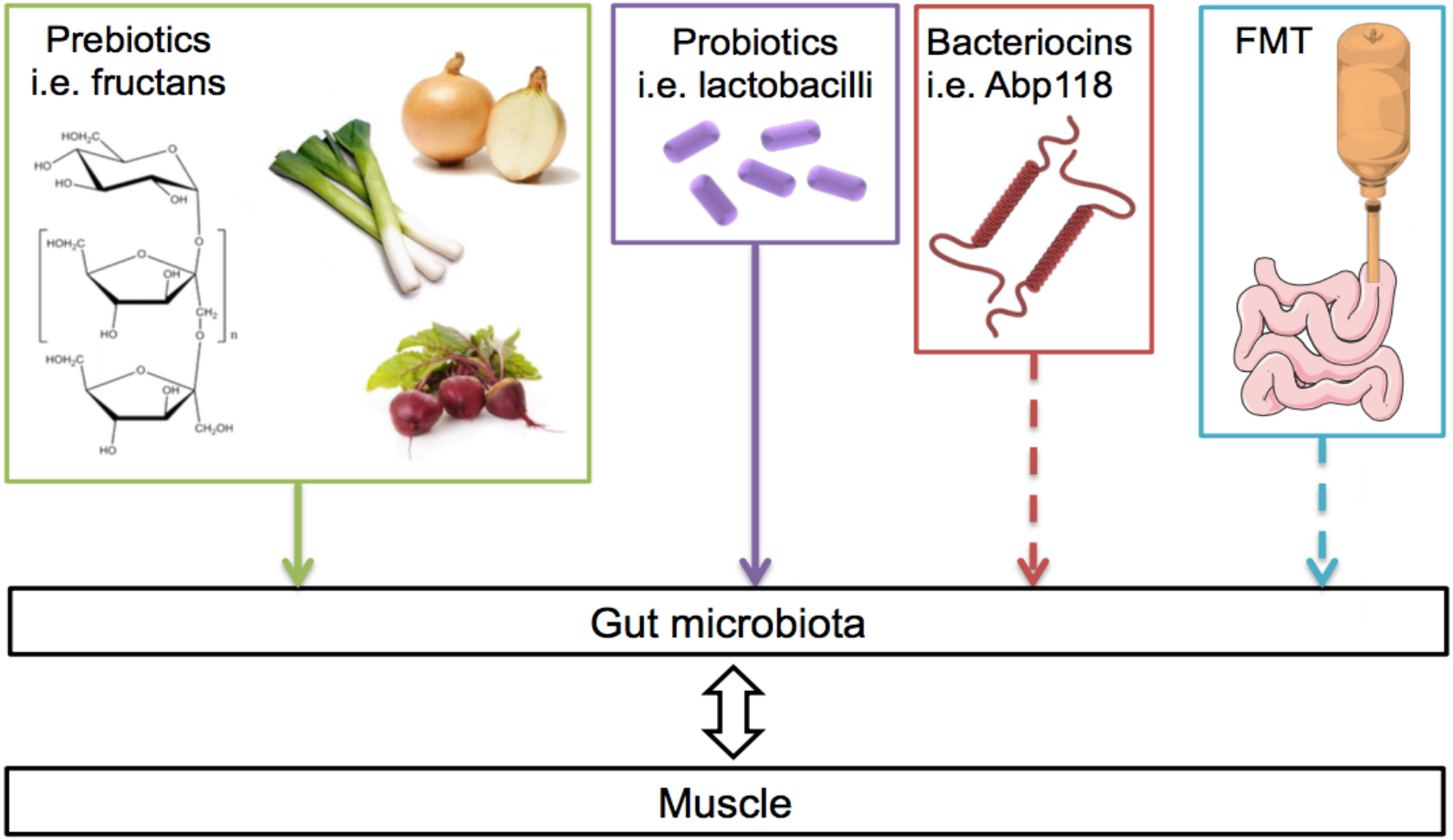
Candela M et al. Mech Ageing Dev 2013

Gut microbiota and inflammation



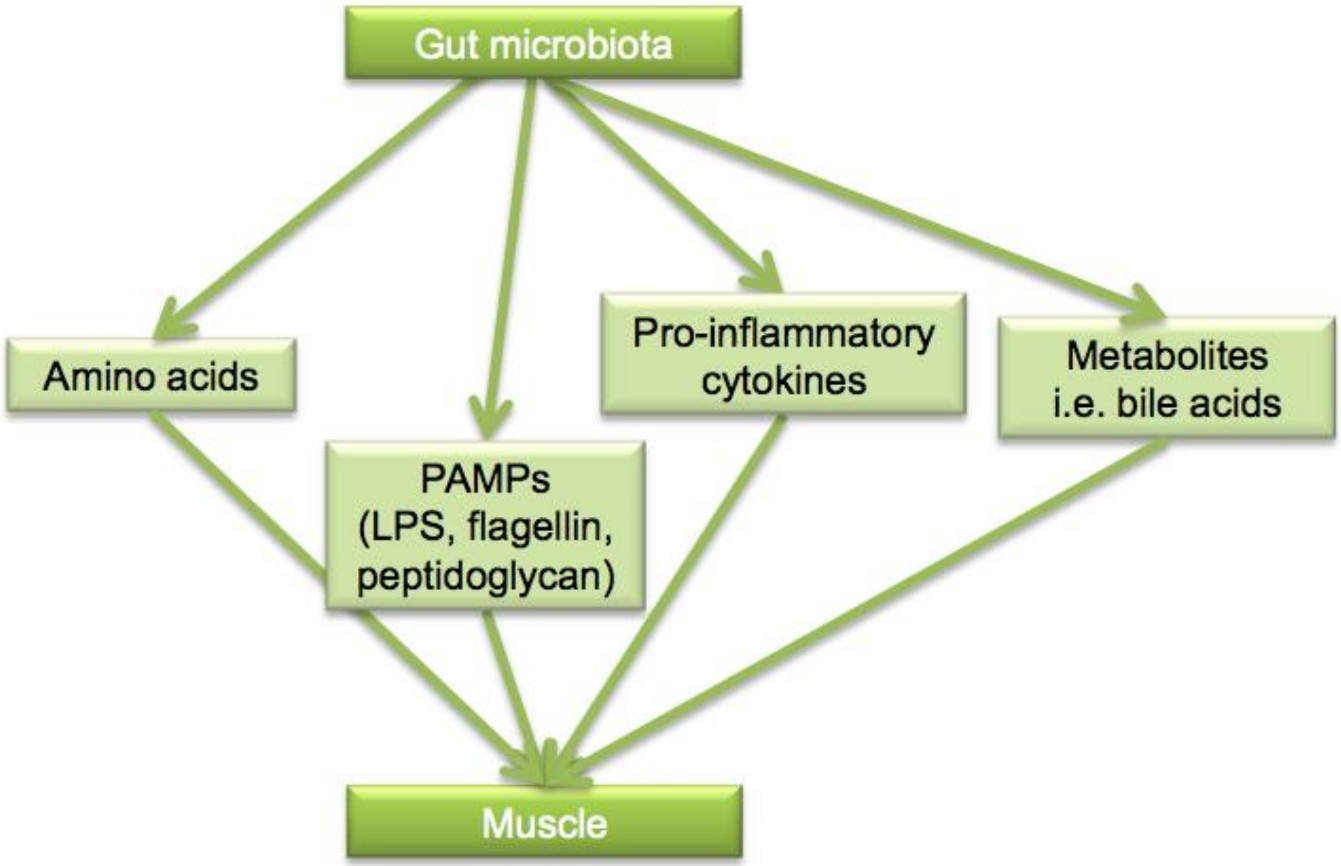
ANTI-INFLAMMATORY REGULATORS *Cavenini E et al. Curr Pharm*

Muscle wasting: the gut microbiota as a new therapeutic target?



