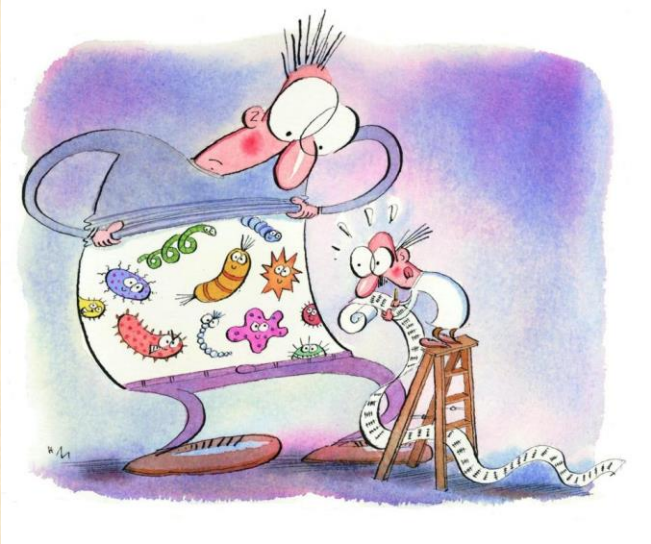
UNIVERSITA' degli STUDI di ROMA
TOR VERGATA
FACOLTA' DI MEDICINA E CHIRURGIA

Ruolo Chiave del Microbiota nello Sviluppo del Disturbo Autistico

Unical – 15 Novembre 2019



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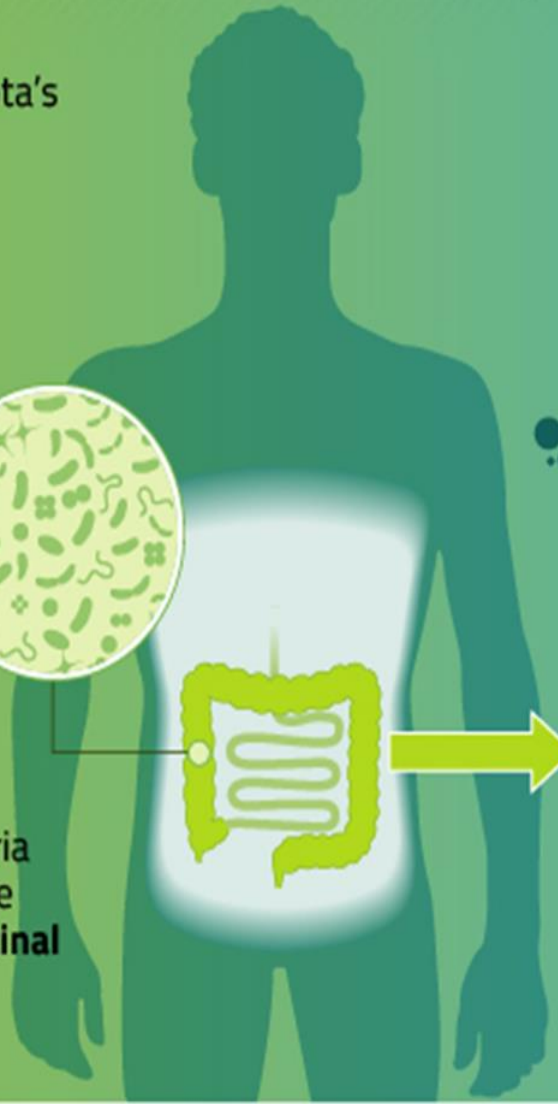
Getting to know your **gut microbiota**

A huge quantity (hundreds of trillions) of bacteria and other microorganisms inhabit your intestines fulfilling key functions for your health and wellbeing



Gut microbiota's **weight** can reach up to

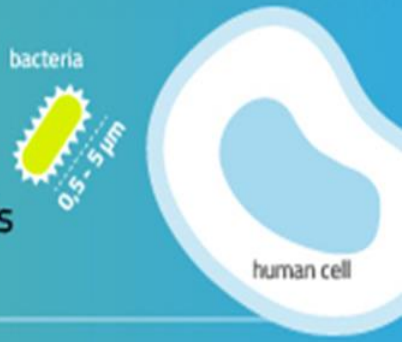
1 to 2 Kg

95% of our bacteria located in the **gastrointestinal (GI) tract**

The **GI tract** surface is as big as 2 tennis courts

400 m²

Bacteria are **10 to 50** times smaller than human cells



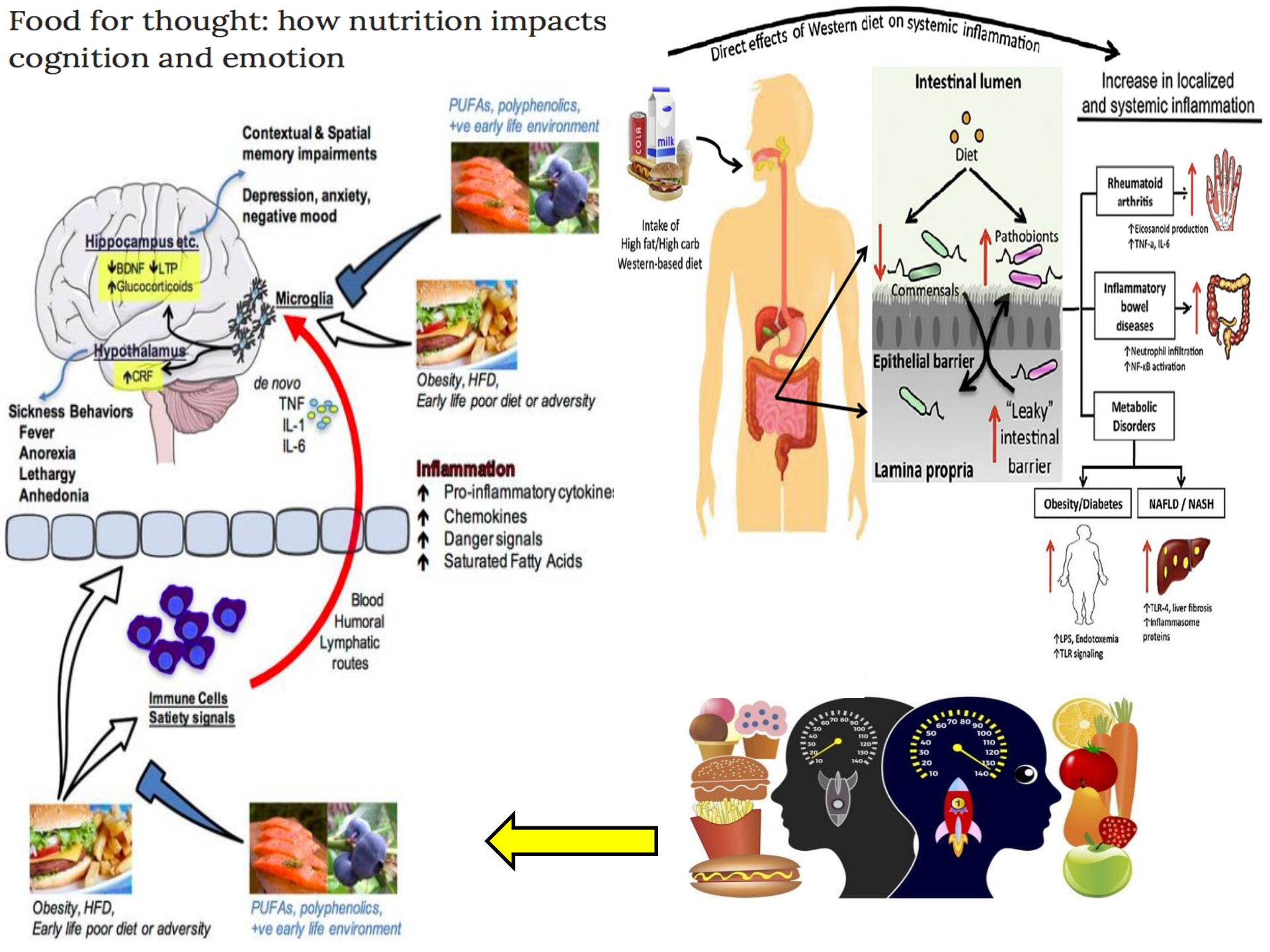
In our body, **microbes outnumber** human cells by

