

We Are Not Alone in This Endless Universe



PoliFormazione
Messina

STAFF DELLA DIREZIONE STRATEGICA AZIENDALE
U.O.S. FORMAZIONE

*Dalle attuali conoscenze sul microbiota a nuove
strategie terapeutiche.*

Paolo Mainardi

1982 Laurea in Chimica

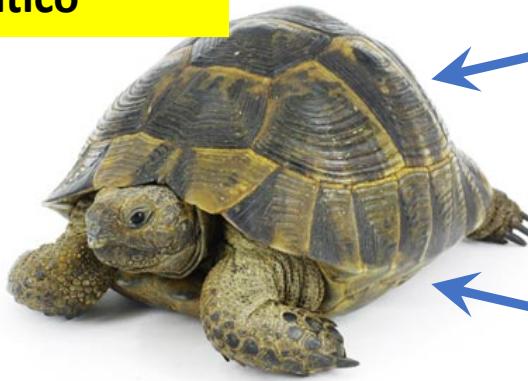
1982-2017 Centro Epilessia UNIGE

2017-oggi Consulente Scientifico Kolfarma Srl

2019-oggi Presidente Università Popolare delle
Scienze dell'Alimentazione e Salute (UNIPSAS)

il 60% del codice DNA dei moscerini della frutta e degli esseri umani è identico

- Microbial body is ten time cellular body



Cellular body: 10^{13}

23000 genetic units

Microbial body: 10^{14}

4 Million genetic units



“Surprisingly, each of us can be identified by the DNA of our gut microbes”.

George Weinstock, Genoma Institute, Washington University



- It compensates for our genetic damage
- It is able to repair our DNA
- It is able to modify our genetic expression

Nobel per la Chimica 2015 a Tomas Lindahl, Paul Modrich e Aziz Sancar per aver scoperto i processi riparativi del DNA.

- la struttura del DNA è intrinsecamente **moltò fragile**: a 37 °C circa 18 000 basi azotate al giorno sono perse da ogni cellula.

DANNI AMBIETALI:

- Le **radiazioni ultraviolette** producono sul DNA una distorsione della doppia elica.
- **Radiazioni ionizzanti** possono provocare rotture del legame fosfodiesterico su uno o entrambi i filamenti del DNA.
- **Composti chimici** utilizzati in lavorazioni industriali, presenti nel fumo di sigaretta o anche in componenti della nostra dieta quotidiana, possono causare lesioni e danni sul DNA.

- **più o meno 10^{21} possibilità di errore al giorno!!**
- senza i **meccanismi riparativi** il **nostro codice genetico** sarebbe in **balia delle mutazioni provocate dall'ambiente** .

DNA spazzatura: il 72,5% del DNA non è utilizzato. È materiale per la riparazione?

Physiological functions, i.e.:

Microbial body controls:



- **Blood pressure** (Yang T, Zubcevic J. Gut-Brain Axis in Regulation of Blood Pressure. *Front Physiol.* 2017 Oct 25;8:845).
- **Plasma levels of cholesterol** (Gérard P. Metabolism of cholesterol and bile acids by the gut microbiota. *Pathogens.* 2013 Dec 30;3(1):14-24.)
- **Heart functions** (Luedde M, Winkler T, Heinsen FA, Rühlemann MC, Spehlmann ME, Bajrović A, Lieb W, Franke A, Ott SJ, Frey N. Heart failure is associated with depletion of coreintestinal microbiota. *ESC Heart Fail.* 2017 Aug;4(3):282-290)
- **Kidney functions** (Jiang S, Xie S, Lv D, Wang P, He H, Zhang T, Zhou Y, Lin Q, Zhou H, Jiang J, Nie J, Hou F, Chen Y. Alteration of the gut microbiota in Chinese population with chronic kidney disease. *Sci Rep.* 2017 Jun;6(1):2870)
- **Neuroendocrine system** (Farzi A, Fröhlich EE, Holzer P. Gut Microbiota and the Neuroendocrine System. *Neurotherapeutics.* 2018 Jan;15(1):5-22)
- ...

RISULTA

ALTERATO

È un caso o la causa?

CONTROLLA

Altered Microbiota in:



- **Parkinson's** (Qian Y, Yang X, Xu S, Wu C, Song Y, Qin N, Chen SD, Xiao Q. Alteration of the fecal microbiota in Chinese patients with Parkinson's disease. *Brain Behav Immun.* 2018 Mar 2. pii: S0889-1591(18)30028-X.)
- **Alzheimer's** (Di Sabatino A, Lenti MV, Cammalleri I, Corazza GR, Pilotto A. Frailty and the gut. *Dig Liver Dis.* 2018 Mar 16)
- **ALS** (Brenner D, Hiergeist A, Adis C, Mayer B, Gessner A, Ludolph AC, Weishaupt JH. The fecal microbiome of ALS patients. *Neurobiol Aging.* 2018 Jan;61:132-137.)
- **Huntington's**
- **MS** (Tremlett H, Waubant E. Gut microbiome and pediatric multiple sclerosis. *Mult Scler.* 2018 Jan;24(1):64-68.)
- **Autism** (Campion D, Ponzo P, Alessandria C, Saracco GM, Balzola F. Role of microbiota in the autism spectrum disorders. *Minerva Gastroenterol Dietol.* 2018 Mar 30.)
- **Metabolic diseases** (Clavel T, Desmarchelier C, Haller D, Gérard P, Rohn S, Lepage P, Daniel H. Intestinal microbiota in metabolic diseases: from bacterial community structureand functions to species of pathophysiological relevance. *Gut Microbes.* 2014 Jul;5(4):544-519)
- ...

Intestinal Microbiota: A moderator in health and diseases.

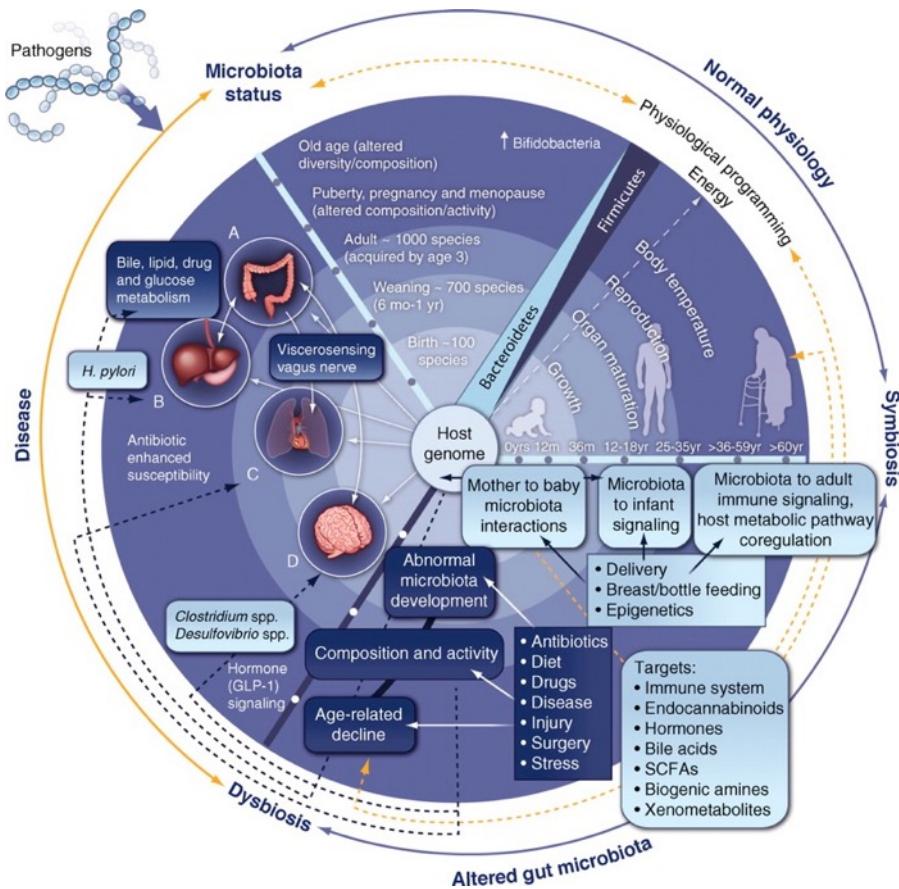
4573 articles on pubmed



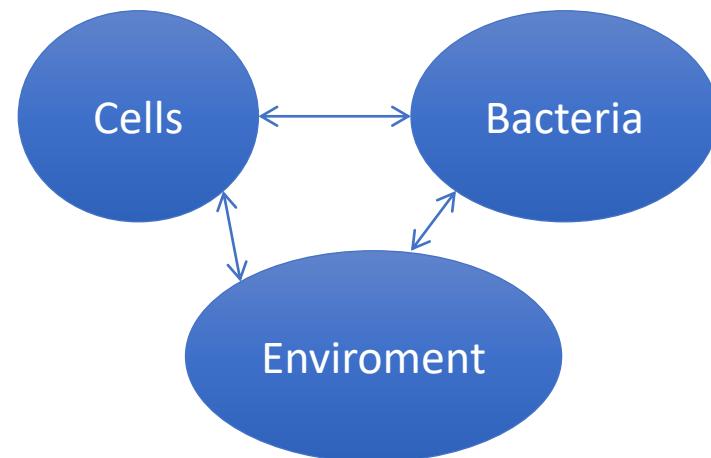
Ago della bilancia tra salute e malattia.

Feng Q, Chen W-D and Wang Y-D (2018) Gut Microbiota: An Integral Moderator in Health and Disease. *Front. Microbiol.* 9:151

THE GUT ECOSYSTEM



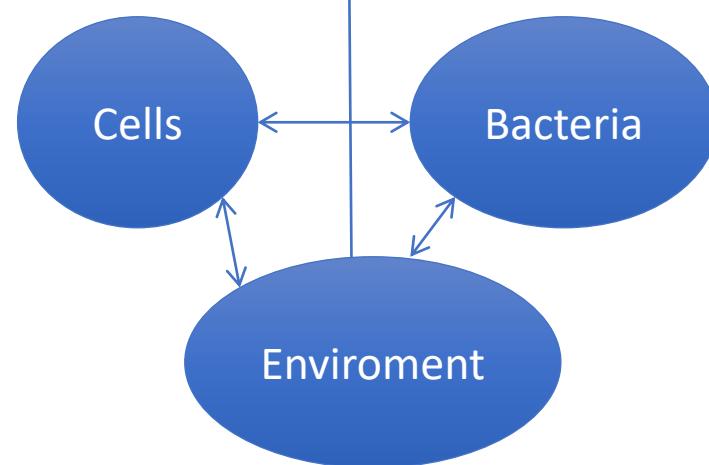
... **Gut microecological imbalance** caused by various biogenic and abiogenic agents and factors can produce different epigenetic abnormalities and the onset and progression of metabolic diseases associated ...



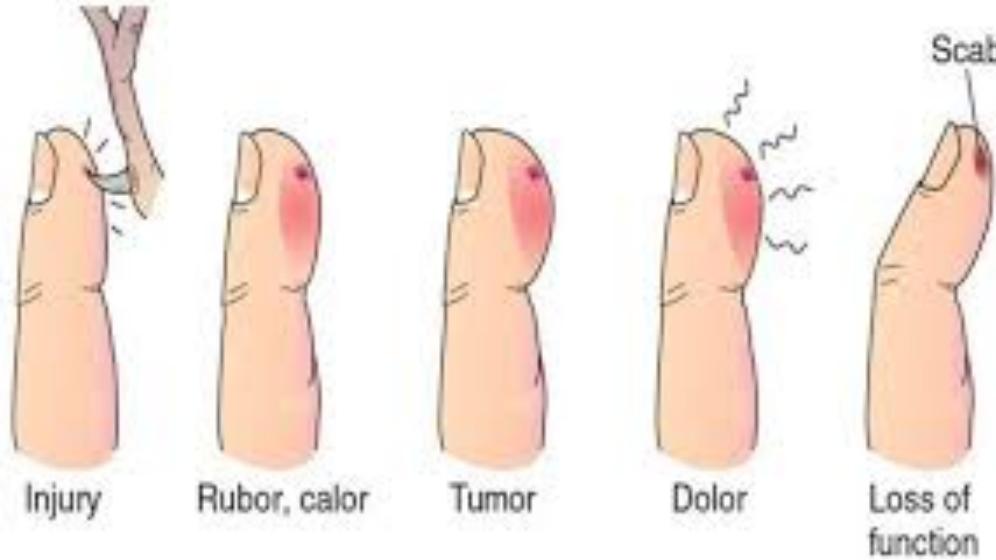
Il risultato finale dipende da un intimo colloquio...