Laure B. Bindels and Nathalie M. Delzenne
The International Journal of Biochemistry & Cell Biology
http://dx.doi.org/doi:10.1016/j.biocel.2013.06.021

Muscle wasting: the gut microbiota as a new therapeutic target?



Laure B. Bindels and Nathalie M. Delzenne
The International Journal of Biochemistry & Cell Biology
http://dx.doi.org/doi:10.1016/j.biocel.2013.06.021

Possible influence of the gut microbiota on muscle physiology

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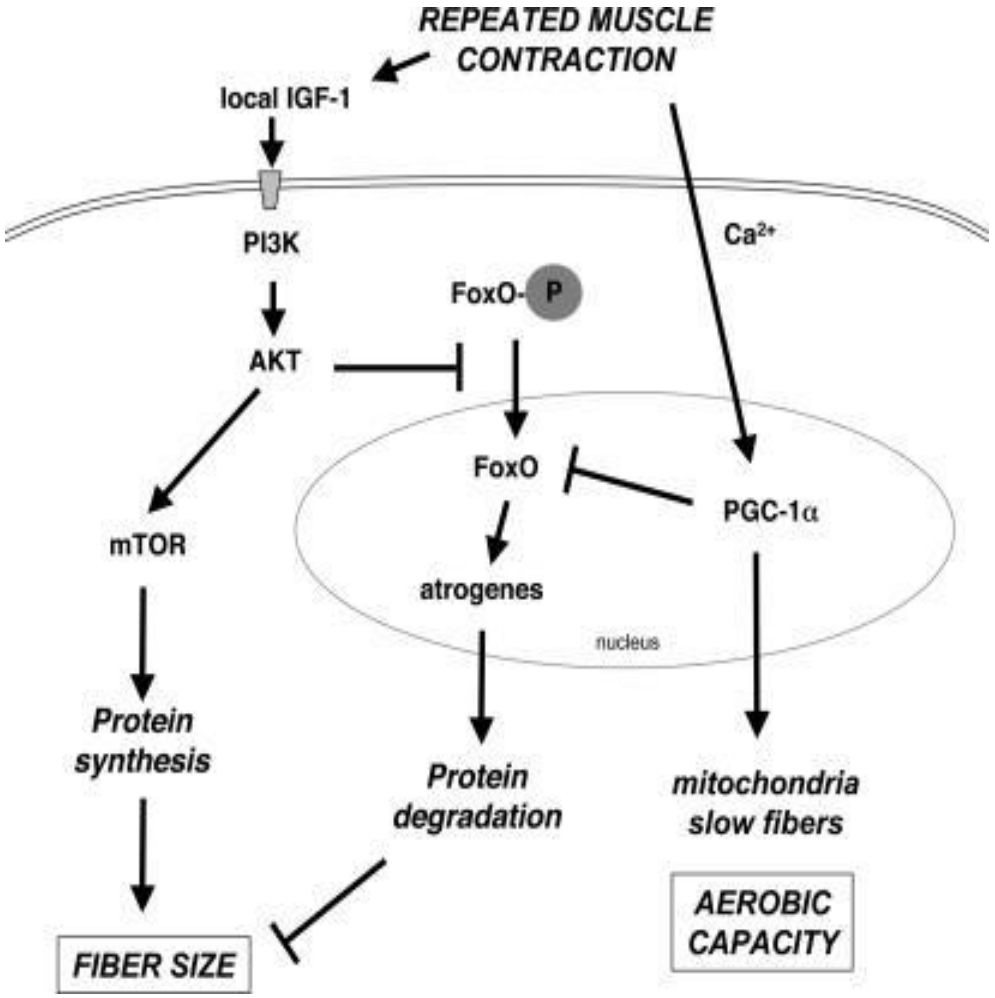
Protective effect of Peroxisome proliferator-activated receptor gamma co-activator 1-alpha (PGC-1alfa) overexpression in mice towards skeletal muscle atrophy achieved through the reduction of the impact of denervation and fasting on muscle fiber diameter and on the ubiquitin-proteasome pathway activity, consequently inhibiting protein catabolism