10:1

Laid end to end, our body's bacteria would **circle the Earth**

2,5 times

Food for thought: how nutrition impacts cognition and emotion



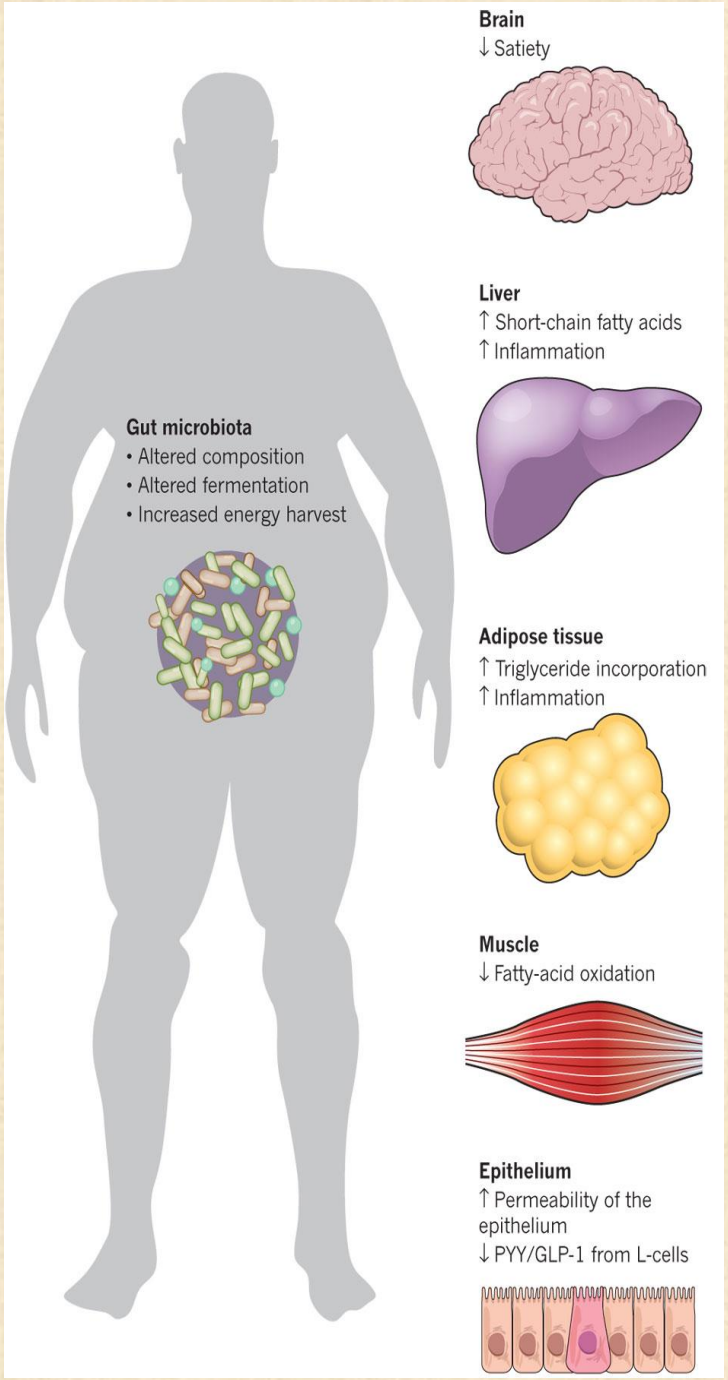
Microbiota e obesità "MicrObesity"

↑ **Firmicutes**

↓ **Bacteroidetes**

↑ **Lactobacillus reuteri e gasseri**

↓ **Lactobacillus paracasei**



Il microbiota intestinale e l'obesità

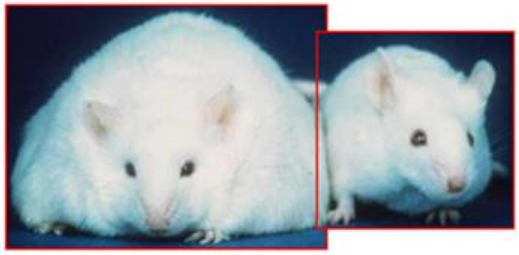
Vol 444|21/28 December 2006|doi:10.1038/nature05414

nature

An obesity-associated gut microbiome with increased capacity for energy harvest

Peter J. Turnbaugh[1], Ruth E. Ley[1], Michael A. Mahowald[1], Vincent Magrini[2], Elaine R. Mardis[1,2] & Jeffrey I. Gordon[1]

The worldwide obesity epidemic is stimulating efforts to identify host and environmental factors that affect energy balance. Comparisons of the distal gut microbiota of genetically obese mice and their lean littermates, as well as those of obese and lean human volunteers have revealed that obesity is associated with changes in the relative abundance of the two dominant bacterial divisions, the Bacteroidetes and the Firmicutes. Here we demonstrate through metagenomic and biochemical analyses that these changes affect the metabolic potential of the mouse gut microbiota. Our results indicate that the obese microbiome has an increased capacity to harvest energy from the diet. Furthermore, this trait is transmissible: colonization of germ-free mice with an 'obese microbiota' results in a significantly greater increase in total body fat than colonization with a 'lean microbiota'. These results identify the gut microbiota as an additional contributing factor to the pathophysiology of obesity.



Al fine di determinare se il microbiota e il suo contenuto in geni (microbioma) sono un fattore che contribuisce all'obesità, è stato caratterizzato il microbiota del cieco di topi geneticamente obesi (*ob/ob*) e dei loro fratelli magri (+/+ o *ob*/+) attraverso 16S rRNA gene library e il microbioma attraverso un approccio metagenomico di sequenziamento *shotgun random*.

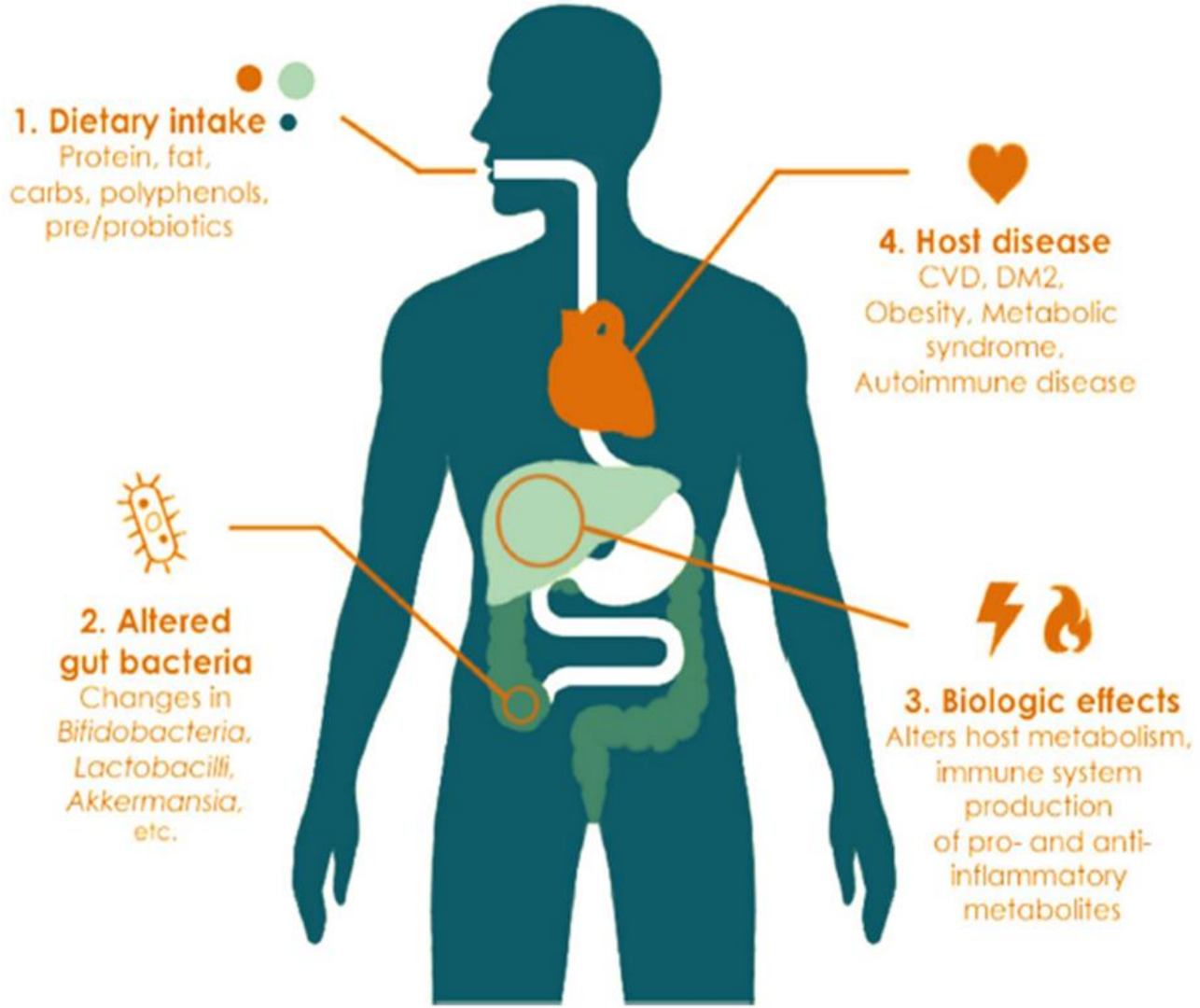
Da tali analisi è emerso che: (i) il microbiota dei topi obesi presenta un più elevato rapporto Firmicutes/Bacteroidetes e (ii) ***il metagenoma dei topi obesi è significativamente più ricco in geni che codificano per il trasporto e la metabolizzazione dei carboidrati non digeribili della dieta***