Malattia

Salute



Controlla (anche) la risposta infiammatoria:



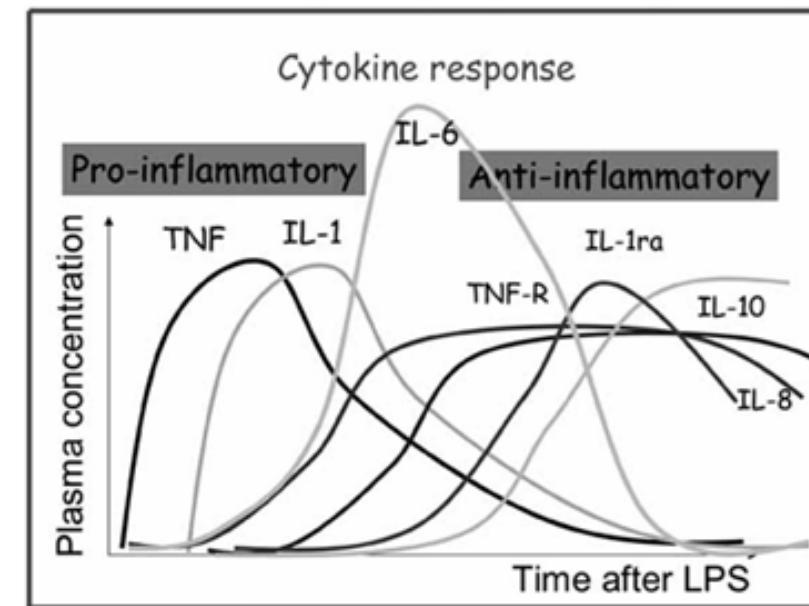
Utilizzata anche per riparare i tessuti

Inflammatory cascade:

Pro- and anti-inflammatory Modulate from APR to CPR

APR: Acute Phase Reaction

CPR. Chronic Phase Reaction



- The Pro-Inflammatory Cytokines produce necrosis
- The Anti-inflammatoty Cytokines rebuild tissues

In CNS:

- The Pro-inflammatory cytokines inhibit synaptogenesis and neurogenesis,
- The Anti-inflammatory cytokines restart Synpatogenesis and neurogenesis processes

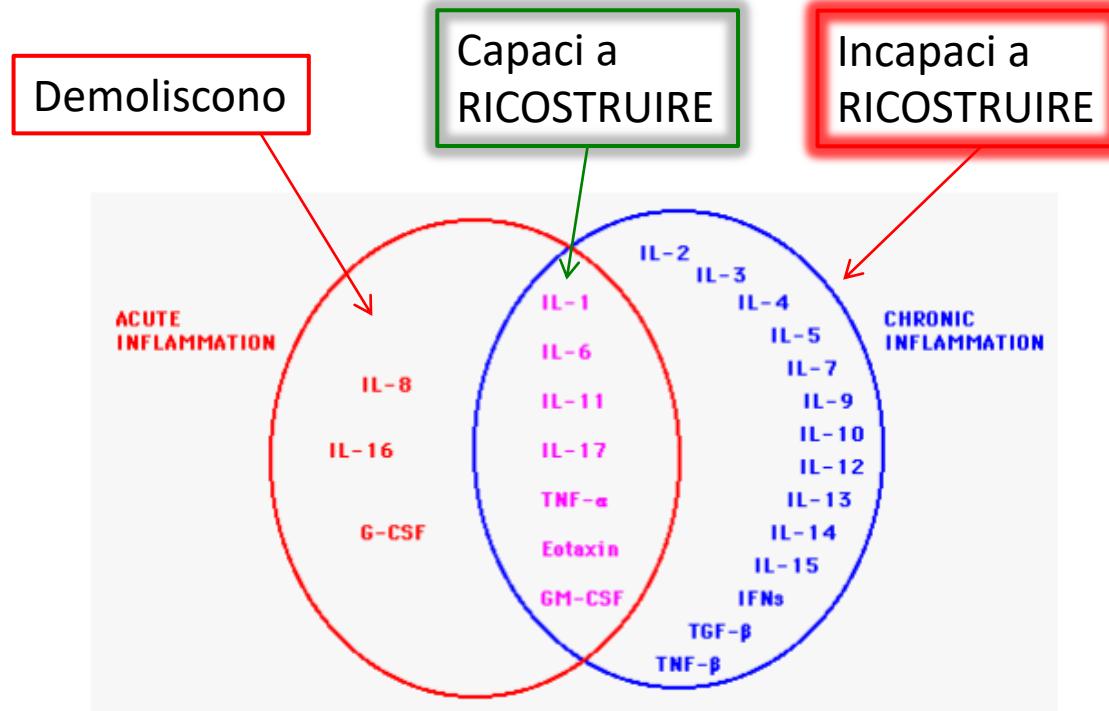


FIGURE 1: Cytokines involved in acute and chronic inflammatory responses.

In Chronic Inflammation are produced different anti-inflammatory cytokines: unable to rebuilt tissues, unble to restart synaptogenesis and neurogenesis processes in CNS

Infiammazione cronica:

- Capaci a demolire
- Incapaci a ricostruire

La madre di tutte le patologie

***Stig Bengmark, Acute and “chronic” phase reaction - a mother of disease.
Clinical Nutrition (2004) 23, 1256–1266***



Contributions of peripheral inflammation to seizure susceptibility: Cytokines and brain excitability

Kiarash Riazi*, Michael A. Galic, Quentin J. Pittman

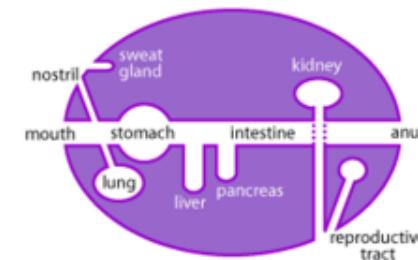


Figure 1: Schematic diagram of the mucous membranes of the body and surfaces with which they are in contact.

K. Riazi et al.

- Chronic Inflammation is able to migrate from intestine to other tissues.
- It starts to repair tissues but it is able only to demolish them, not to rebuild them.
- In the brain it is able to disconnect bad function neurons, but it is unable to substitute them with good function neurons (synaptogenesis) or to realize new neurons (neurogenesis)

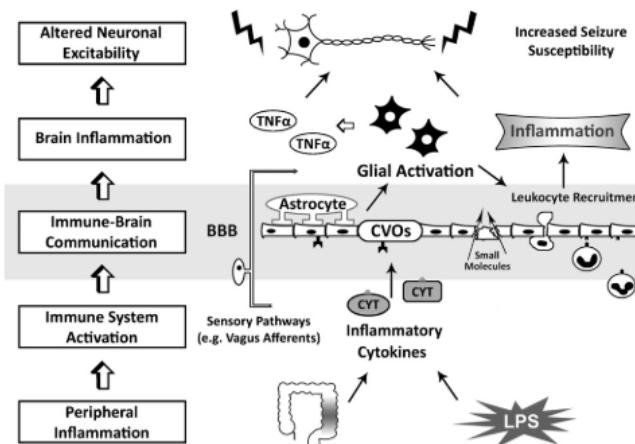


Figure 1 Schematic representation of the hypothetical cascade of events through which peripheral inflammation results in increased seizure susceptibility. Activation of a peripheral immune response, either by colitis or LPS, leads to increased cytokine signalling through neuronal or humoral routes triggering an inflammatory response within the CNS. This mirrored inflammation is likely mediated by cytokines (TNF α), along with interactions between leukocytes and glial cells across the blood–brain barrier. The culmination of an activated immune response within the brain may result in changes in neuronal excitability and ultimately a pro-convulsive tendency. BBB, blood–brain barrier; CVO, circumventricular organ; CYT, cytokine.

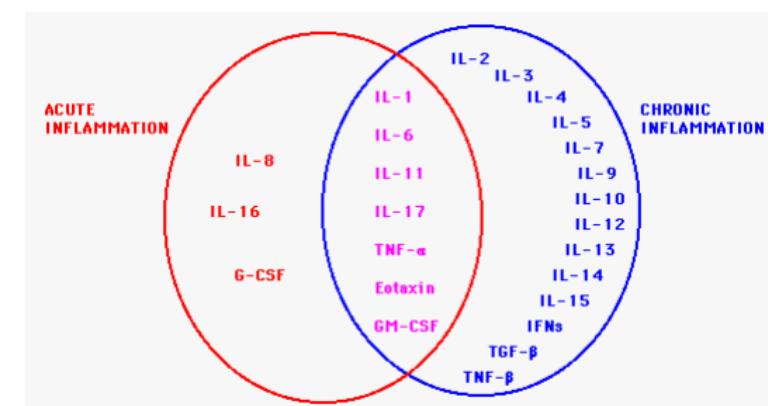
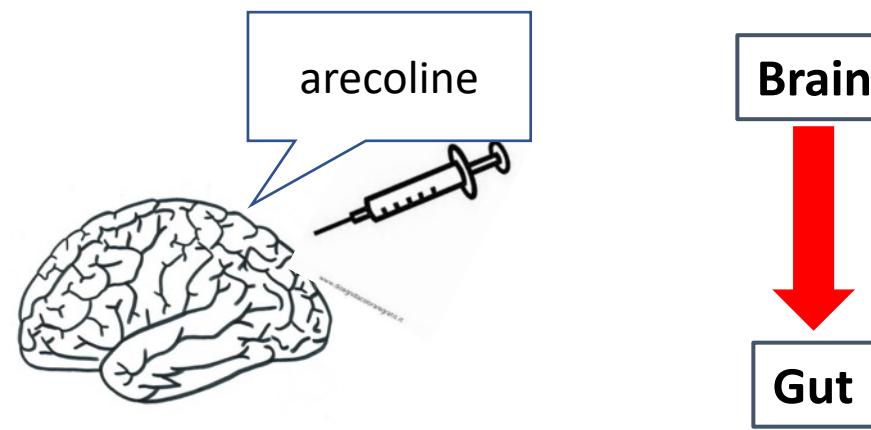


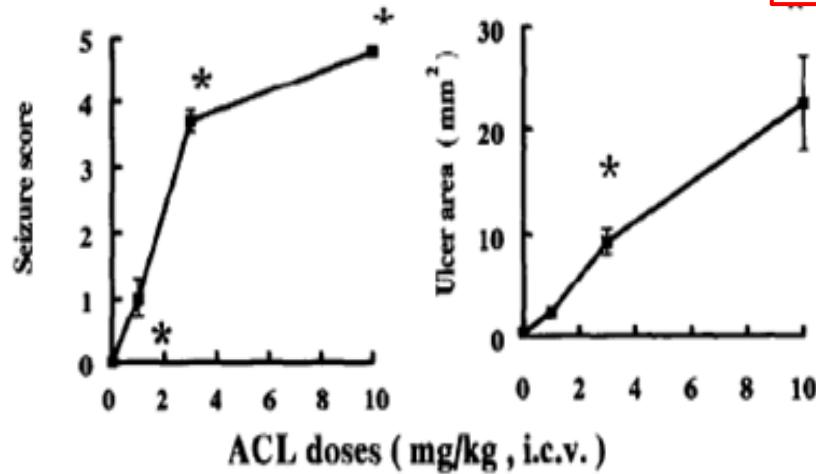
FIGURE 1: Cytokines involved in acute and chronic inflammatory responses.

- The amount of gastric ulcers depend in a dose-dependent manner on the amount of epileptogenic agent injected i.c.v.

Hung CR, Cheng JT, Shih CS. Gastric mucosal damage induced by arecoline seizure in rats. *Life Sci.* 2000 May 5; 66 (24): 2337-49.

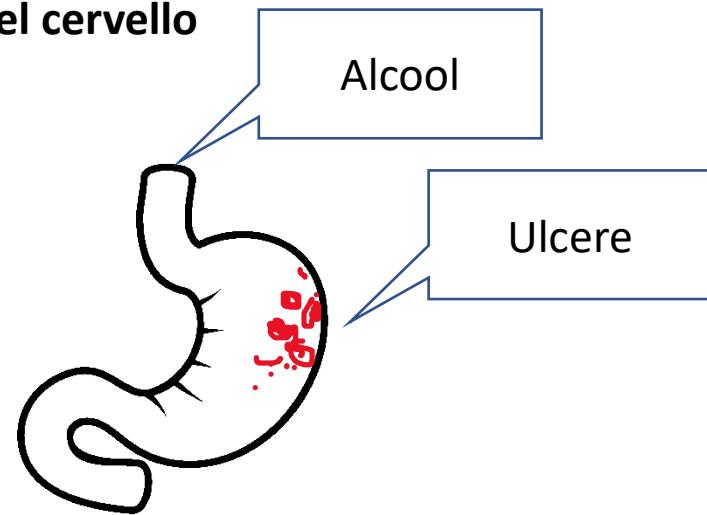


A.Vezzani (Mario Negri): L'infiammazione cerebrale è la causa fisiopatologica dell'epilessia.