Sandri et al. Proc Natl Acad Sci USA 2006

Gut microbiota and protein metabolism

- The gut microbiota can modulate amino acids availability. Antibiotics have been shown to increase the levels of circulating amino acids, which would have been otherwise degraded by intestinal bacteria.

- On the other hand, the administration of specific probiotic strains such as Lactobacilli is associated with a specific faecal amino acids pattern.

- Furthermore, the gut microbiota exerts indirect effects on protein synthesis through the release of linoleic acid, acetate and bile salt able to reach skeletal muscle tissue and producing metabolic effects.

Puiman *Am J Physiol Gastrointest Liver Physiol*, 2013
Torrallardona et al. *J Nutr*, 2003
Martin et al *J Proteome Res*, 2010

Gut microbiota and muscle

UNIVERSITÀ CATTOLICA del Sacro Cuore

Cell

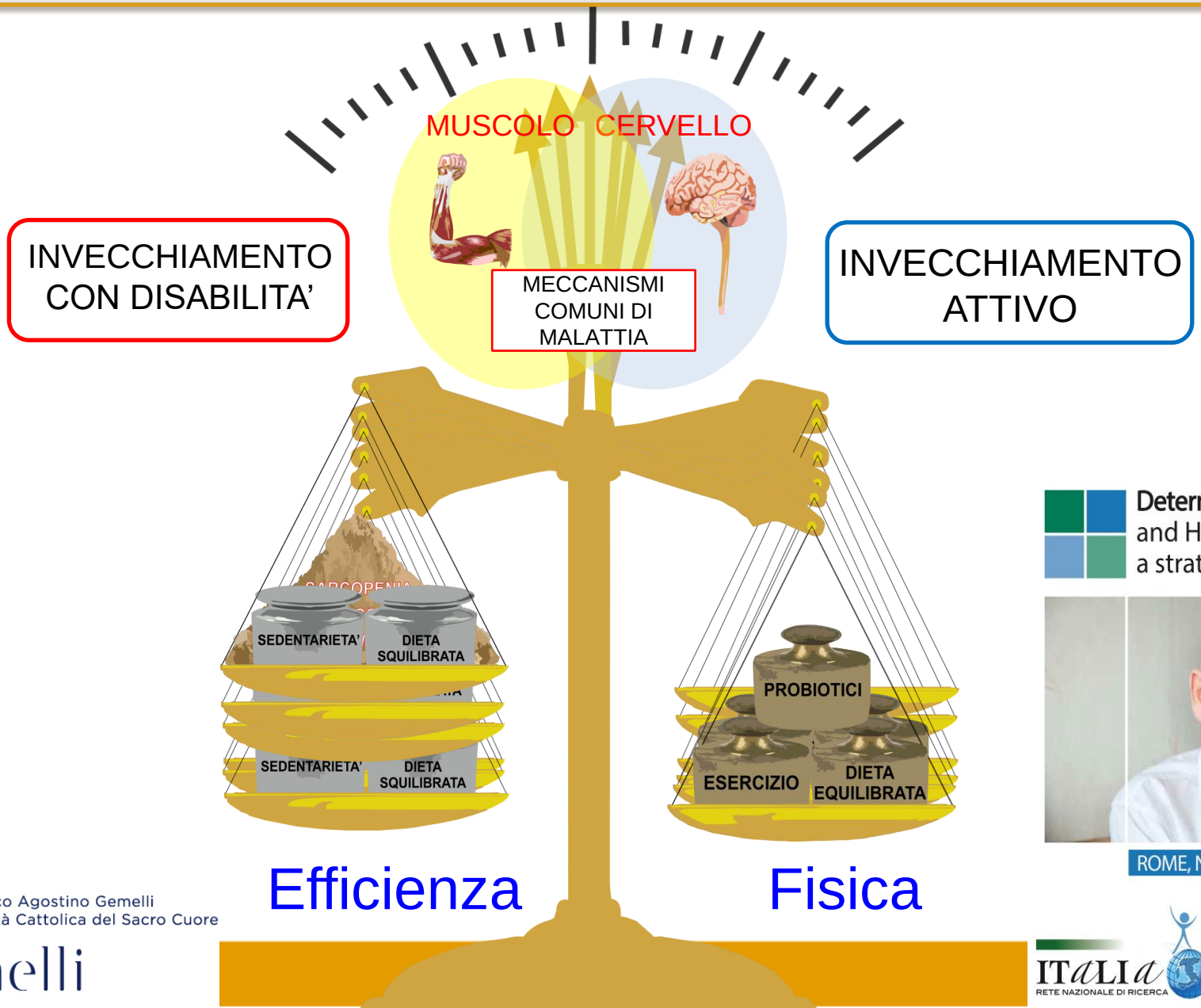
Leading Edge
Previews

Microbiome and Longevity: Gut Microbes Send Signals to Host Mitochondria

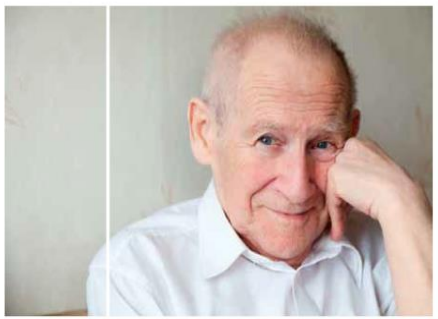
Jan Gruber[1,2] and Brian K. Kennedy[1,3,4,*]
[1]Department of Biochemistry, Yong Loo Lin School of Medicine National University of Singapore, National University of Singapore, MD 7, 8 Medical Drive, Singapore 117596, Singapore
[2]Ageing Research Laboratory, Science Division, Yale-NUS College, Singapore 138527, Singapore
[3]Department of Physiology, Yong Loo Lin School of Medicine National University of Singapore, National University of Singapore, MD 9, 2 Medical Drive, Singapore 117596, Singapore
[4]Buck Institute for Research on Aging, Novato, CA 94945, USA
*Correspondence: bkennedy@buckinstitute.org
http://dx.doi.org/10.1016/j.cell.2017.05.048

The microbiome has emerged as a major determinant of the functioning of host organisms, affecting both health and disease. Here, Han et al. use the workhorse of aging research, *C. elegans*, to identify specific mechanisms by which gut bacteria influence mitochondrial dynamics and aging, a first step toward analogous manipulations to modulate human aging.