Journal of Translational Medicine

Influence of diet on the gut microbiome and implications for human health

Singh *et al. J Transl Med* (2017) 15:73
DOI 10.1186/s12967-017-1175-y

Impact of diet on the gut microbiome and human health



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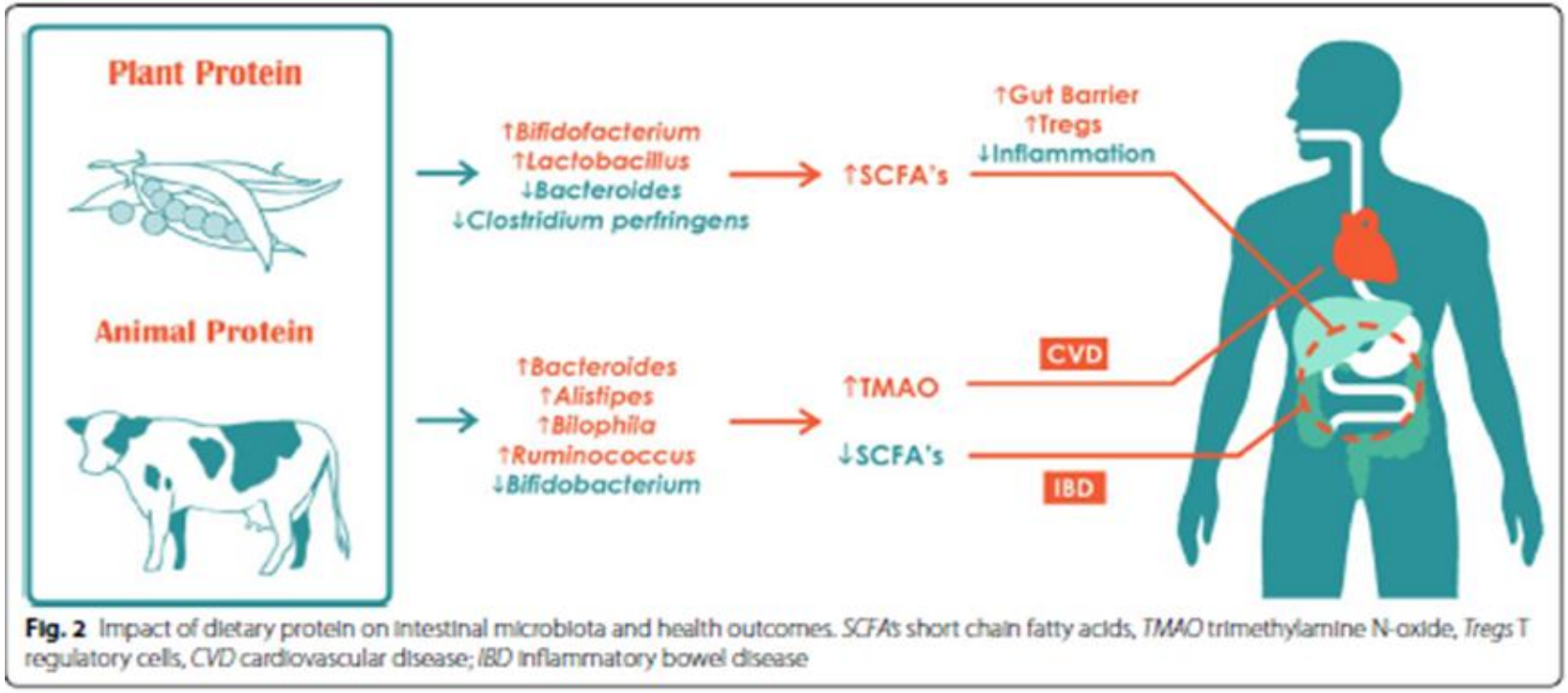


Fig. 2 Impact of dietary protein on intestinal microbiota and health outcomes. *SCFAs* short chain fatty acids, *TMAO* trimethylamine N-oxide, *Tregs* T regulatory cells, *CVD* cardiovascular disease; *IBD* inflammatory bowel disease

Table 2 Effects of protein on gut microbiota

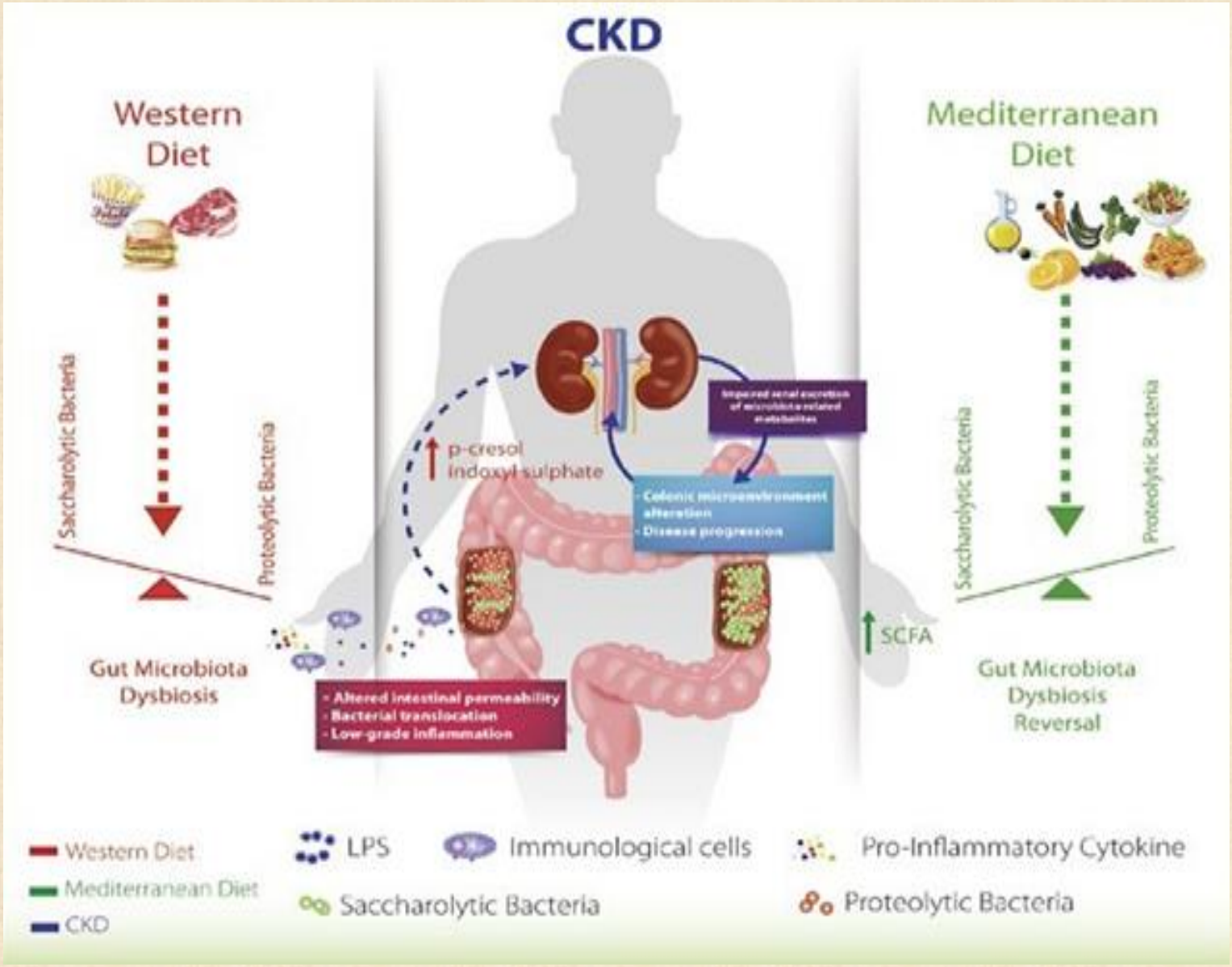
	Microbial diversity	*Bifidobacteria*	*Lactobacilli*	*Bacteroides*	*Alistipes*	*Bilophila*	*Clostridia*	*Roseburia*	*Eubacterium Rectale*	References
Animal protein	↑	↑↓		↑↓	↑	↑	↑	↓	↑↓	[13, 29–35, 38–40]
Whey protein extract	↑	↑	↑	↓			↓			[32, 33]
Pea protein extract	↑	↑	↑							[31]

Arrow thickness corresponds to relative number of studies supporting the relationship

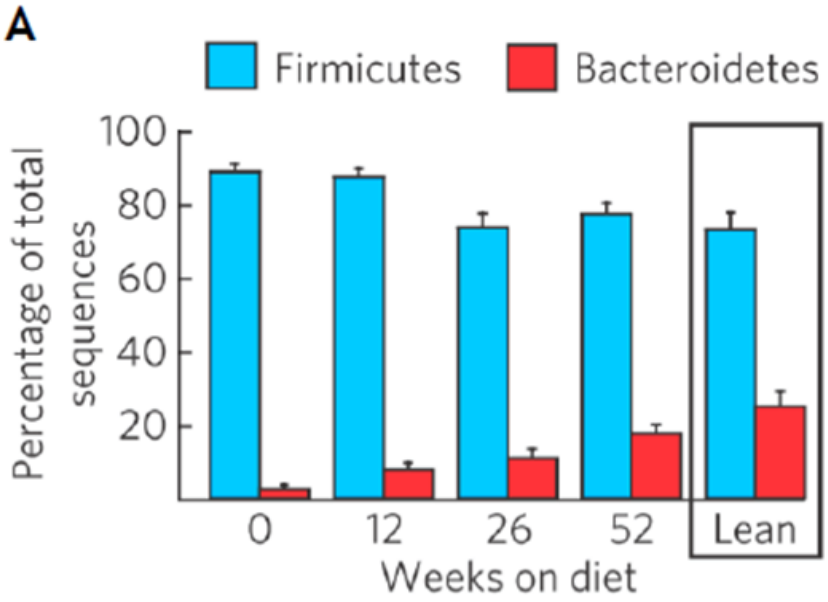
What Would You Like to Eat, Mr CKD Microbiota?