La quantità di ulcere gastriche prodotte da alcool, dipendono in modo dose dipendente dalla quantità di agente epilettogeno iniettata nel cervello

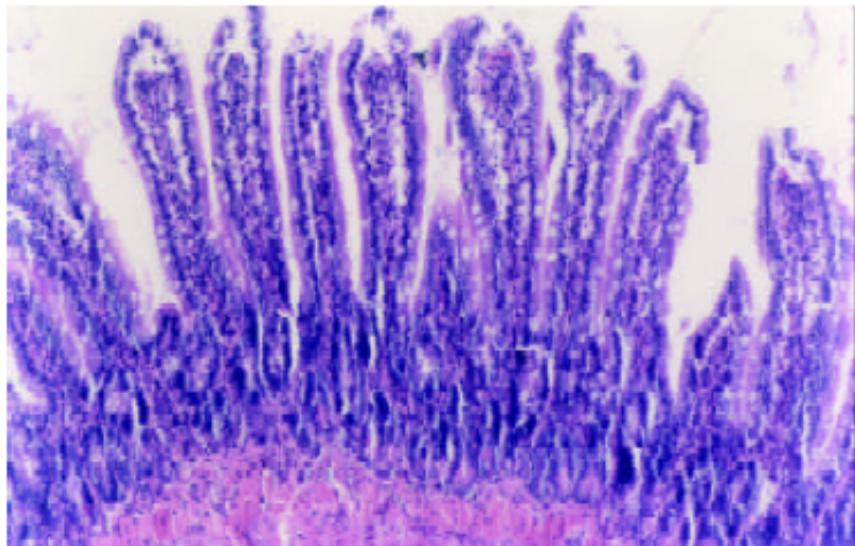
- ✓ più dose nel cervello (icv)
- ✓ più crisi epilettiche
- ✓ più ulcere gastriche



Brain

Gut

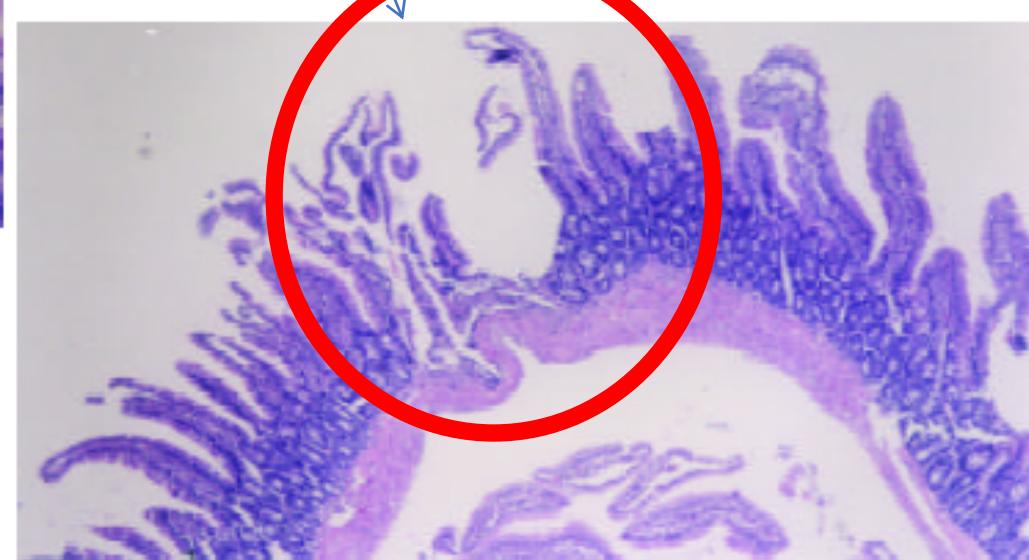
3 days after TBI collapses the intestinal membrane



Before TBI

DANNI ANATOMICI

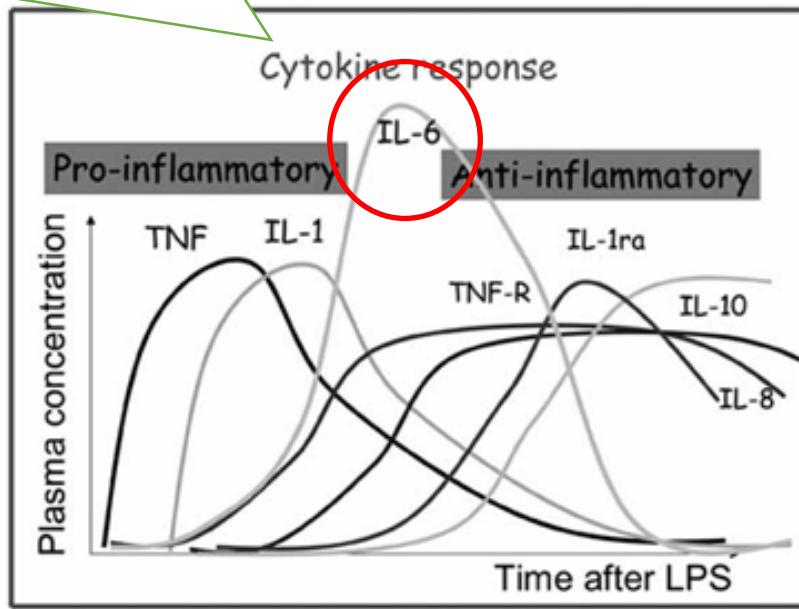
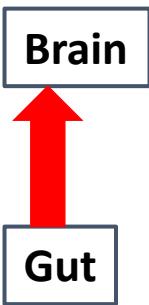
Intestinal mucosa



3 days After TBI

Una infiammazione cronica rallenta la velocità di formazione delle TJs

IL-6 Insiste nel chiamare le corrette citochine anti-infiammatorie,
se è elevata significa che non sono prodotte



Produce danni neuroanatomici

IL-6 elevation in the brain is involved in the mediation of autism-like behaviors through impairments of neuroanatomical structures and neuronal plasticity

Wei H, Alberts I, Li X. Brain IL-6 and autism. Neuroscience. 2013 Nov 12;252:320-5.

Danni di struttura come quelli provocati nell'intestino da trauma cranico

L'INFIAMMAZIONE CRONICA DANNEGGIA I TESSUTI

Tessuto muscolare:

- Nei topi (MCP-1 -,-), privati del gene che codifica una citochina, si ha una minore rigenerazione tissutale dopo trauma muscolare.

Shireman PK, Contreras-Shannon V, Ochoa O, Karia BP, Michalek JE, McManus LM. MCP-1 deficiency causes altered inflammation with impaired skeletal muscle regeneration. *J Leukoc Biol.* 2007 Mar;81(3):775-85.

Tessuto cerebrale:

- **IL-6 inibisce neurogenesi nell'ippocampo**

L'infiammazione cronica inibisce neurogenesi...

Monje M, Toda H, Palmer T (2003) Inflammatory blockade restores adult hippocampal neurogenesis. *Science* 302:1760–1765

- **Elevate IL-1, IL-6 come fattore di rischio patologie mentali e neurologiche.**

L'infiammazione cronica fattore di rischio ...

Zubarev OE, Klimenko VM. [Elevation of proinflammatory cytokines level at early age as the risk factor of neurological and mental pathology development]. *Ross Fiziol Zh Im I M Sechenova.* 2011 Oct;97(10):1048-59.

- **IL-6: meccanismo patogenetico autismo.**

L'infiammazione cronica patogenetica dell'autismo...

Wei H, Alberts J, Li X. Brain IL-6 and autism. *Neuroscience.* 2013 Nov 12;252:320-5.

IL-6 elevation in the brain is involved in the mediation of autism-like behaviors through impairments of neuroanatomical structures and neuronal plasticity

Elevati livelli di IL-6 indicano una risposta infiammatoria cronica,

incapace e a produrre le corrette citochine anti-infiammatorie.

L'infiammazione è l'arte di riparare e rigenerare i tessuti.

L'infiammazione CRONICA è la MADRE di TUTTE le PATOLOGIE

*Stig Bengmark, Acute and “chronic” phase reaction - a mother of disease.
Clinical Nutrition (2004) 23, 1256–1266*

È orchestrata dal microbiota:

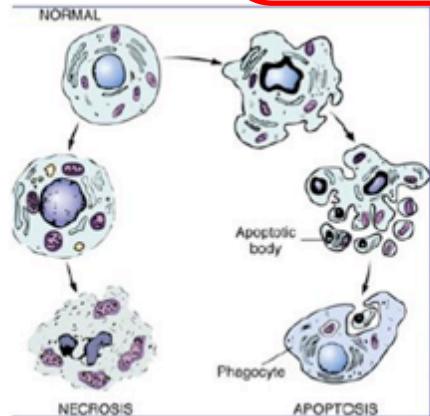
- ✓ **Microbiota forte:** risposta infiammatoria **abile** a riparare
- ✓ **Microbiota debole:** risposta infiammatoria **non abile** a riparare

- **Citochine partecipano allo sviluppo neuronale al funzionamento cerebrale.**
Una inappropriata attività può produrre diversi sintomi neurologici

Goines PE, Ashwood P. Cytokine dysregulation in autism spectrum disorders (ASD): possible role of the environment. Neurotoxicol Teratol. 2013 Mar-Apr;36:67-81.

Meccanismi di morte cellulare

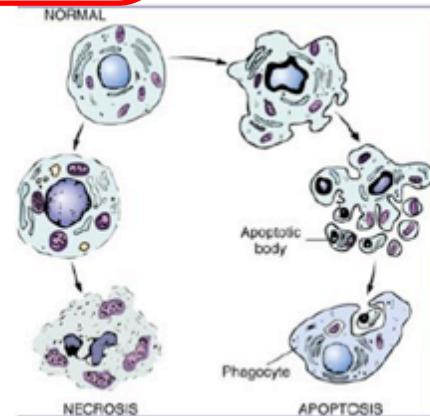
- Apoptosi
 - Morte programmata
 - Contrazione
 - Corpi apoptotici
- Necrosi
 - Morte accidentale
 - Espansione
 - Infiammazione



Meccanismi di morte cellulare

Cytokine-related Mechanisms of Apoptosis

- Apoptosi
 - Morte programmata
 - Contrazione
 - Corpi apoptotici
- Necrosi
 - Morte accidentale
 - Espansione
 - Infiammazione

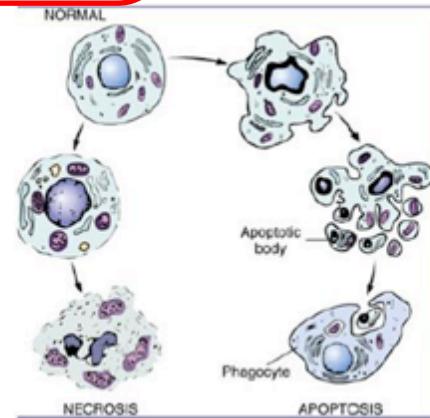


Le citochine INABILI:

- non consentono una corretta rigenerazione cellulare. (**degenerazione**)

Meccanismi di morte cellulare

- Apoptosi
 - Morte programmata
 - Contrazione
 - Corpi apoptotici
- Necrosi
 - Morte accidentale
 - Espansione
 - Infiammazione



Le citochine INABILI:

- non consentono una corretta rigenerazione cellulare. (degenerazione)
- Non eseguono una corretta scrematura dei linfociti-T
- Non controllano la tolleranza dei linfociti B

Patologie autoimmuni: (sistema immunitario impazzito?)

Linfociti T: prodotti casualmente, eliminati il 97% per **apoptosi**

Linfociti B: le **citochine** controllano la tolleranza.

Autoanticorpi= UTILI cacciatori nella caccia di selezione nei parchi naturali



Le citochine riconoscono e gestiscono i nuovi virus:

Le citochine, dette interferoni, possono BLOCCARE la replicazione del virus.



Se diverse da quelle abili: sintomi da lievi a forti, fino al decesso.



Stiamo cercando molecole esogene che facciano quello che le endogene non riescono più a fare.



Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. *J Infect*. 2020;80(6):607-613.



Cytokines called interferons can even interrupt viral replication.

InformedHealth.org [Internet]. Cologne, Germany: Institute for Quality and Efficiency in Health Care (IQWiG); 2006-. The innate and adaptive immune systems.

Host Remodeling of the Gut Microbiome and Metabolic Changes during Pregnancy

Denny Korsen,¹ Julia K. Goodrich,¹ Tyler G. Cullender,² Ayşenur Sipari,^{1,12} Kira Lathimer,^{1,4} Helens Kling Bäckhed,^{6,7} Antonio González,⁸ Jeffrey J. Werner,^{2,12} Largus T. Angenent,² Rob Knight,^{3,10} Fredrik Bäckhed,^{5,7} Erika Isaksson,⁹ Seppo Salminen,⁴ and Ruth E. Ley^{1,2}



Metabolic changes during pregnancy:

- Same nutritional intake
- Increased energy extraction by foods:

Leptin (ng/ml) ^f	30.72 (± 1.83)	37.58 (± 2.47)	0.0008
Cholesterol (mmol/l) ^f	4.76 (± 0.09)	6.37 (± 0.12)	1.72×10^{-33}
Insulin (mU/l) ^f	6.48 (± 0.59)	10.92 (± 0.88)	1.01×10^{-8}
Homeostatic model assessment (HOMA) ^f	1.35 (± 0.12)	2.28 (± 0.19)	1.93×10^{-7}
Quantitative insulin sensitivity check index (QUICKI) ^f	0.39 (± 0.01)	0.35 (± 0.00)	2.39×10^{-9}
Glucose (mmol/l)	4.65 (± 0.03)	4.61 (± 0.05)	0.5799
GHBa1c (%) ^f	5.01 (± 0.03)	5.23 (± 0.03)	9.92×10^{-10}

Cell 150, 470–480, August 3, 2012 ©2012 Elsevier Inc.