Understanding Longevity



Determinants of Active and Healthy Ageing: a strategy for Europe



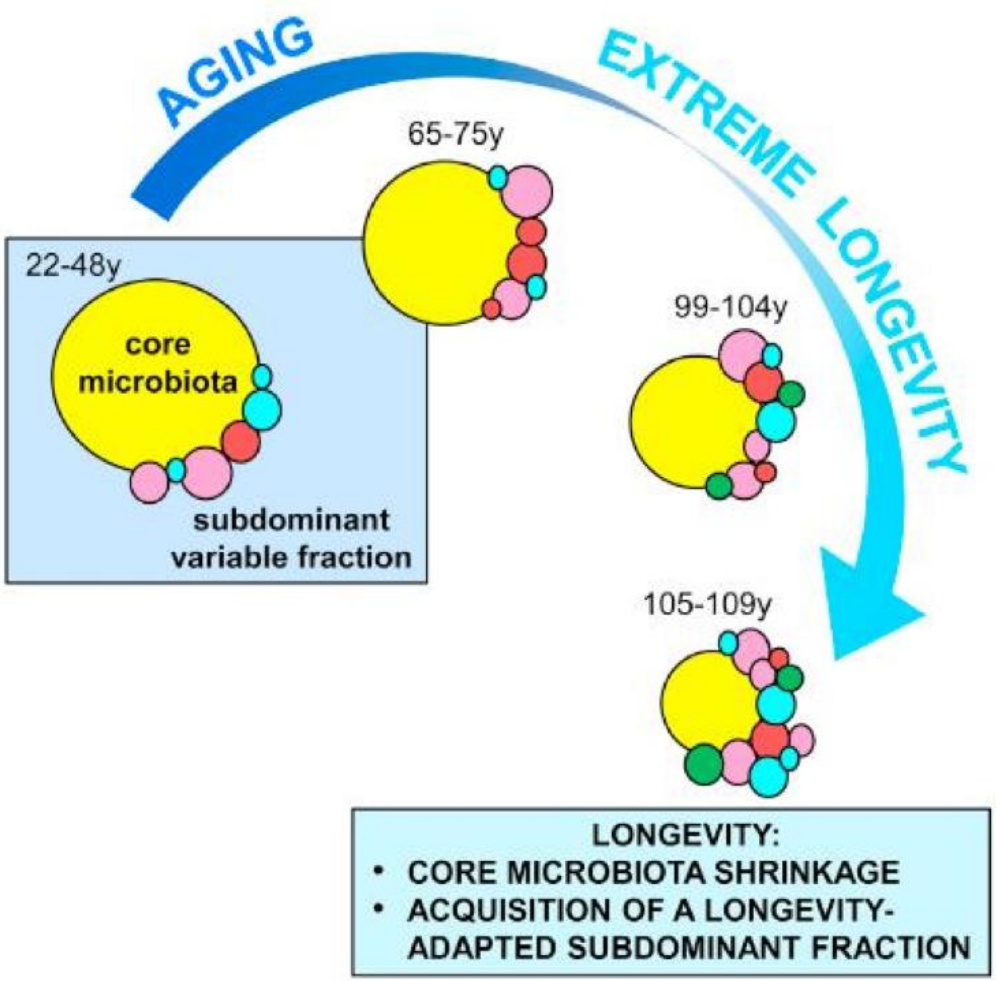
ROME, November 15-16 2014

Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore

Gemelli

ITALIA LONGEVA
RETE NAZIONALE DI RICERCA
SULL'INVECCHIAMENTO E LA LONGEVITA' ATTIVA

“Aged” gut microbiota: ...only deranged or a trajectory towards a different stability?



Accommodating opportunistic and allochthonous bacteria might possibly support health maintenance during aging, such as an enrichment and/or higher prevalence of health associated groups (e.g., Akkermansia , Bifidobacterium , and Christensenellaceae).

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

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- 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