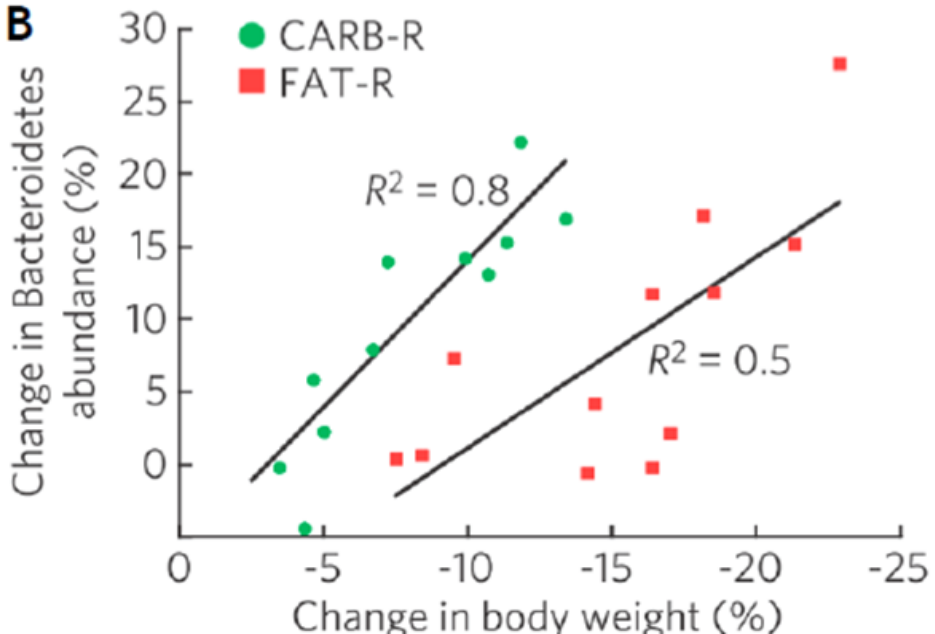
A Mediterranean Diet, please!

Montemurno E. Kidney Blood Press Res 2014;39:114-123



Ley, R. E. et al. 2006. Nature 444, 1022-1023





Correlazione tra la perdita di peso e l'ecologia microbica intestinale

A, Abbondanza relativa di Bacteroidetes e Firmicutes. Per ogni tempo, n = 11 o 12. Valori medi ± errore standard

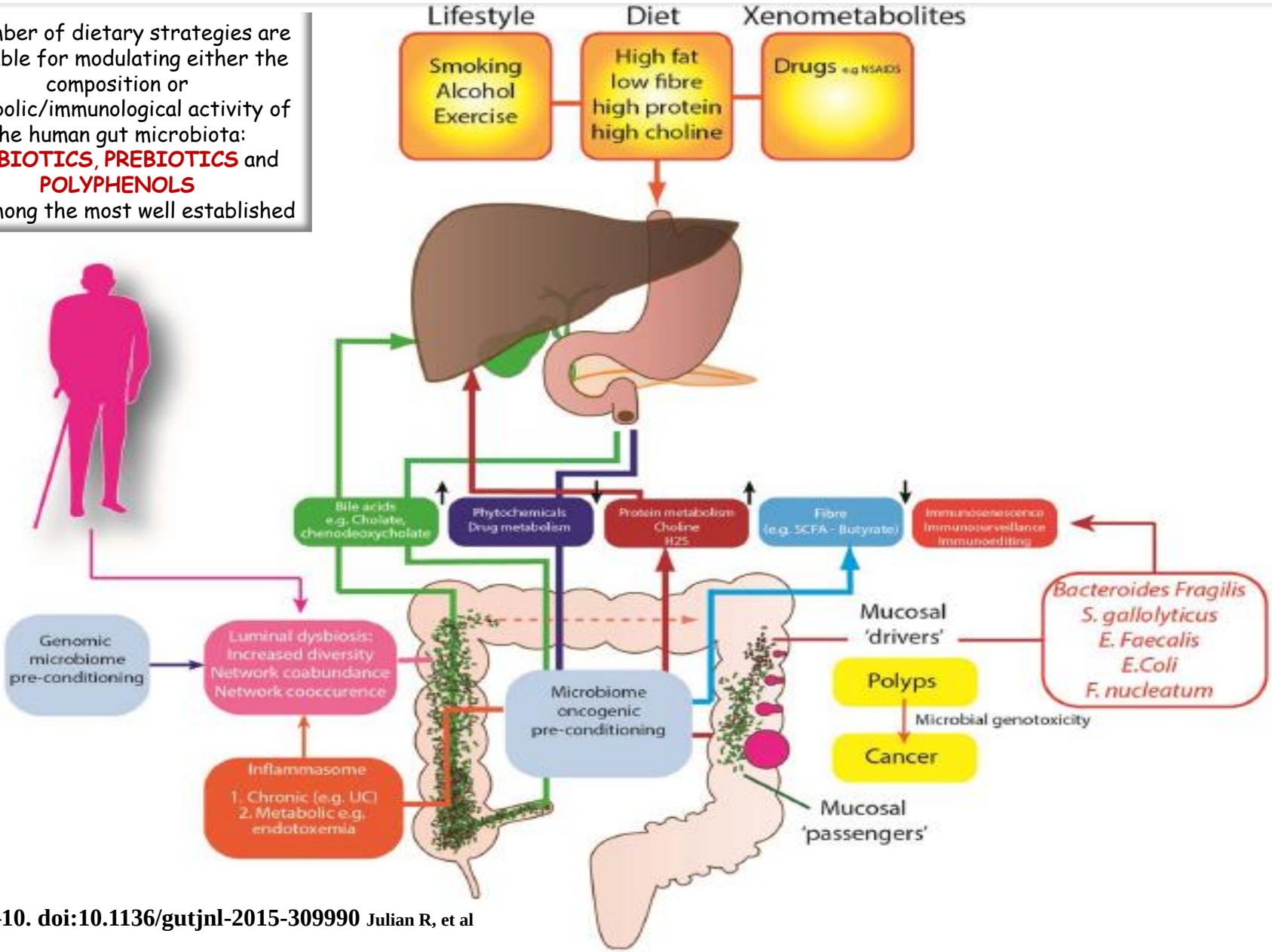
B, Cambiamenti nell'abbondanza relativa di Bacteroidetes nei soggetti in funzione della perdita di peso per le due diete (CARB-R: dieta povera di carboidrati; FAT-R dieta povera di grassi)

La proporzione relativa di Bacteroidetes è minore negli obesi rispetto ai soggetti magri. Questa proporzione incrementa progressivamente con la perdita di peso che è stata ottenuta con entrambe le diete ipocaloriche

La manipolazione mirata del microbiota intestinale potrebbe diventare un nuovo approccio per il trattamento dell'obesità

The gut microbiota and host health: a new clinical Frontier

A number of dietary strategies are available for modulating either the composition or metabolic/immunological activity of the human gut microbiota: **PROBIOTICS**, **PREBIOTICS** and **POLYPHENOLS** are among the most well established



Gut 2015;0:1–10. doi:10.1136/gutjnl-2015-309990 Julian R, et al

L'attività cognitiva è influenzata dalla flora batterica intestinale alterata da diete ricche di zuccheri o di grassi !!

"…dopo solo quattro settimane di dieta ricca di grassi o di zuccheri, la performance dei topi in vari test su funzioni fisiche o mentali incominciò a decadere.
Il cambiamento più significativo si è avuto nella "flessibilità cognitiva":

"Il decadimento della flessibilità cognitiva è stato forte." Questo vuol dire che di fronte a un problema inatteso – anche piccolo – non si è in grado di trovare soluzioni efficaci. Questo studio è stato condotto su animali giovani, i quali normalmente hanno un sistema biologico più integro e perciò più capace di resistere alle influenze patologiche del loro microbiota."