- the microbiota undergoes profound changes in T3 vs T1
- It is not due to nourish the fetus, but to realize his tissues by anti-inflammatory cytokines

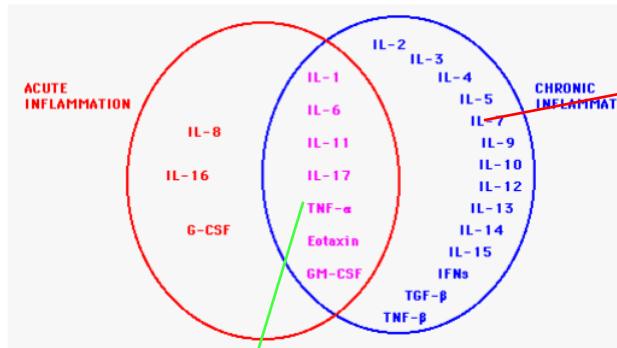


FIGURE 1: Cytokines involved in acute and chronic inflammatory responses.

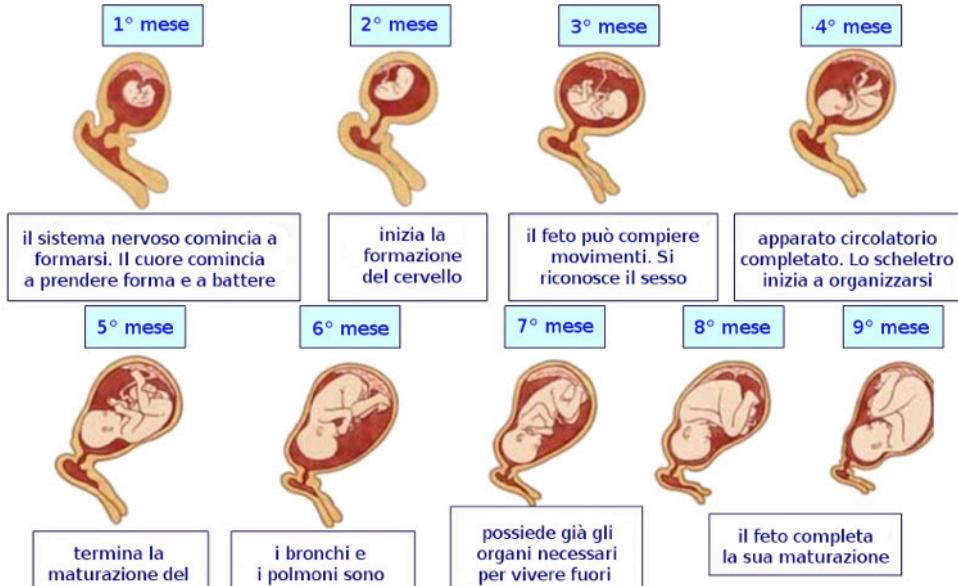
No-problems

Houston, we have a problem!



Ricavare più energia dal cibo per
REALIZZARE i tessuti del feto, attraverso
citochine anti-infiammatorie.

PROGRAMMA DI MATURAZIONE FETALE



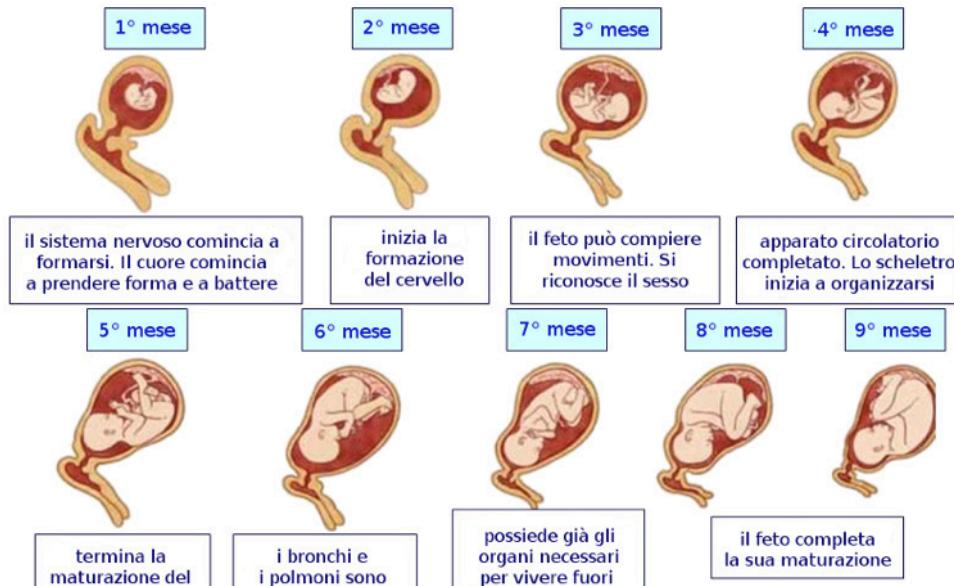
La forza del microbiota della mamma determina la capacità di seguire le fasi dello sviluppo fetale

La forza del microbiota del neonato determina la capacità di seguire le fasi dello sviluppo post-natale

PROGRAMMA DI MATURAZIONE POST-NATALE



PROGRAMMA DI MATURAZIONE FETALE



the neonatologist, and then the pediatric neurologist, must know the entire clinical history of the child.

Non ci possono essere protocolli comuni di svezzamento, terapeutici e vaccinali.

PROGRAMMA DI MATURAZIONE POST-NATALE



Indici di fattori di rischio:

- Parti podalici
- Parti prematuri
- Aborti spontanei
- Precedenti Infertilità
- ...

Il corpo microbico si evolve nei primi 1000 giorni di vita, aumenta la biodiversità dei ceppi

Tende a diventare simile a quello della mamma a T1, non a T3 , ossia a quello «forte», se fosse stato debole, la mamma sarebbe stata infertile.

Con parto cesareo e troppo medicalizzato possiamo impedirlo

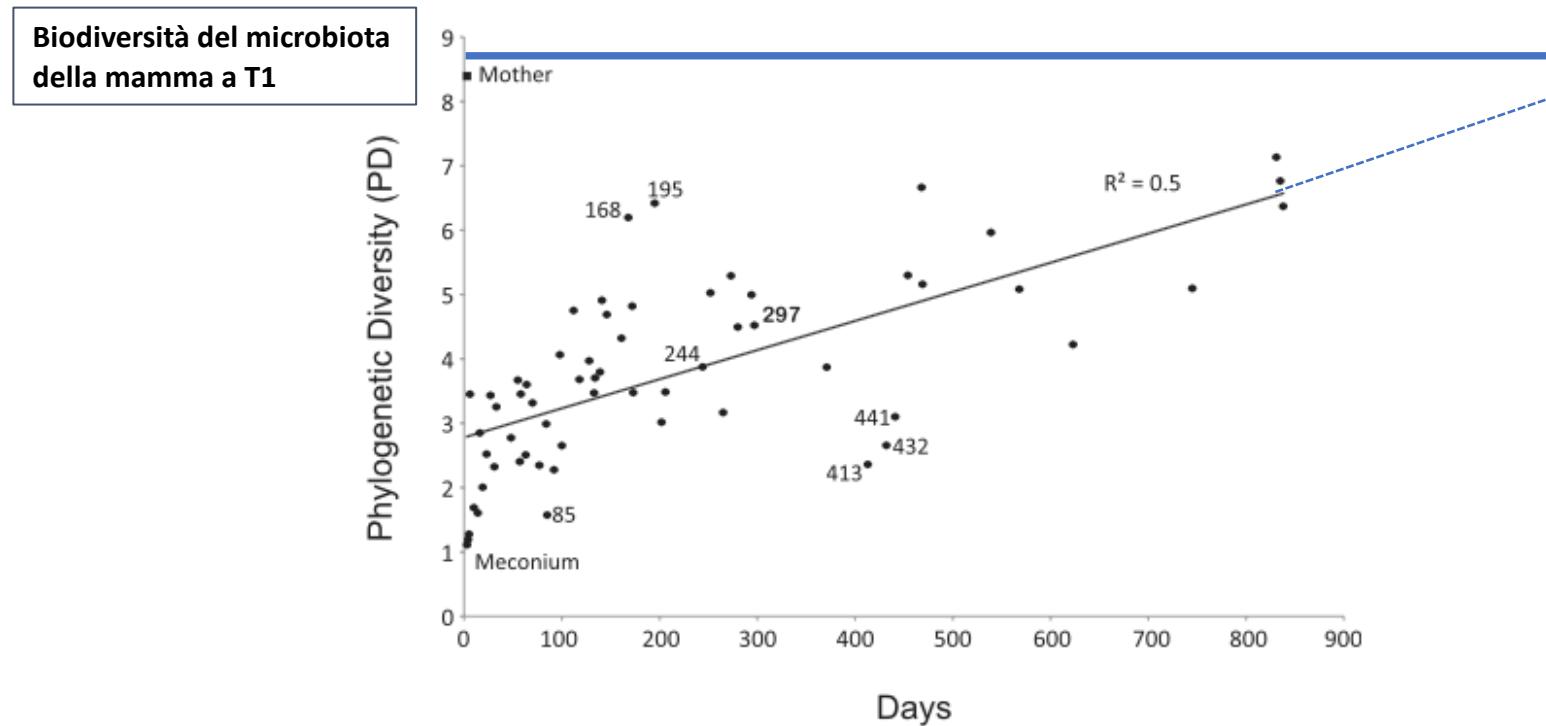
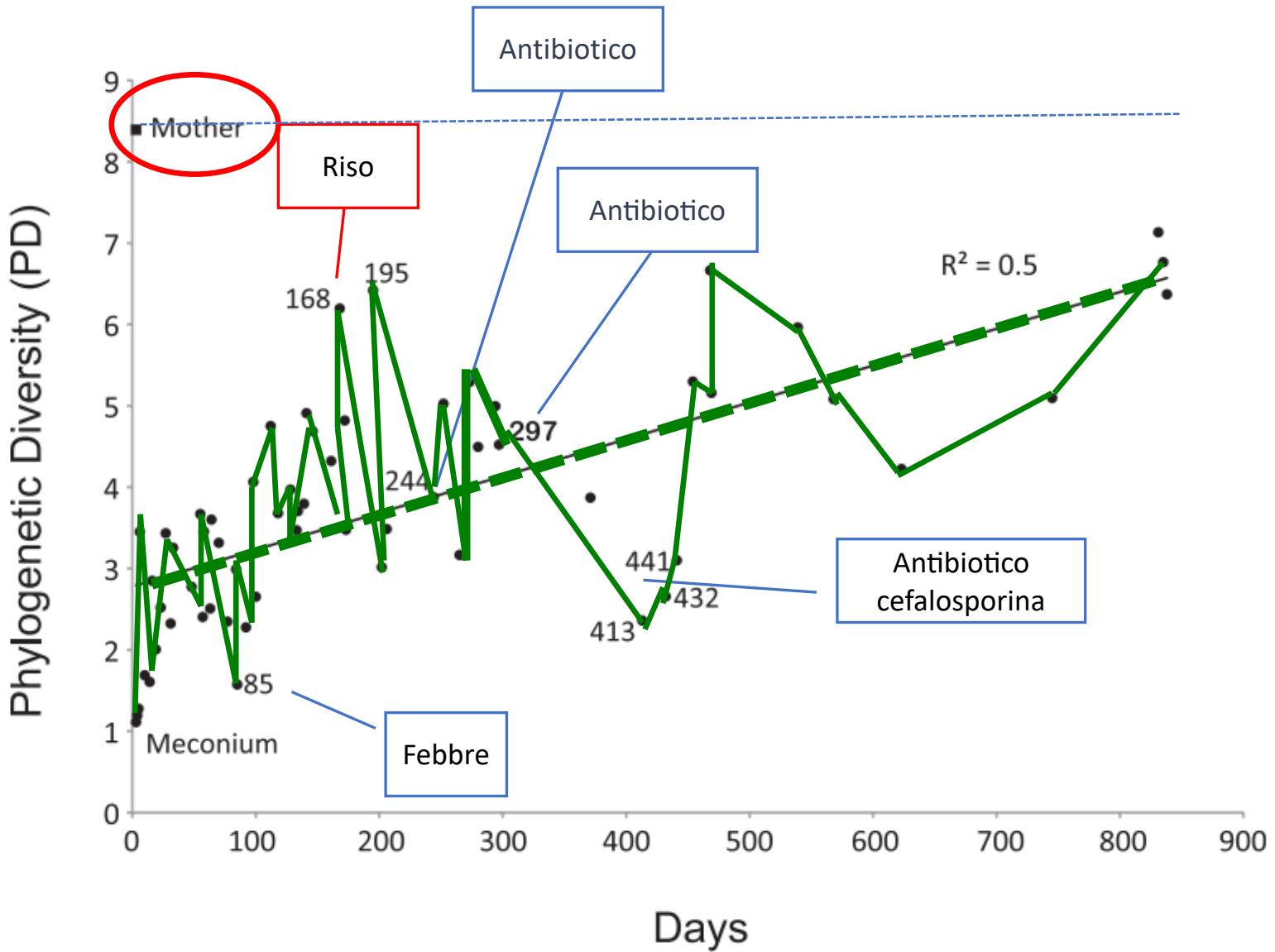