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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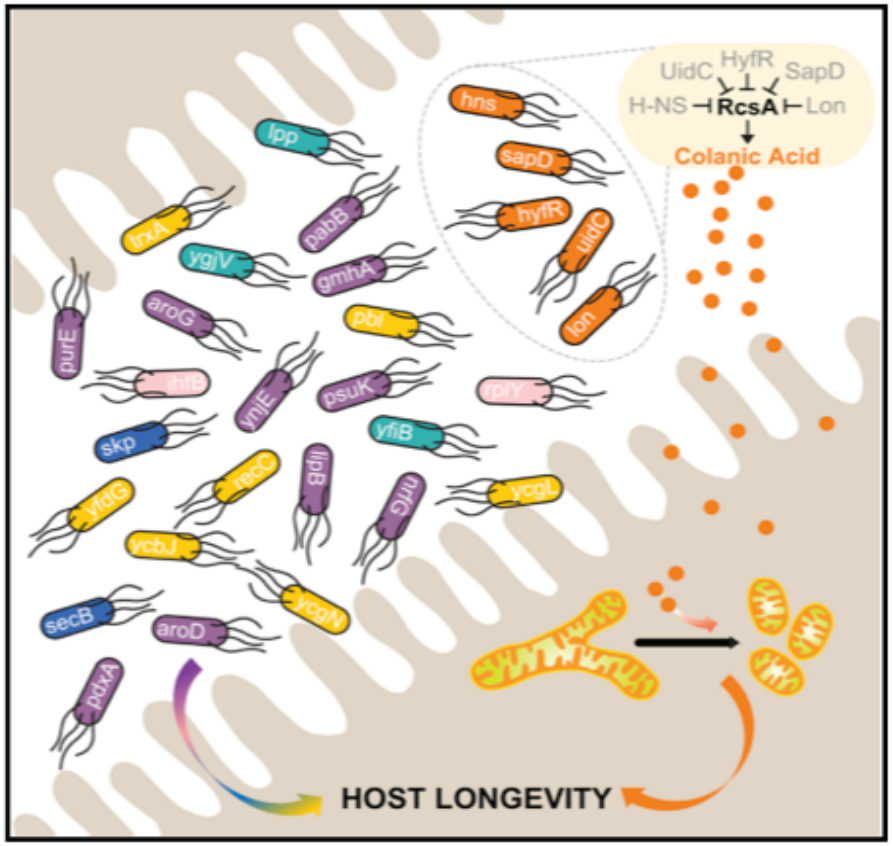
Microbial Genetic Composition Tunes Host Longevity

Graphical Abstract



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In Brief

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

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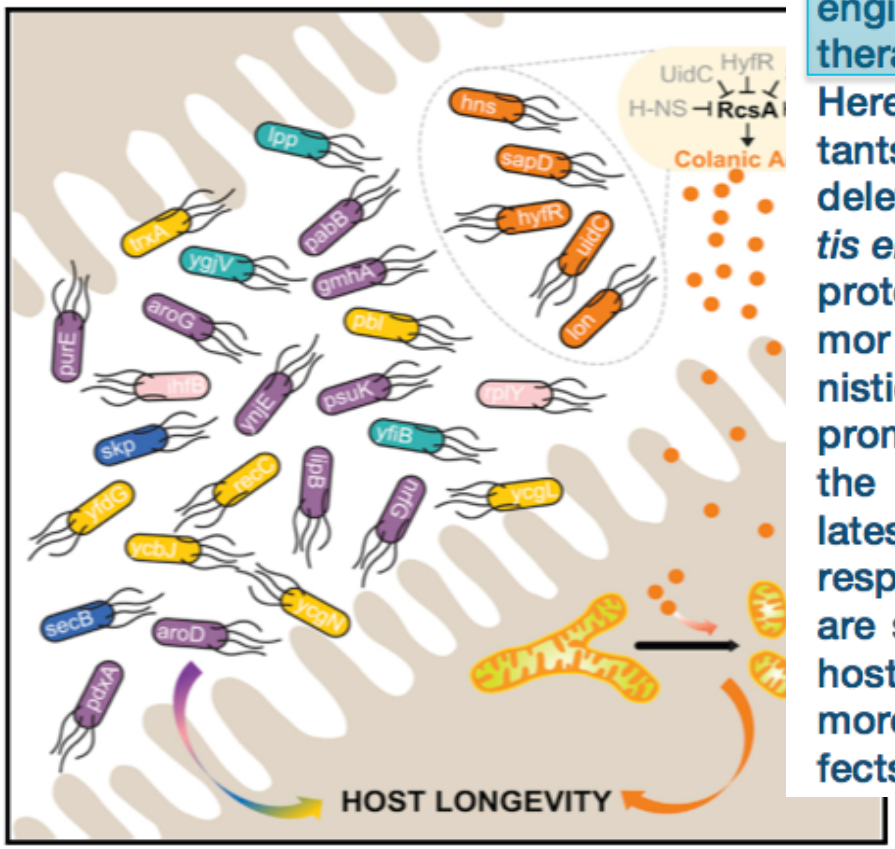
Microbial Genetic Composi Longevity