Quella che viene indicata come "dieta occidentale", ricca di grassi e zuccheri semplici è stata messa in relazione con una varietà di malattie croniche negli Stati Uniti, includenti l'obesità sempre più diffusa e un'aumentata incidenza di malattia di Alzheimer.

(***Science daily, June 22, 2015***)

Microbiota e Neurodegenerazione

World Journal of Gastroenterology

Submit a Manuscript: http://www.f6publishing.com
World J Gastroenterol 2018 October 7; 24(37): 4217-4223
DOI: 10.3748/wjg.v24.i37.4217
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

EDITORIAL

Focus on the gut-brain axis: Multiple sclerosis, the intestinal barrier and the microbiome

Carlos R Camara-Lemarroy, Luanne M Metz, V Wee Yong

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Published online: October 7, 2018

International Journal of Molecular Sciences

MDPI

Review

Microbiome-Gut-Brain Axis and Toll-Like Receptors in Parkinson's Disease

Valentina Caputi [1,2] and Maria Cecilia Giron [1,*]

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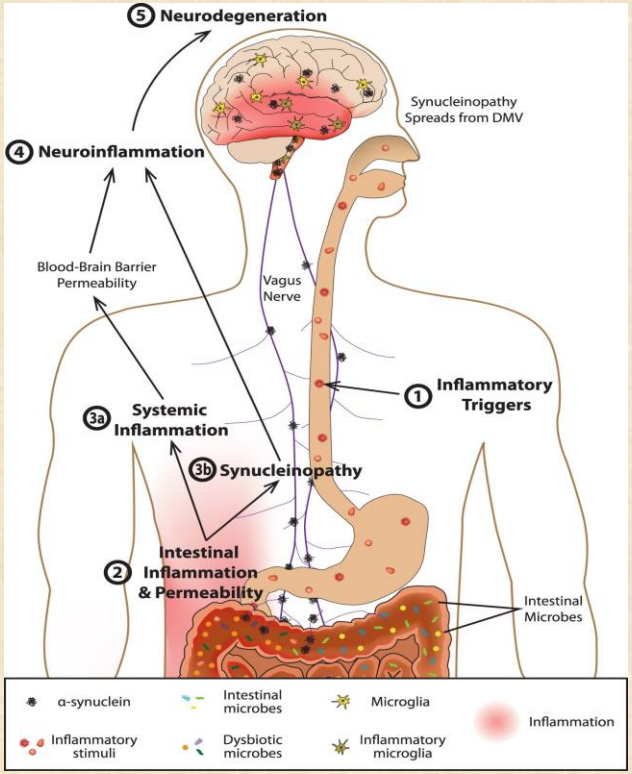


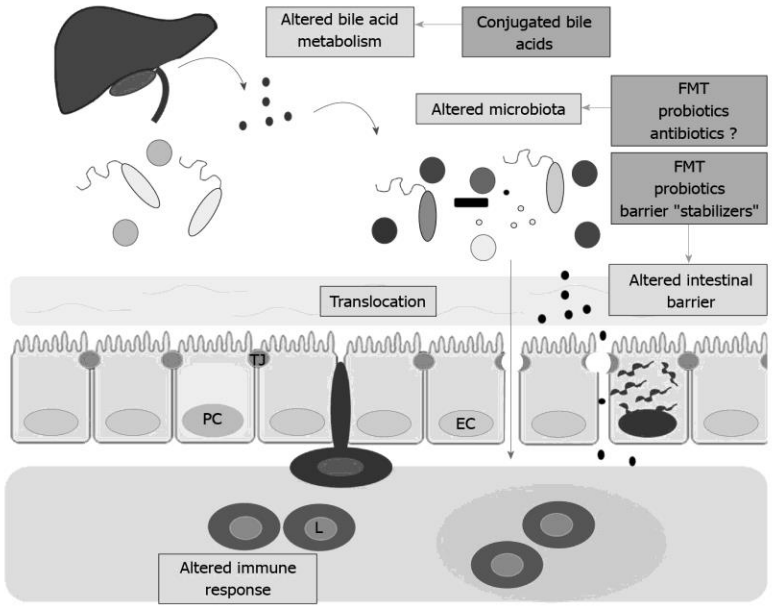


Figure 1 Alterations in intestinal homeostasis described in multiple sclerosis as therapeutic targets. Altered bile acid metabolism, altered microbiota and alterations in intestinal barrier function all lead to local and systemic alterations in immune responses that could negatively impact MS pathophysiology (grey squares). Bile acid supplementation, fecal microbiota transplantation, probiotics, antibiotics and barrier protectors are all possible therapeutic interventions (blue squares). MS: Multiple sclerosis; FMT: Fecal microbiota transplantation; PC: Paneth cells; EC: Epithelial cells; TJ: Tight junctions; L: Lymphocytes.

Microbiota ed Autismo

Emerging Roles for the Gut Microbiome in Autism Spectrum Disorder

Helen E. Vuong and Elaine Y. Hsiao

ABSTRACT

Autism spectrum disorder (ASD) is a se
United States, with a similarly striking pre
etiology and manifestations remain poo
severity of impaired social communicatio
are common comorbidities. The microb
changes in the gut microbiota can modul
between particular bacteria from the indig
question of whether microbial dysbiosis p
review reports of microbial dysbiosis ir
associated symptoms, drawing on signali
gut function, and behavior. In addition,
interface between environmental and ger
integration of pathways across multiple b
changes in the microbiome may contribu

Keywords: Autism, Gastrointestinal tract

http://dx.doi.org/10.1016/j.biopsych.2016

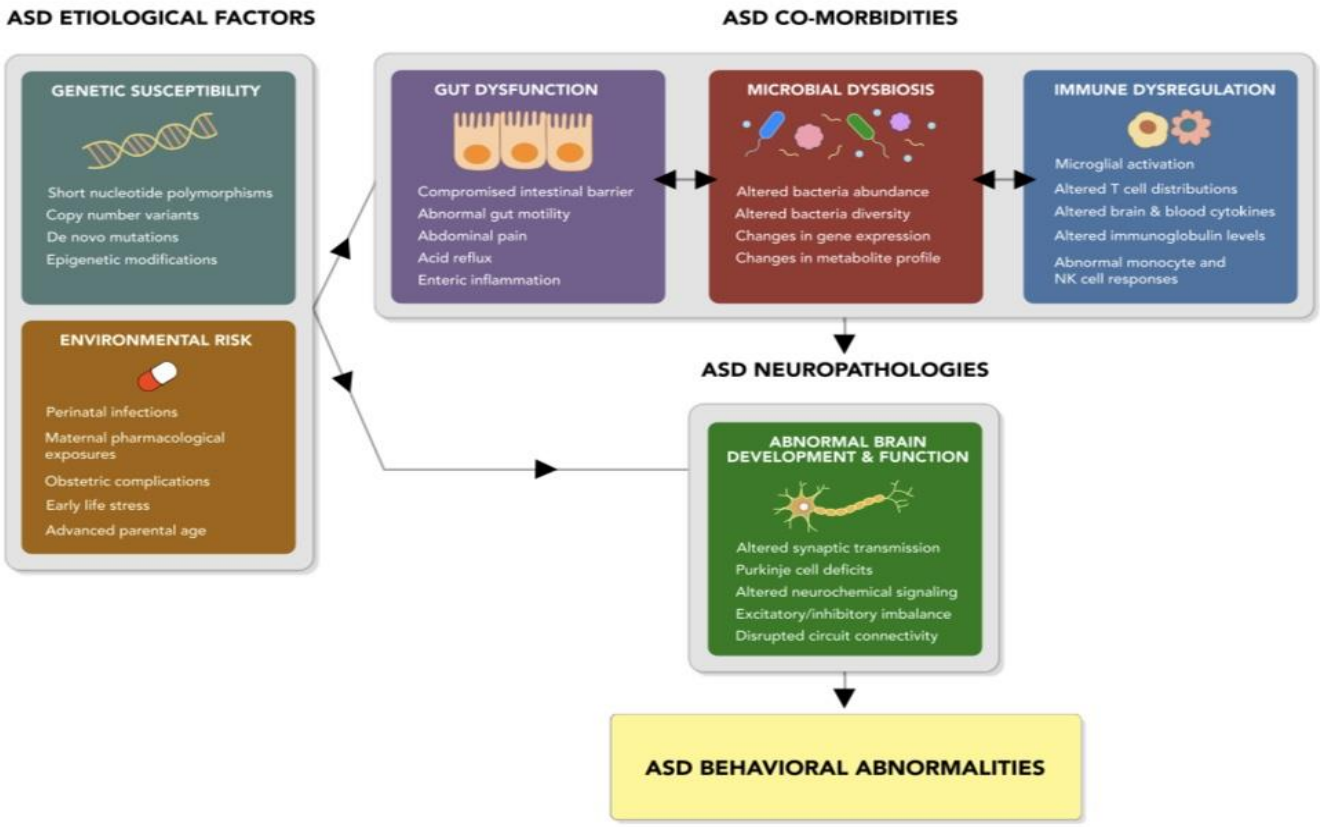


Figure 1. Model for roles of the microbiome in autism spectrum disorder (ASD). The microbiota is shaped by host genetics and environmental exposures. Select genetic and environmental risk factors for ASD could directly cause changes in the indigenous microbiota. Alternatively, the microbiota could be indirectly influenced by other medical comorbidities associated with ASD, including gastrointestinal issues and immune dysfunction. The microbiota exhibits reciprocal interactions with the gastrointestinal tract, immune system, brain, and behavior, and abnormalities in any one component of this integrated system could affect the others. In particular, dysbiosis of the intestinal microbiota, in addition to immune and gastrointestinal symptoms seen in ASD, can influence neurodevelopment, neural activity, and the manifestation of abnormal behaviors characteristic to ASD. NK, natural killer.