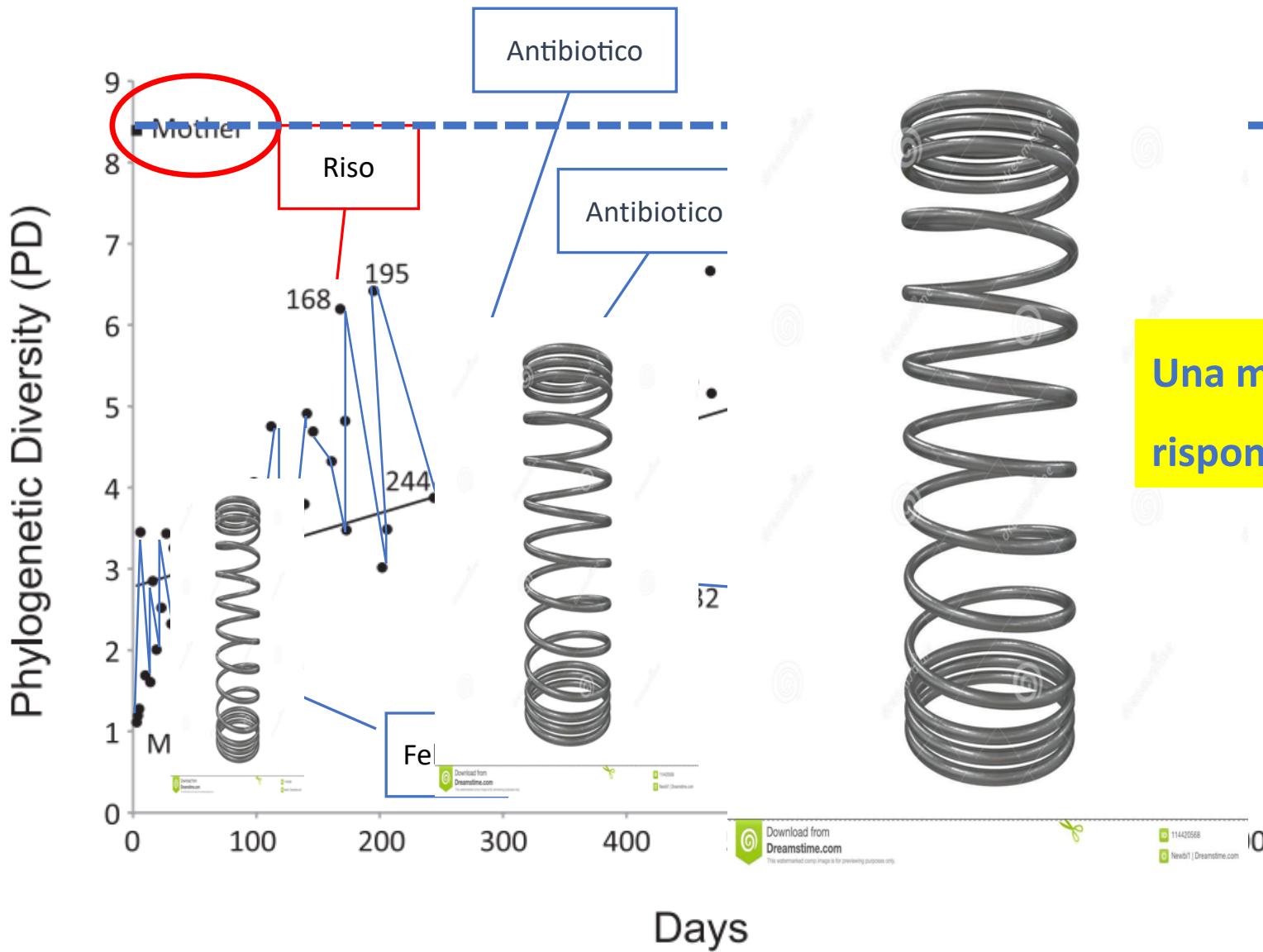
Fig. 1. Bacterial PD of the infant gut microbiota over time. PD provides a measure of the diversity within a community based on the extent of the 16S rRNA phylogenetic tree that is represented by that community. Symbols are fecal samples. The mother's fecal sample, collected at day 3, is denoted as a filled square.

Non è sempre positivo assomigliare alla mamma. Dipende...



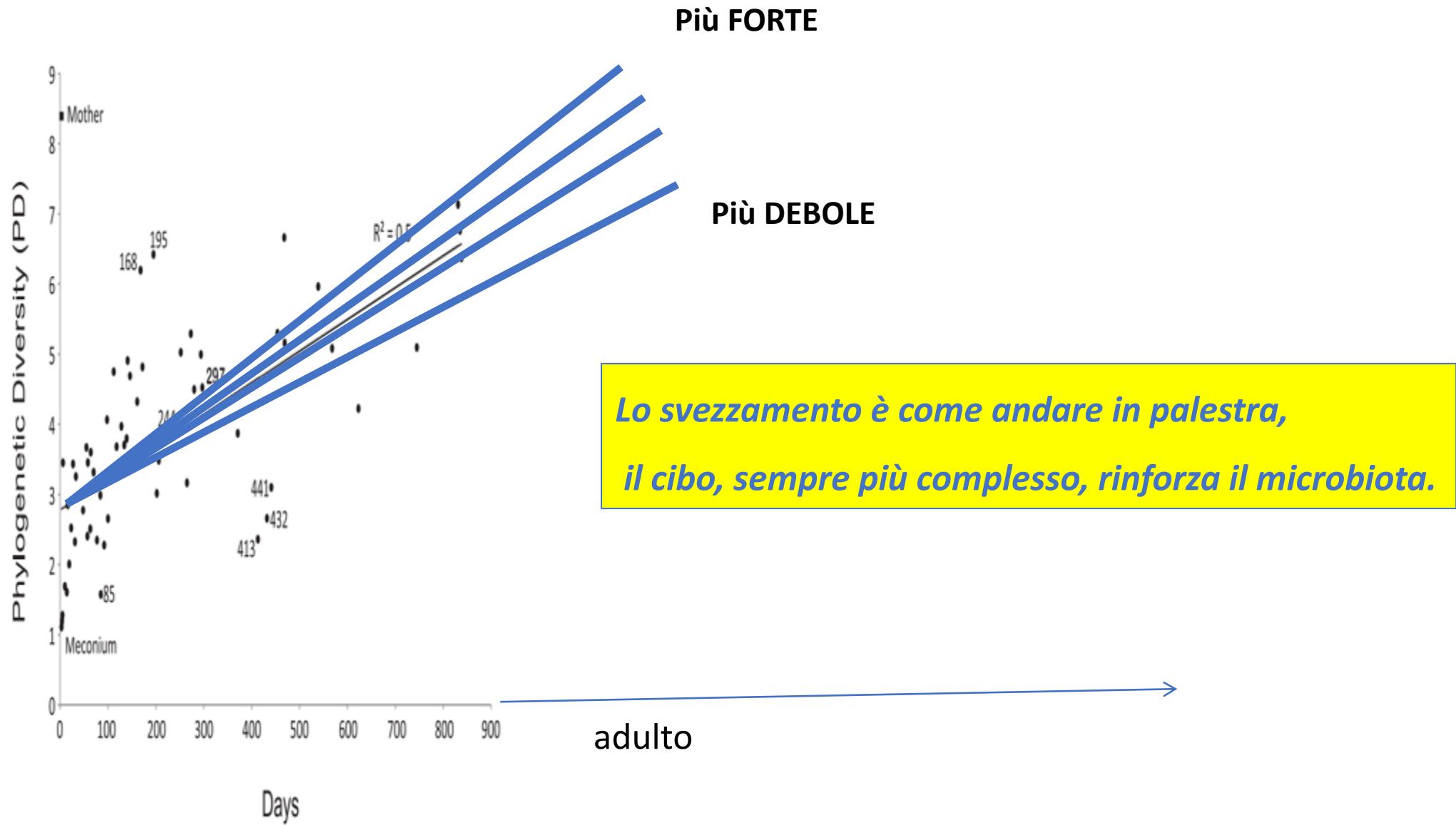


Jeremy E. Koenig et al. Succession of microbial consortia in the developing infant gut microbiome Proceedings of the National Academy of Sciences Mar 2011, 108 (Supplement 1) 4578-4585;



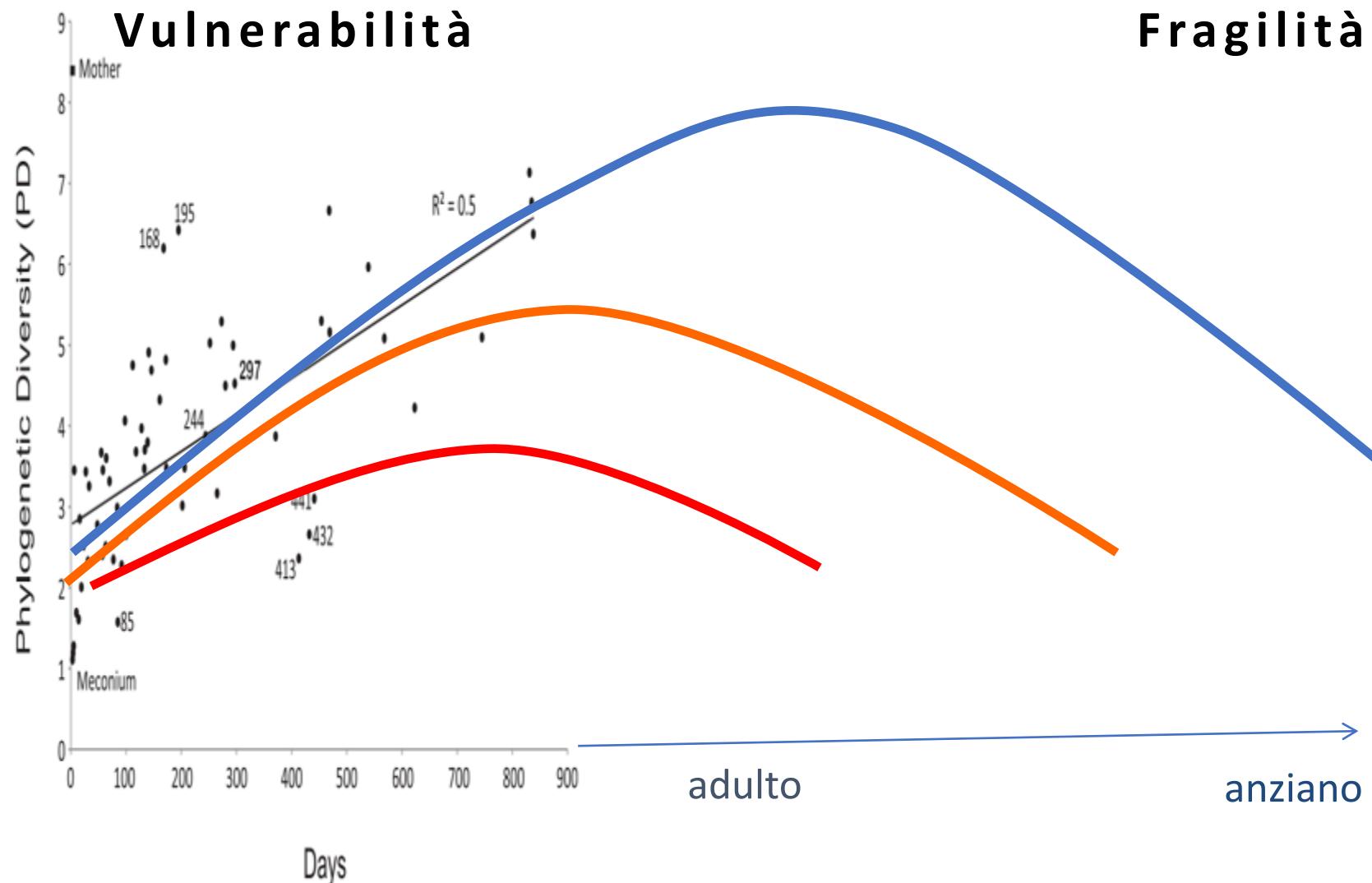
Una molla che si rinforza
rispondendo alle stimolazioni

Jeremy E. Koenig et al. Succession of microbial consortia in the developing infant gut microbiome Proceedings of the National Academy of Sciences Mar 2011, 108 (Supplement 1) 4578-4585;