Graphical Abstract



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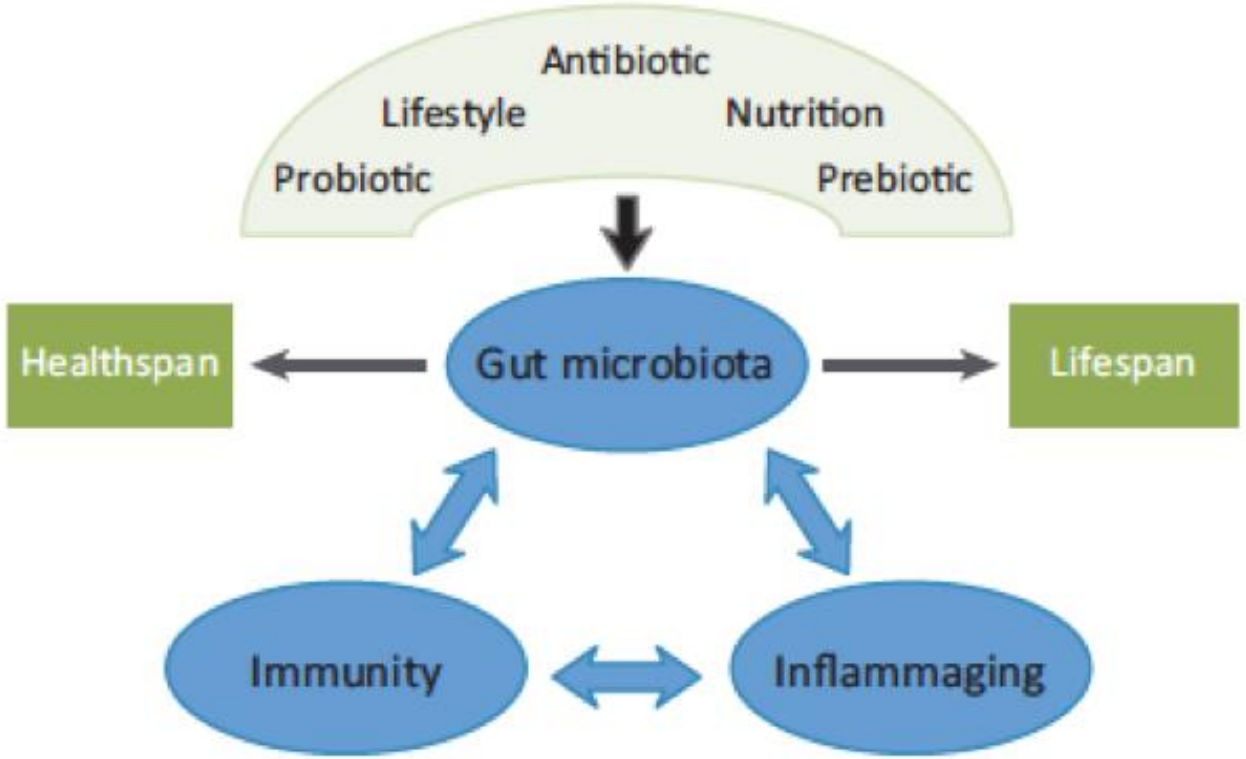
The age-tailored and personalized modulation of the gut microbiota will be aimed at maintaining the microbial profile **with the highest probability to help the host in preventing diseases and promoting (muscle) health**



Nikoletopoulou V et al.
Trend in Endocrinology and Metabolism 2014

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… Thank you !