A **Microbiota–gut–brain axis** | **B** **Autism spectrum disorder**

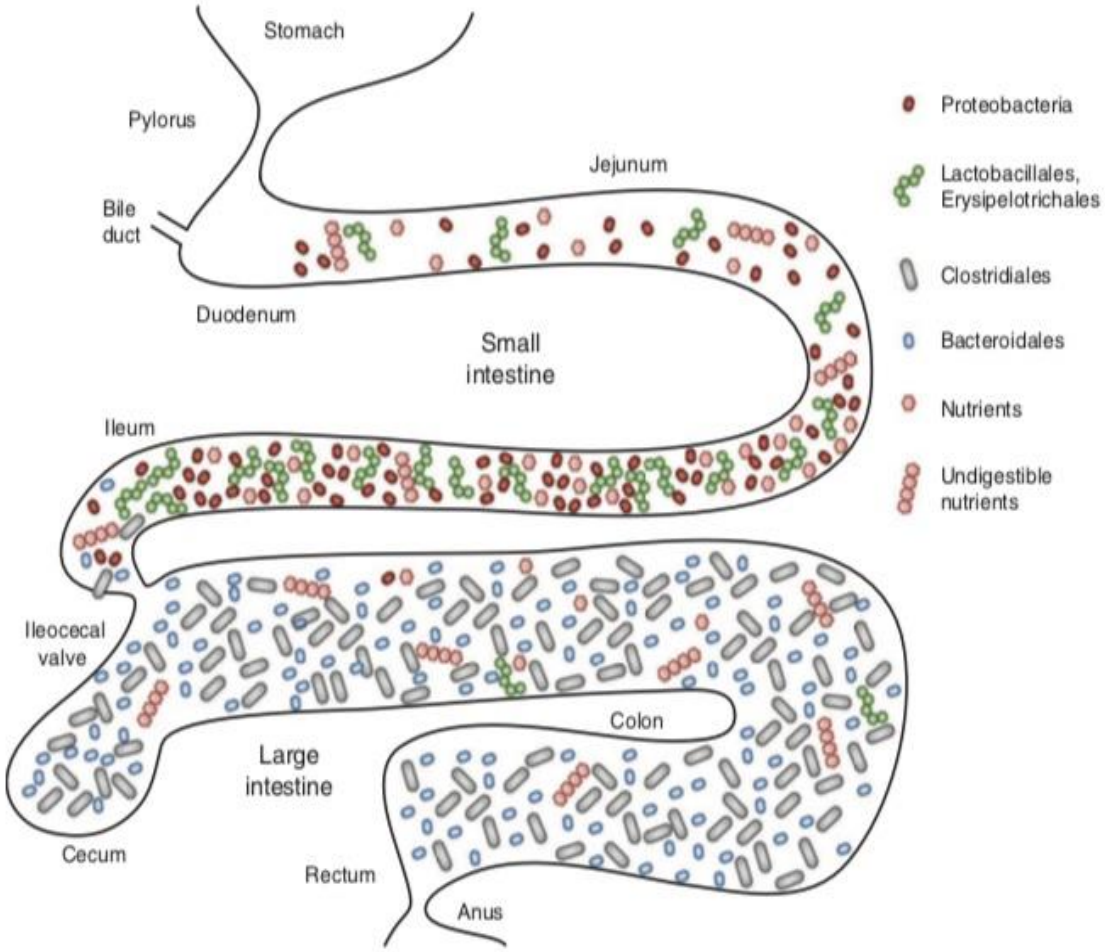


Figure 1 Localization of dominant bacterial groups in the intestine. The small intestine is rich in nutrients used by both the host and the microbe for growth. Proteobacteria spp. (mainly Enterobacteria), Lactobacillales and Erysipelotrichales (especially *Turicibacter* spp.) are dominant in the small intestine. In contrast, the large intestine is poor in such nutrients and therefore has fewer of these bacteria, whereas Bacteroidetes and Clostridia, which can use host-indigestible fibers as energy sources, are enriched.

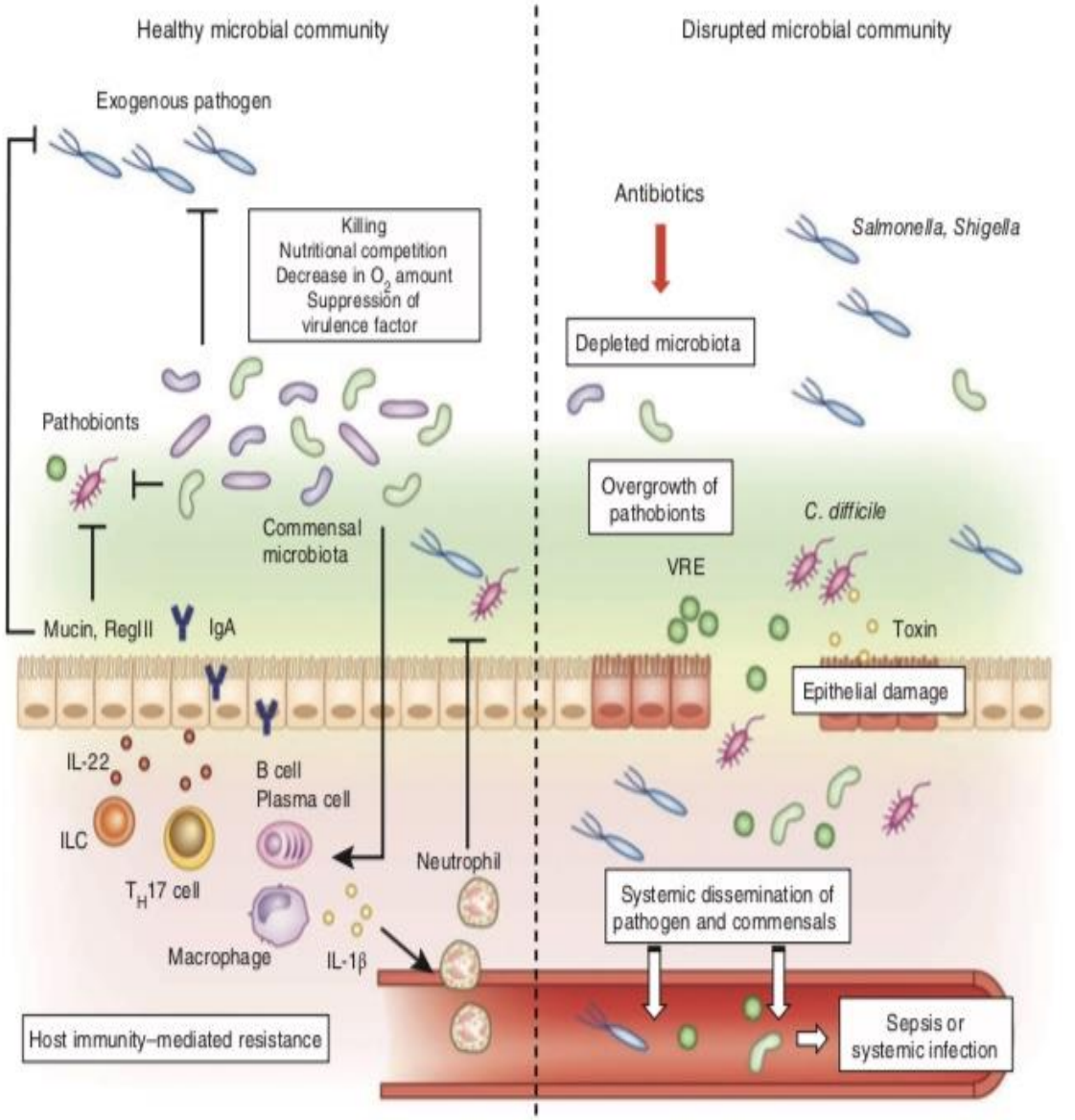


Figure 2 Commensal microbiota prevents colonization by exogenous pathogens and pathobionts. In the healthy gut, the resident bacteria occupy intestinal colonization niches. Commensal microbiota suppresses the proliferation and colonization of incoming enteric pathogens, as well as of opportunistic pathobionts, through multiple mechanisms. Microbiota produces bacteriocins and short-chain fatty acids, which directly inhibit the growth of pathogens and pathobionts. Commensals can also modify virulence-factor expression in pathogens by consuming residual oxygen or suppressing growth by their metabolites. Commensal microbiota facilitates host barrier function through upregulation of the mucus layer, induction of antimicrobial molecules, such as RegIIIβ and γ (RegIII), and regulating secretion of IgA. Commensal bacteria also prime intestinal macrophages by upregulating pro–IL-1β. Pathogen infection results in the conversion of pro–IL-1β into the enzymatically active mature form of IL-1β, which promotes neutrophil recruitment and pathogen eradication. Commensal microbiota promotes differentiation and/or activation of T_H17 cells and innate lymphoid cells (ILCs), which control both commensals and pathogens through secreted cytokines, such as IL-22. Antibiotic treatment or other environmental factors that disrupt the commensal microbial community result in diminished resistance to colonization by pathogens (for example, *Salmonella* and *S. flexneri*) and allow the outgrowth of indigenous pathobionts (for example, *C. difficile* and VRE) that have the potential to disseminate systemically and induce septic shock and/or systemic organ infection.