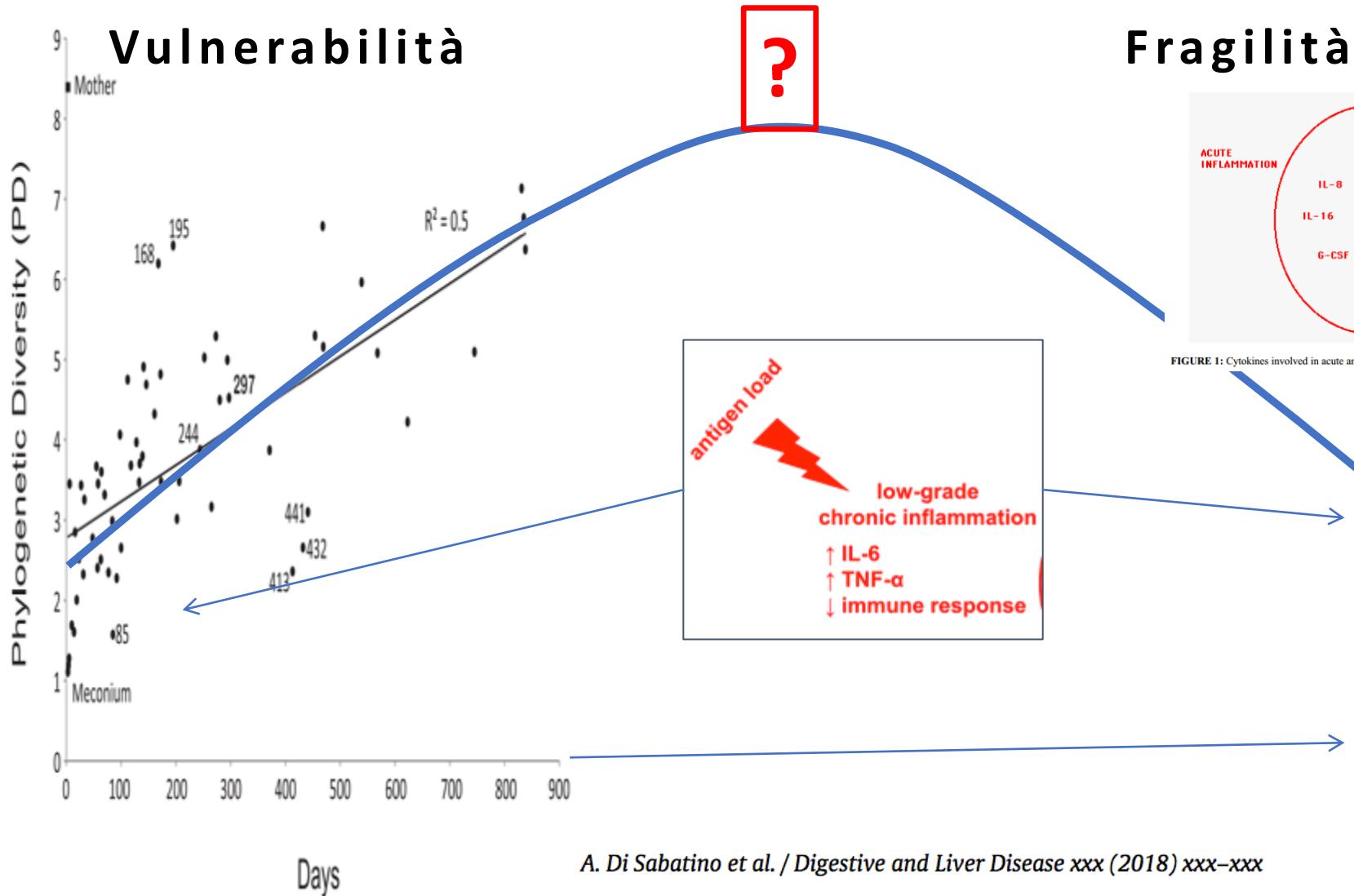
Invecchiando si torna bambini.

Si riduce la biodiversità dei ceppi batterici.



Alla bassa biodiversità dei ceppi corrisponde una risposta infiammatoria cronica.

Quando iniziamo ad invecchiare?



Ridotta diversità dei ceppi batterici= ridotta capacità a:

- riparare i danni, rigenerare i tessuti,
- scremare linfociti T, a controllare la tolleranza dei linfociti B
- controllare funzionamento organi, i parametri vitali,
- gestire nuovi virus,
- riparare il DNA.
- ...

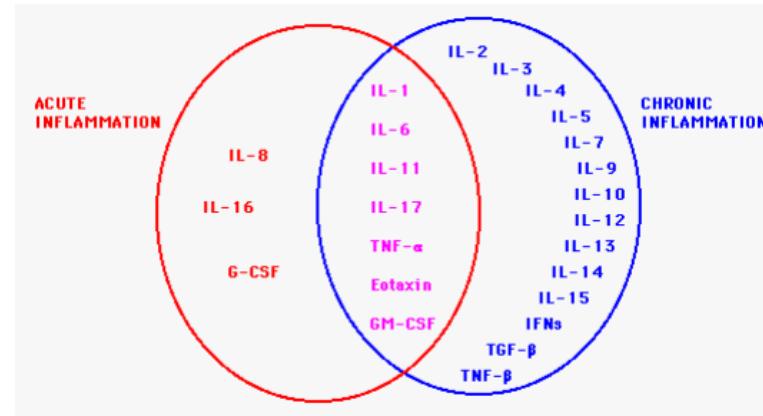
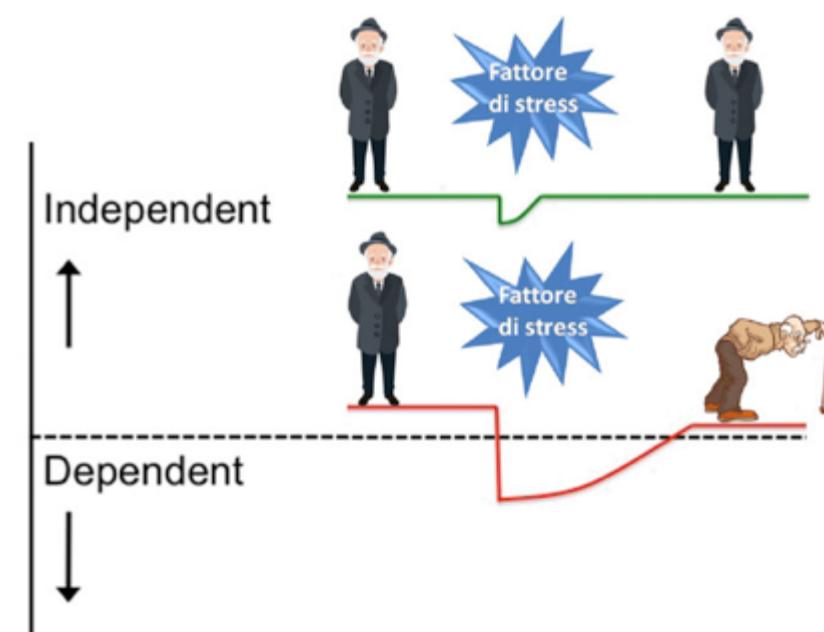
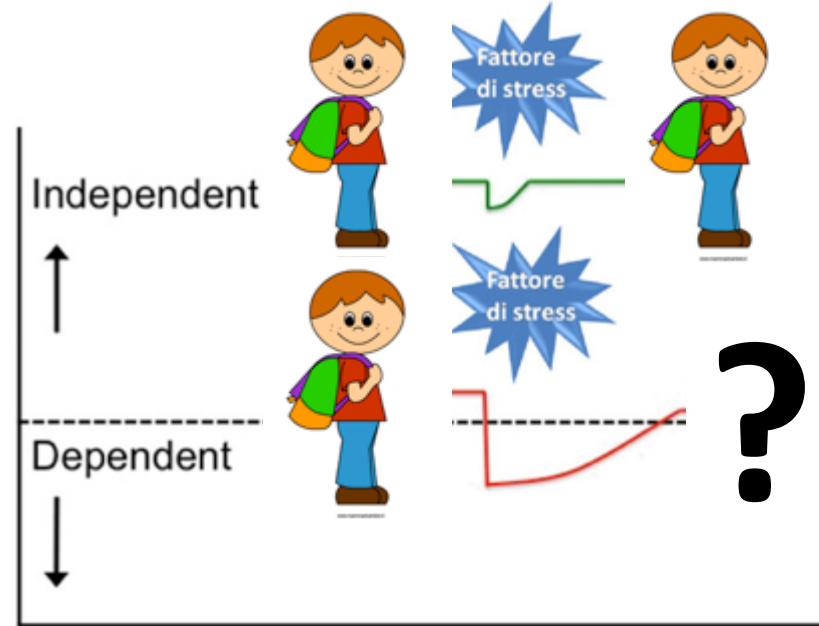


FIGURE 1: Cytokines involved in acute and chronic inflammatory responses.

Le recenti acquisizioni sul microbiota modificano anche concetti della nutrizione.

Caloria alimentare= calore emesso da 1 g di cibo quando bruciato.

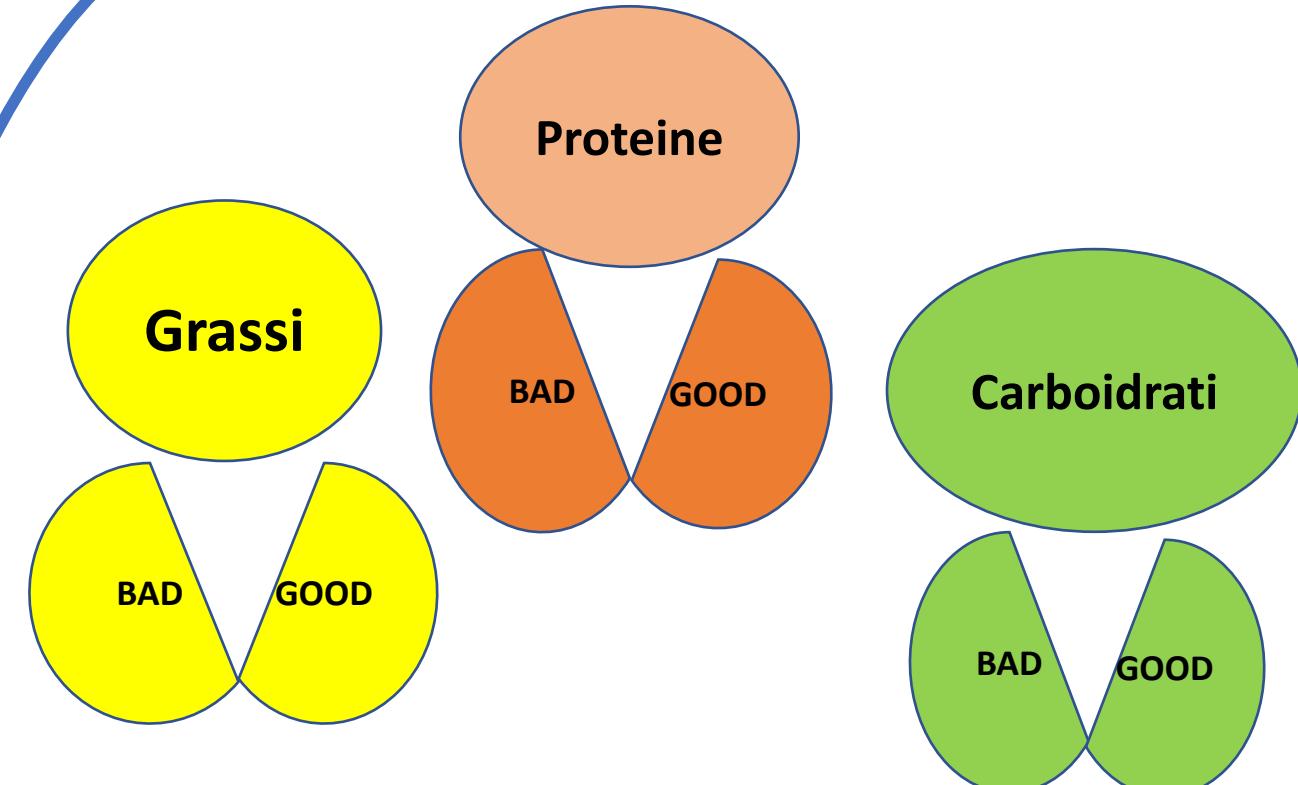
ALIMENTI (VALORI NUTRIZIONALI PER 100 G)	Kcal	proteine (g)	grassi (g)	carbohidrati (g)
Latte intero	64	3,3	3,6	4,9
Latte addensato semiscremato	46	3,5	1,5	5
Yogurt intero	89	3,8	1,9	6,3
Yogurt semiscremato	70	3,8	1,2	5,2
Yogurt magro alla frutta	53,5	4,4	0,1	7,46
Yogurt ai cereali	113	3,01	3,5	16,5
Succo di Frutta	55	0,3	9,1	14,5
Frutta e legumi	39	1,5	0,1	27
Marmellata	242	0,1	0	18,7
Zucchero	392	0	0	104,5
Pasta	214	0,6	0,6	89,3
Biscotto fruttato	429	2,2	21,2	23,7
Biscotto secco	41	0,9	7,9	29,8
Brioches	356	5,3	20	38
Pretzel integrali	375	14,2	1,0	82
Wursti	364	9,7	6	72,2
Pasta integrale	213	2,9	2,9	72,2
Pasta	333	10,9	1,6	79,1
Riso	312	8,7	0,4	88,6
Patate	85	2,1	1	17,9
Cottura (valori medi)	17,7	25,63	3,83	3,06
Proteine animali (med.)	9,1	21,7	1,7	1,7
Uova gallina intere (60g)	126	12,4	8,7	0
Salumi (valori medi)	141,6	27,39	6,34	0,2
Prosciutto cotto agroalimentare	112	23,2	4,6	0
Prosciutto cotto agroalimentare	147,9	28,03	7,9	0
Formaggio fresco (valori medi)	37,13	29,95	21,35	1,05
Granella pane (100g)	392	33	28	0
Ricotta vacche	146	8,8	10,8	5,5
Mozzarella	133	10,8	19,4	0,2
Scamorza	37	9,7	25,4	1
Frutta (valori medi)	35,39	0,68	0,18	8,28
Vermute (valori medi)	20,13	1,74	9,2	3,01
Legumi secchi (valori medi)	243,7	22,09	2	49,16
Legumi verdi (valori medi)	118,7	17,7	1,7	7,46
Olio di semi extravergine	819	0	57,9	0
Burro	358	0,9	83,46	1,14



NON SIAMO STUFE CHE BRUCIANO IL CIBO!!!

Diete espresse in

x% Proteine, y% Carboidrati, z% Grassi

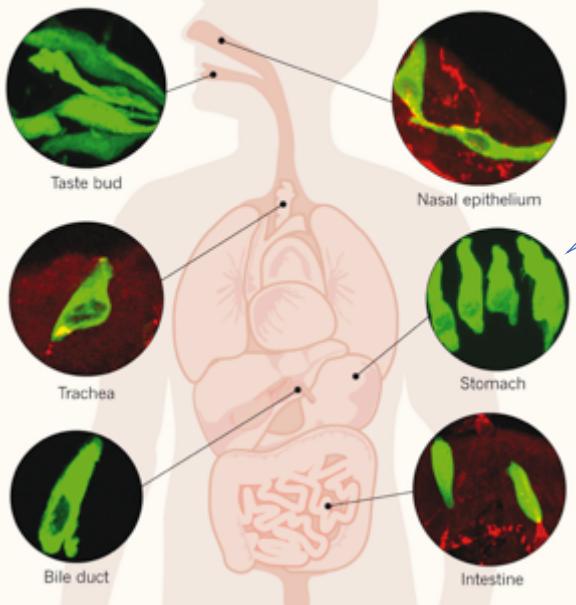


All'interno di ogni classe, cibi facili, difficili, utili,...!!!

Recettori del gusto in tutto il digerente, non solo sulla lingua.

TASTE CIRCUITS

Cells with taste receptors are found throughout the body (shown in green)¹⁰. Along the digestive tract, their presence is probably related to food. But in bile ducts — that carry only secretions produced by the body — their purpose is more enigmatic.



T1R3 receptors secrete ghrelin, **encouraging eating** when important nutrients are available .

The sweet receptor on L cells produce the gastrointestinal incretin hormone GLP-1, which stimulates insulin production and sends a satiety signal to the brain

Jang,H.J.et.al.Proc.NatlAcad.Sci.USA104, 15069–15074 (2007).

Il cibo è riconosciuto in base al gusto.

**Il microbiota decide cosa dobbiamo mangiare
e come trasformarlo.**

Ci incoraggiano a mangiare se c'è cibo "buono" (Proteine e carboidrati),
ma se ingeriamo carboidrati indigeribili, questi, poi, ci danno senso di sazietà.

Margolskee, R. F. et al. Proc. Natl Acad. Sci. USA 104, 15075–15080 (2007).

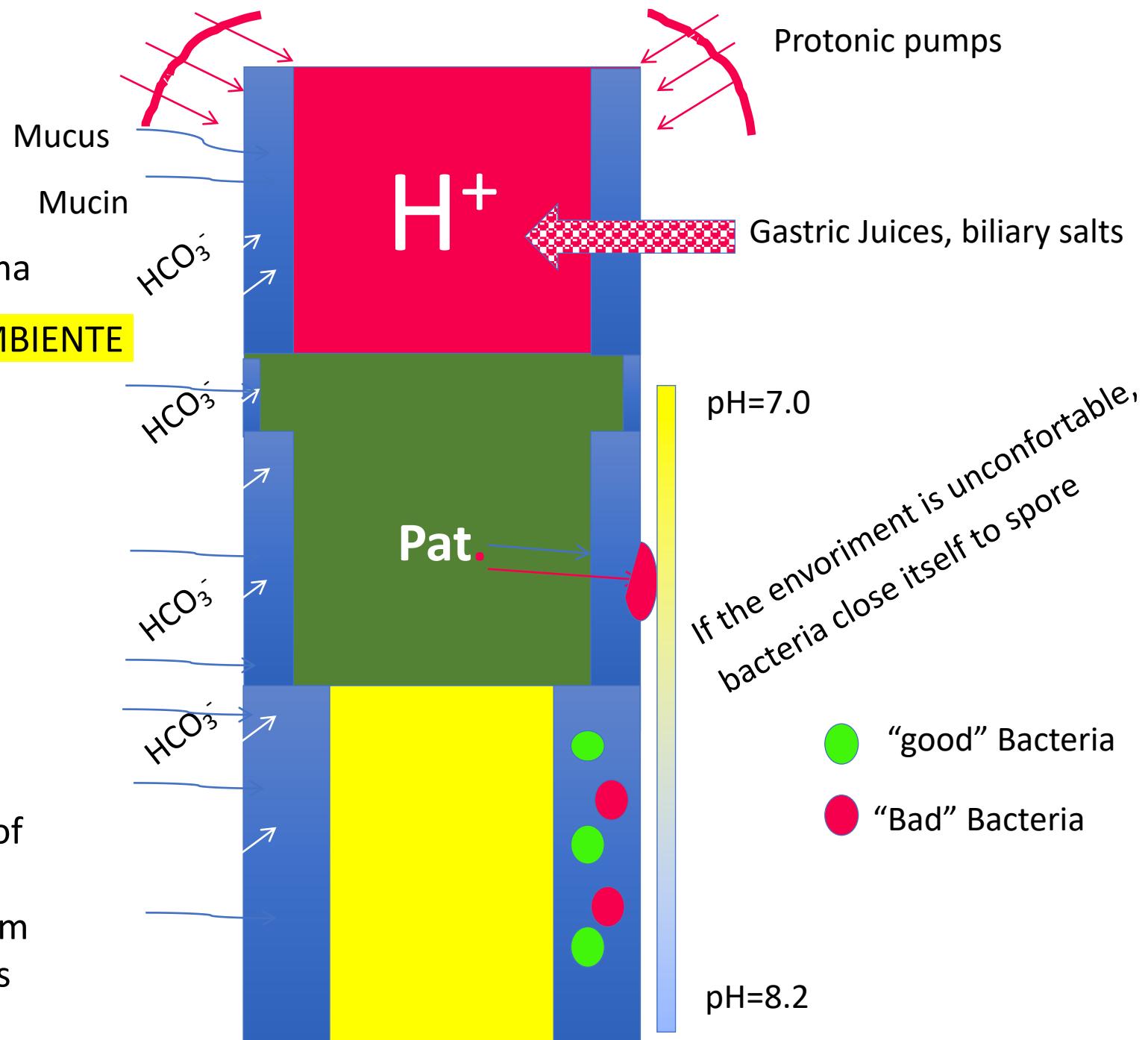
Compito principale del sistema

digerente: PROTEGGERE L'AMBIENTE

dove vive il microbiota.

SCFAs:

The nutrients of
the cells of
digestive system
of all mammals



Un ambiente confortevole permette una elevata diversità filogenetica dei ceppi batterici:

- Per mantenerlo le cellule del sistema digerente devono essere:
 - **nutrite**: grassi saturi e/o SCFAs (burro)
 - il sistema digerente deve essere **stimolato** con il cibo.
- Per ripristinarlo può essere utile stimolarlo con la stessa sieroproteina che, nel colostro, ha il compito di attivarlo: **l'Alfa-lattoalbumina (*)**

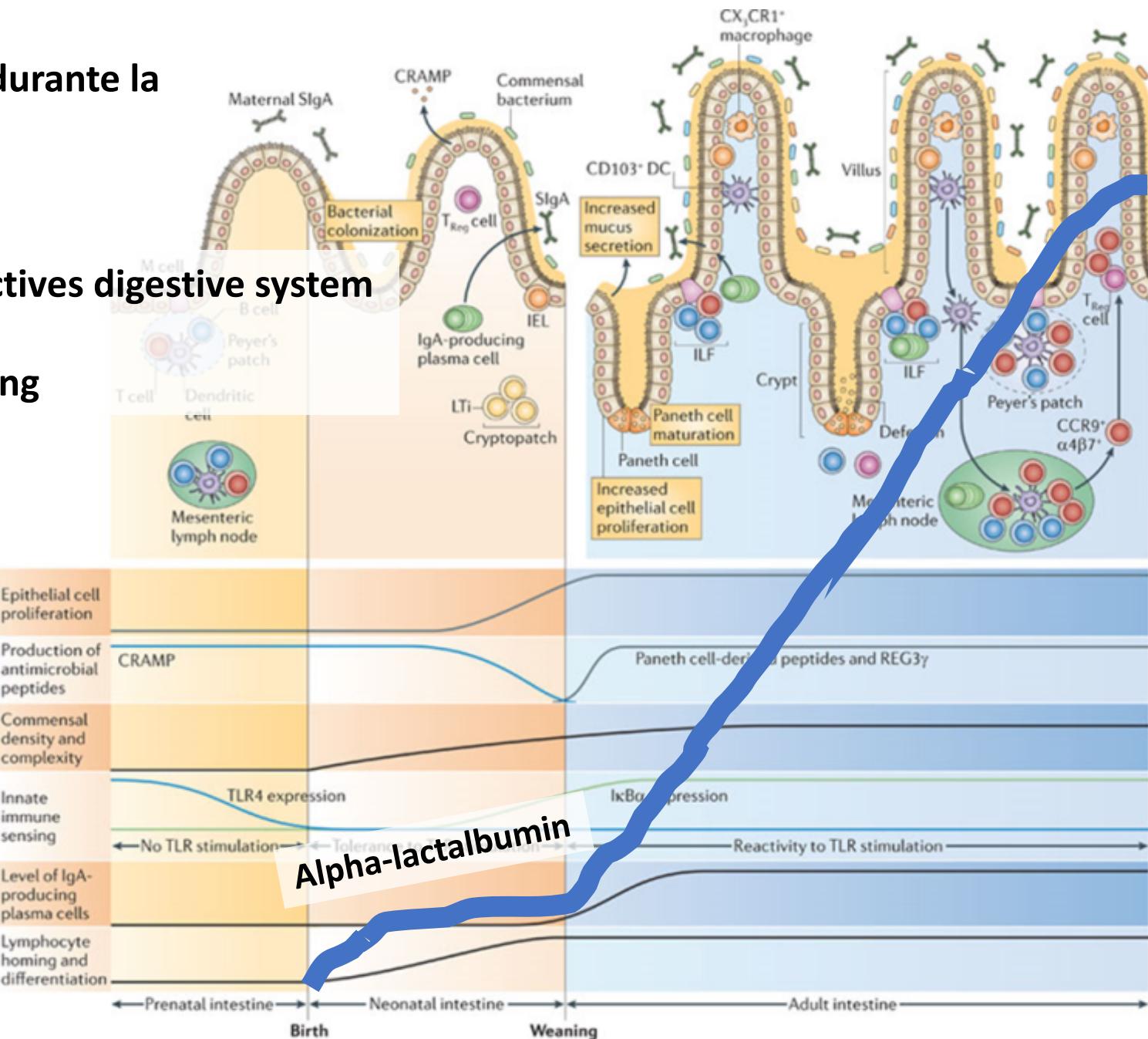
(*) Scelta in base alla sua capacità di aumentare la sintesi cerebrale di serotonina.

Choi et al. Dimostrano che assunzioni orali aumentano da 3 a 5 volte la velocità di sintesi cerebrale di serotonina, neurotrasmettore che controlla la SOGLIA DEL DOLORE.

Il sistema digerente non ha mai funzionato durante la vita fetale

Alpha-lactalbumin in human colostrum actives digestive system

Prepare it to became strong during weaning





Alpha-lactalbumin in epilepsy

Preclinical activity profile of α -lactalbumin, a whey protein rich in tryptophan, in rodent models of seizures and epilepsy

Rita Citraro¹, Francesca Scicchitano¹, Salvatore De Fazio¹, Riccardo Raggio², Paolo Mainardi³, Emilio Perucca⁴, Giovambattista De Sarro^{1*}, Emilio Russo¹.

Main results:

- Repeated daily administrations are needed
- It is able to control both types of seizures induced by **Pilocarpine (*)**



Neuroscience 226 (2012) 282–288

PROTECTIVE ACTIVITY OF α -LACTOALBUMIN (ALAC), A WHEY PROTEIN RICH IN TRYPTOPHAN, IN RODENT MODELS OF EPILEPTOGENESIS

E. RUSSO,^{1,2*} F. SCICCHITANO,^{1*} R. CITRARO,^{1*} R. AIELLO,¹ C. CAMASTRA,¹ P. MAINARDI,³ S. CHIMIRRI,¹ E. PERUCCA,⁴ G. DONATO¹ AND G. DE SARRO¹

More than 400 animals, experimental models:

- GEPR-9 rats
- Pilocarpine
- MES test
- WAG Rij rats

- Adiogenic mice: after 3 weeks of daily administrations, the seizures control last for at least one month since the end of treatment..