Materiali e Metodi

Nello studio che stiamo mettendo a punto insieme alla University of California di San Diego ed il San Raffaele di Milano andremo a valutare se effettivamente il microbiota interviene in modo significativo nello sviluppo dello spettro autistico. *Avolio et al., 2018*

40 Ratti → **20 Valproico + Feci Autistici**

4 Weeks → **SWIM TEST** → **LDT and EPM** → **CPP and Novel object**

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Probiotics modify body weight together with anxiety states via pro-inflammatory factors in HFD-treated Syrian golden hamster

Ennio Avolio[a,b,*], Gilda Fazzari[a], Merylin Zizza[a], Antonino De Lorenzo[b], Laura Di Renzo[b], Raffaella Alò[a], Rosa Maria Facciolo[a], Marcello Canonaco[a]

Clinical Study

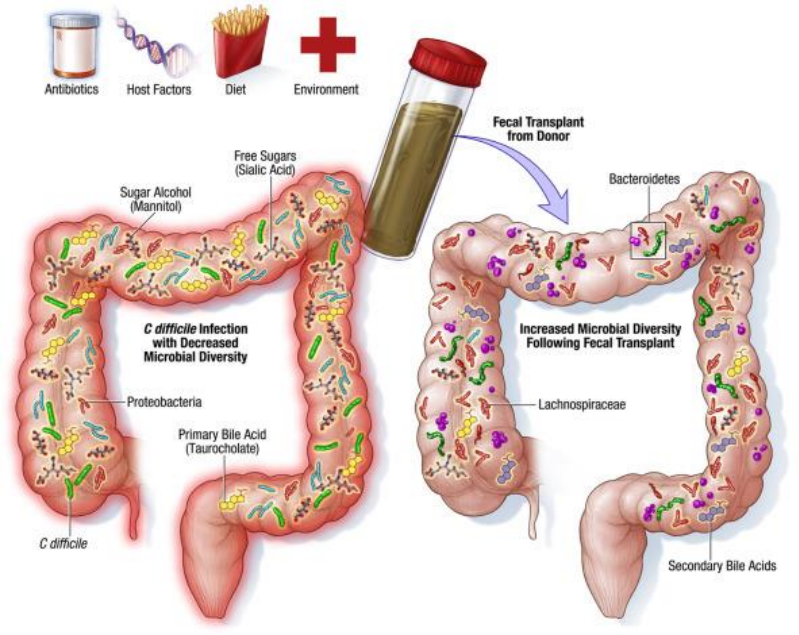
Evidences of a New Psychobiotic Formulation on Body Composition and Anxiety

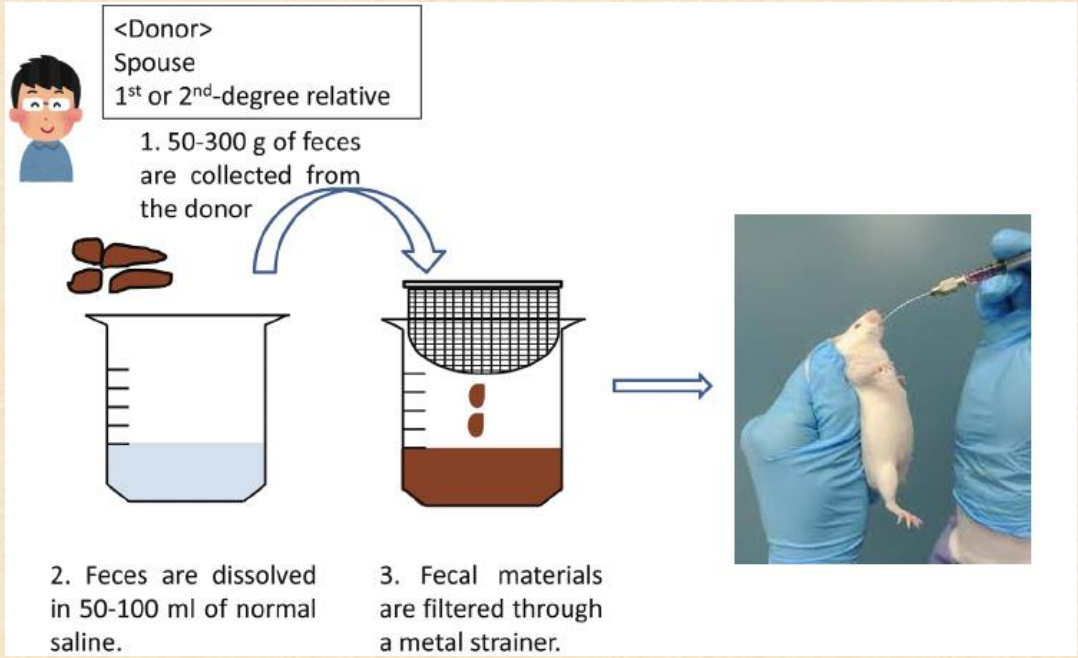
Carmela Colica,[1] Ennio Avolio,[2] Patrizio Bollero,[3] Renata Costa de Miranda,[4,5] Simona Ferraro,[6] Paola Sinibaldi Salimei,[7] Antonino De Lorenzo,[7] and Laura Di Renzo[7]

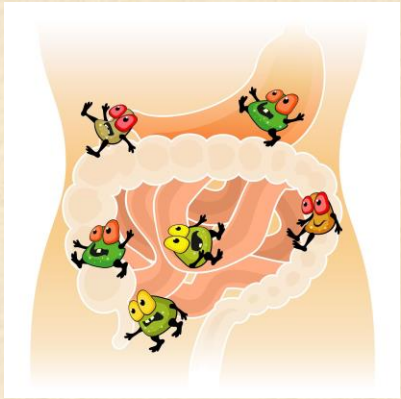
4 Groups

CTRL - Valproico - Feci - Valproico + Feci. Vasostatina 1?

Trapianto Fecale



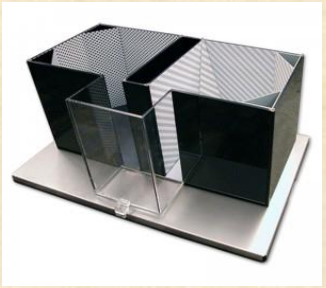


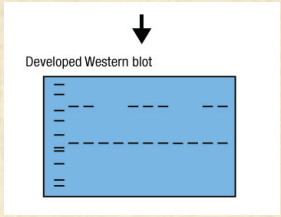


Materiali e Metodi

After protocol, mice were subjected to LDT and EPM, on the same day but at different time periods for 3 consecutive days in morning, noon and afternoon.
Avolio et al., 2018
At the end of LDT and EPM, animals were subjected to CPP and novel object for 7 days before being sacrificed, in which plasma and other organs were collected for western molecular analysis.

SWIM TEST → **LDT and EPM** → **CPP and Novel object** → **WB and Molecular Analysys**





Ipotesi…..

Cambiamento comportamentale

Western e PCR citochine

Analisi genetica sulle feci

Immunoistochimica

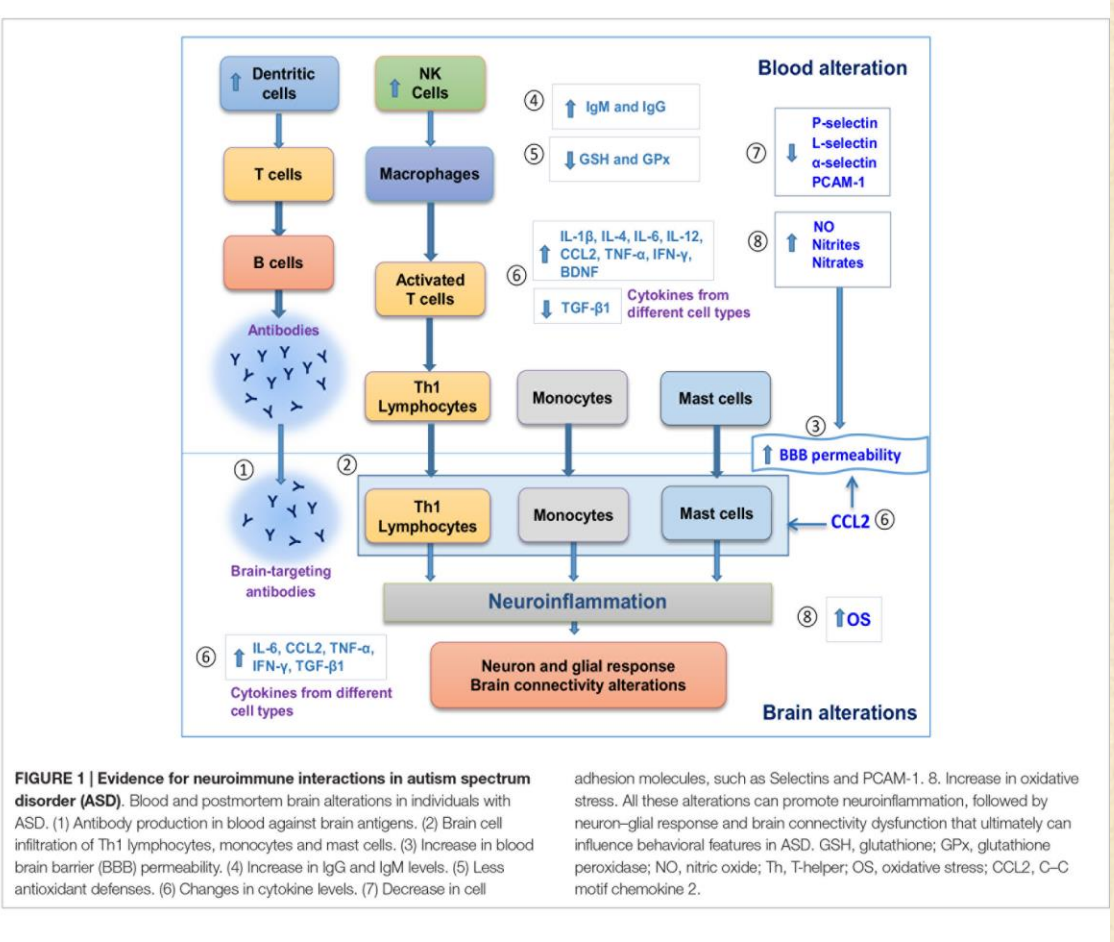
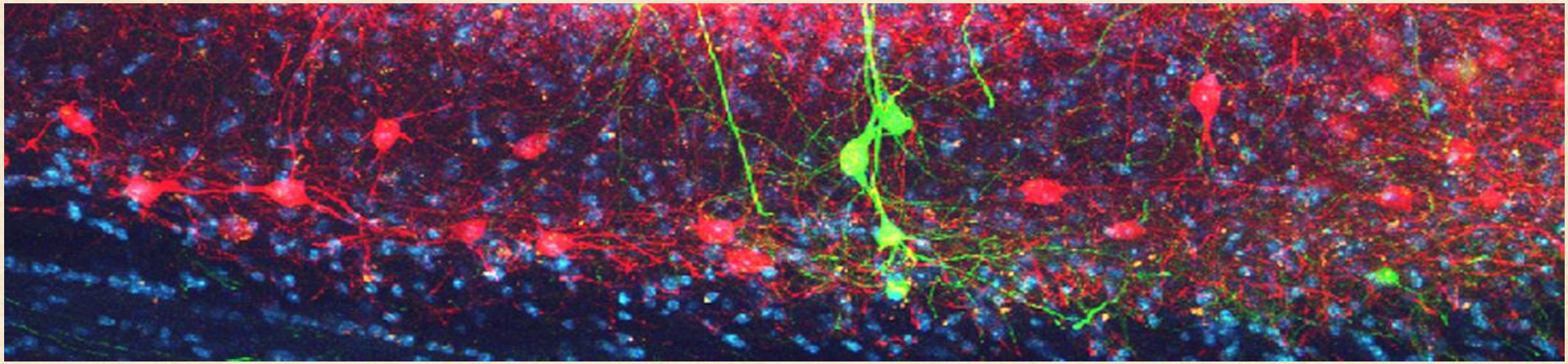


FIGURE 1 | Evidence for neuroimmune interactions in autism spectrum disorder (ASD). Blood and postmortem brain alterations in individuals with ASD. (1) Antibody production in blood against brain antigens. (2) Brain cell infiltration of Th1 lymphocytes, monocytes and mast cells. (3) Increase in blood brain barrier (BBB) permeability. (4) Increase in IgG and IgM levels. (5) Less antioxidant defenses. (6) Changes in cytokine levels. (7) Decrease in cell adhesion molecules, such as Selectins and PCAM-1. 8. Increase in oxidative stress. All these alterations can promote neuroinflammation, followed by neuron–glial response and brain connectivity dysfunction that ultimately can influence behavioral features in ASD. GSH, glutathione; GPx, glutathione peroxidase; NO, nitric oxide; Th, T-helper; OS, oxidative stress; CCL2, C–C motif chemokine 2.



Take the message…

- Esiste una stretta correlazione tra microbiota ed autismo;
- La permeabilità intestinale è alla base dello sviluppo di una serie di patologie cronico degenerative;
- Le citochine pro-infiammatorie intervengono in modo significativo nello sviluppo delle disbiosi intestinali;
- Esiste la necessità di isolare i ceppi batterici responsabili dello sviluppo di patologie come l'autismo in modo da mettere a punto delle terapie mirate;
- Abbiamo ancora molto da scoprire sui diversi tipi di microbiota che popolano il nostro organismo e come essi regolano l'omeostasi tissutale.

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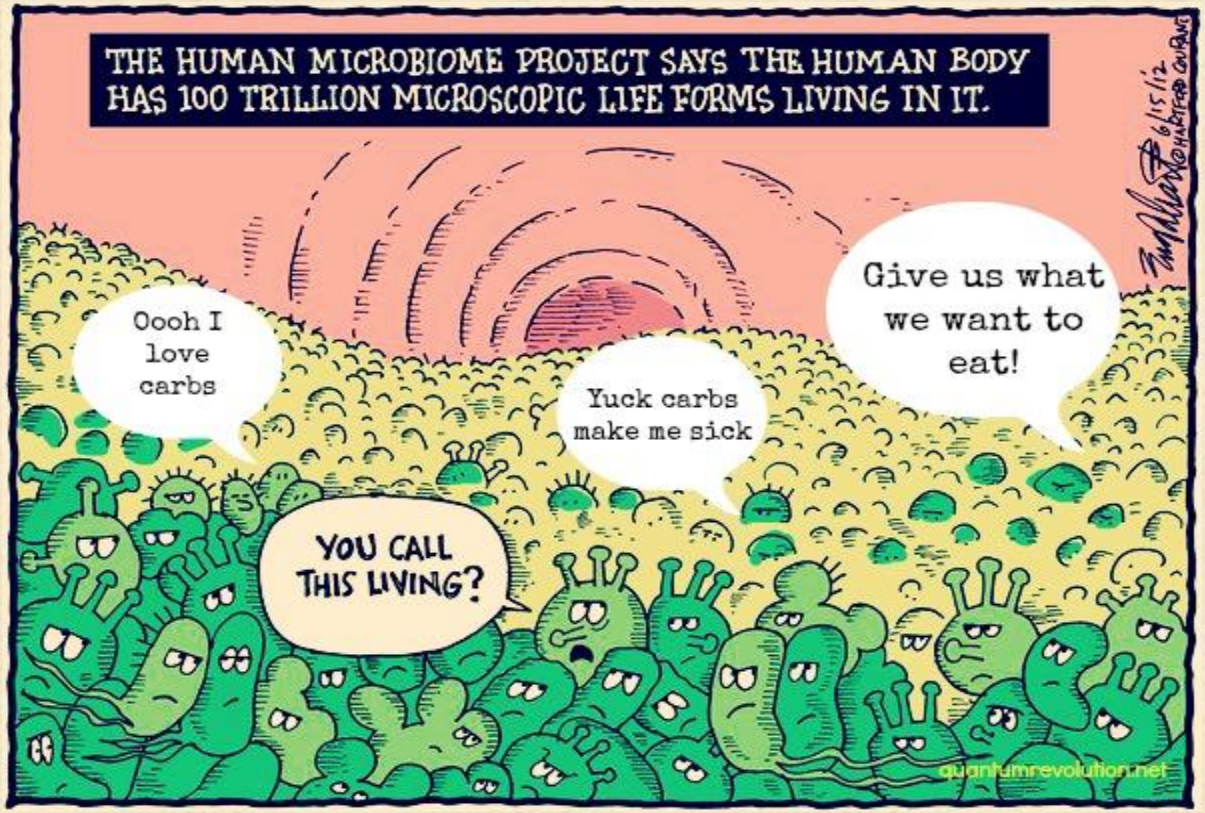
Grazie dell'attenzione!



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