(*) Mainly for this result, ALAC entered in the NIH new drug program screening



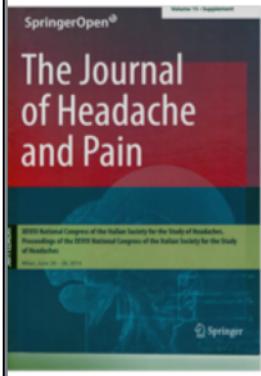
Master in "NUTRIZIONE CLINICA"

Alpha-lactalbumin in autism

Alpha-lactalbumin is reported in a Thesis of Master of Nutrition on the basis of results on autism.

ASSE INTESTINO-CERVELLO E PATOLOGIE COLLEGATE:
L'importanza dell'alimentazione e dell'integrazione prebiotica e probiotica per la riduzione dei sintomi nei bambini affetti da disturbo dello spettro autistico

Candidato:
DR. ANDREA TOLLETO
Relatore:
PROF. CARMELLO RIZZO



The Journal of Headache and Pain

Volume 15 • Supplement
2010 National Congress of the Italian Society for the Study of Headaches
Proceedings of the 2010 National Congress of the Italian Society for the Study of Headaches

Introduction The aim of the present study was to assess the frequency of dietary supplement of α -lactalbumin with POC and its relationship with headache frequency, severity and grade of disability related to migraine, as well as the degree of children affected by migraine, in a sample of children affected by migraine (27 males). In 10 years aged between 6.97 ± 1.97 years consecutively referred to the Headache Center of the Child and Adolescent Neurology-Pain Clinic of the National University of Naples. The monthly migraine frequency was assessed from daily headache diary kept by all the children. Migraine intensity was assessed on a VAS (visual analog scale), and grade of disability was assessed according to the International Headache Society (IHS) questionnaires. The whole population was assessed according to the Bristol Stool Chart in order to define the presence of constipation or diarrhea. The aim of the present study is to verify inflammatory indices such as CRP and CEF. All parameters were measured at the beginning of the study (75 children). Results: The mean age of the children was 7.01 ± 1.97 years. Migraine prevalence was 70%. Black children showed normal values of all inflammatory indices examined (CEP, mean 13.0 ± 4.8 mm, CEF 12.9 ± 4.8 mm) (n.s.) and no significant differences between the two groups (CEP, p = 0.10; CEF, p = 0.12 mmgl, p = 0.14).

Other 7 months of treatment, 11 children had painless diarrhea (mean 13.0 ± 4.8 mm, CEF 12.9 ± 4.8 mm) (n.s.) vs. 16 (16.7) stools/month (p < 0.001) with no significant reduction in Migraine severity (10.0 ± 4.7 mm vs 7.9 ± 2.5, p = 0.002) and in CEP (12.0 ± 4.8 mm vs 10.0 ± 4.8 mm, p = 0.002).

Conclusion: The present study trial suggests the potential safety and efficacy for black patients (not prophylaxis of the Alpha-lactalbumin plus POC and mastic complex).

XLIV Congresso Nazionale SINP

28-30 Novembre NAPOLI

Venerdì 29 Novembre

08.30 - 10.00 VISITA POSTER

Moderatori: Mauro Budetta (Salerno), Maurizio Viri (Novara), Antonella Palmieri (Genova), Irene Bagnasco (Torino), Laura Siri (Savona), Maria Fulvia De Leva (Napoli), Gaetano Terzoni (Napoli), Valentina Marchiani (Bologna), Alessandro Orsini (Pisa)

- ✓ Poster su disturbi del sonno del gruppo di Torino (Bagnasco) e di Pisa (Orsini)

11.30 - 13.00 Comunicazioni orali selezionate – N. 3 Sessioni parallele

MALATTIE RARE Moderatori: Giuseppe Gobbi (Bologna), Irene Bagnasco (Torino)
MALATTIE ACUTE Moderatori: Dario Pruna (Cagliari), Giuseppe Capovilla (Mantova)

TERAPIA Moderatori: Pasquale Parisi (Roma), Gianluca Casara (Bolzano)

- ✓ C29: L'UTILIZZO DEL SERPLUS (A-LATTOALBUMINA) IN SOGGETTI CON PANDAS/PANS: LA NOSTRA ESPERIENZA
L. Sabino, F. Greco, M. Motta, E. Pusturino, C. Oliva, G. Gangi, T. Timpanaro, P. Mainardi, P. Pavone
- ✓ C45: RUOLO DELLA ALFA-LATTOALBUMINA (ALAC) NEL TRATTAMENTO PREVENTIVO DELLA EMICRANIA SENZ'AURA PEDIATRICA
N. Ruotolo, F. Provenzano, M. Esposito, V. Lanzara, E. Lauria, M. Carotenuto

Bristol Stool Chart	
Type 1	Separate hard lumps, like nuts (hard to pass)
Type 2	Sausage-shaped but lumpy
Type 3	Like a sausage but with cracks on the surface
Type 4	Like a sausage or snake, smooth and soft
Type 5	Soft blobs with clear-cut edges
Type 6	Fluffy pieces with ragged edges, a mushy stool
Type 7	Watery, no solid pieces. Entirely liquid

49

• **Disturbi del sonno**
(Orsini, Pisa; Bagnasco, Torino)

• **Emicrania**
(Carotenuto, Napoli)

• **Pandas**
(Pavone, Catania)

Alpha-lactalbumin protects in a dose-dependent manner from gastric ulcers induced by alcohol or stress

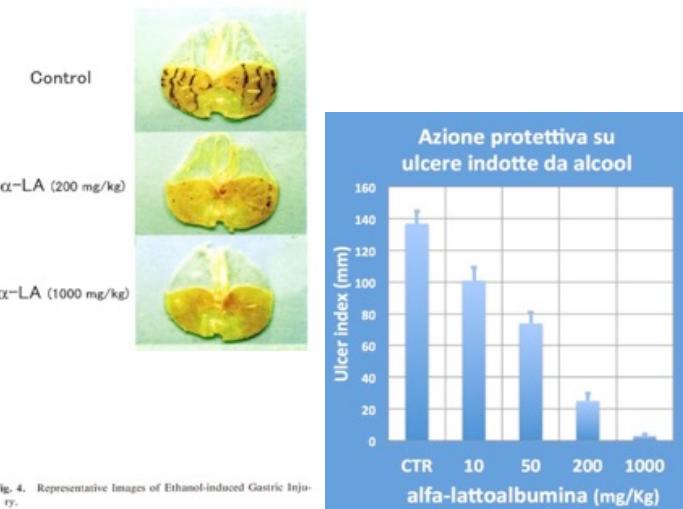


Fig. 4. Representative Images of Ethanol-induced Gastric Injury.
Biosci. Biotechnol. Biochem., 65 (5), 1104-1111, 2001

Biosci. Biotechnol. Biochem., 65 (5), 1104-1111, 2001



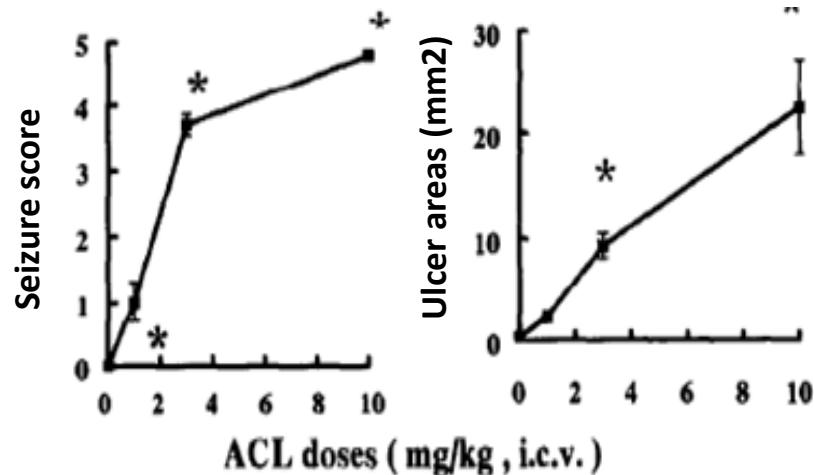
New Biological Function of Bovine α -Lactalbumin: Protective Effect
against Ethanol- and Stress-induced Gastric Mucosal Injury in Rats

Hiroshi MATSUMOTO,[†] Yukiko SHIMOKAWA, Yoshihiko USHIDA, Tomohiro TOIDA,
and Hirotoshi HAYASAWA

Biochemical Research Laboratory, Morinaga Milk Industry Co. Ltd., Zama, Kanagawa 228-8583, Japan

- The amount of gastric ulcers depend in a dose-dependent manner on the amount of epileptogenic agent injected i.c.v.

Hung CR, Cheng JT, Shih CS. Gastric mucosal damage induced by arecoline seizure in rats. *Life Sci.* 2000 May 5; 66 (24): 2337-49.



- ✓ più dose (icv)
- ✓ più crisi epilettiche
- ✓ più ulcere

Alpha-lactalbumin protects in a dose-dependent manner from gastric ulcers induced by alcohol or stress

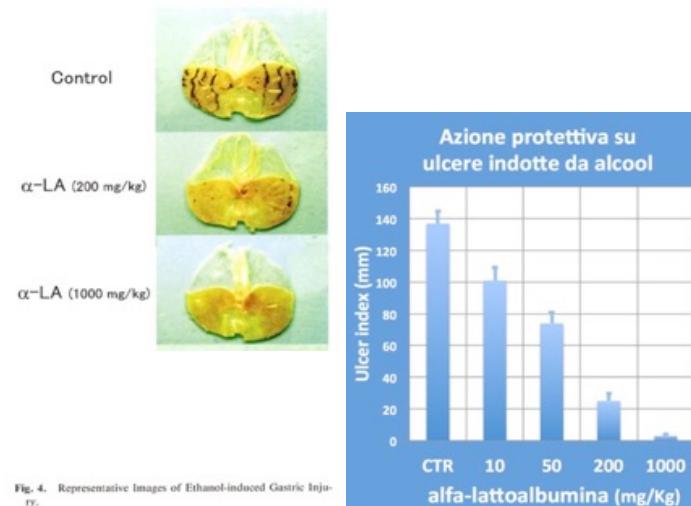


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Biosci. Biotechnol. Biochem., 65 (5), 1104-1111, 2001

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Biochemical Research Laboratory, Morinaga Milk Industry Co. Ltd., Zama, Kanagawa 228-8583, Japan



OPEN

Intestinal inflammation increases convulsant activity and reduces antiepileptic drug efficacy in a mouse model of epilepsy

Received: 3 December 2018
 Accepted: 14 August 2019
 Published online: 27 September 2019

Carmen De Caro¹, Antonio Leo¹, Valentina Nesci¹, Carla Ghelardini², Lorenzo di Cesare Mannelli², Pasquale Striano¹, Carmen Avagliano⁴, Antonio Calignano⁴, Paolo Mainardi⁵, Andrew Constanti⁶, Rita Citraro¹, Giovambattista De Sarro¹ & Emilio Russo¹

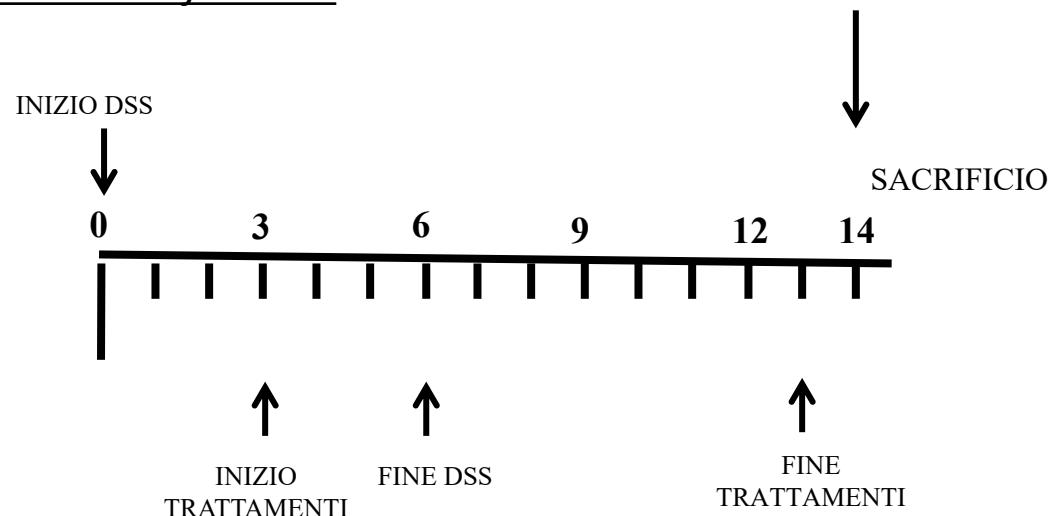
Anticonvulsant activity in all groups and for all drugs will be evaluated as previously reported for ALAC in the PTZ model

Experimental colitis will be induced in mice BALB/c by Dextran Sulfate Sodium (DSS)

Experimental test drugs will be administered as follows:

- ALAC (375 mg/kg)
- Valproic Acid (600 mg/kg)
- Sodium Butyrate (100 mg/kg)
- Mesalazine (15mg/kg)

Time (days)

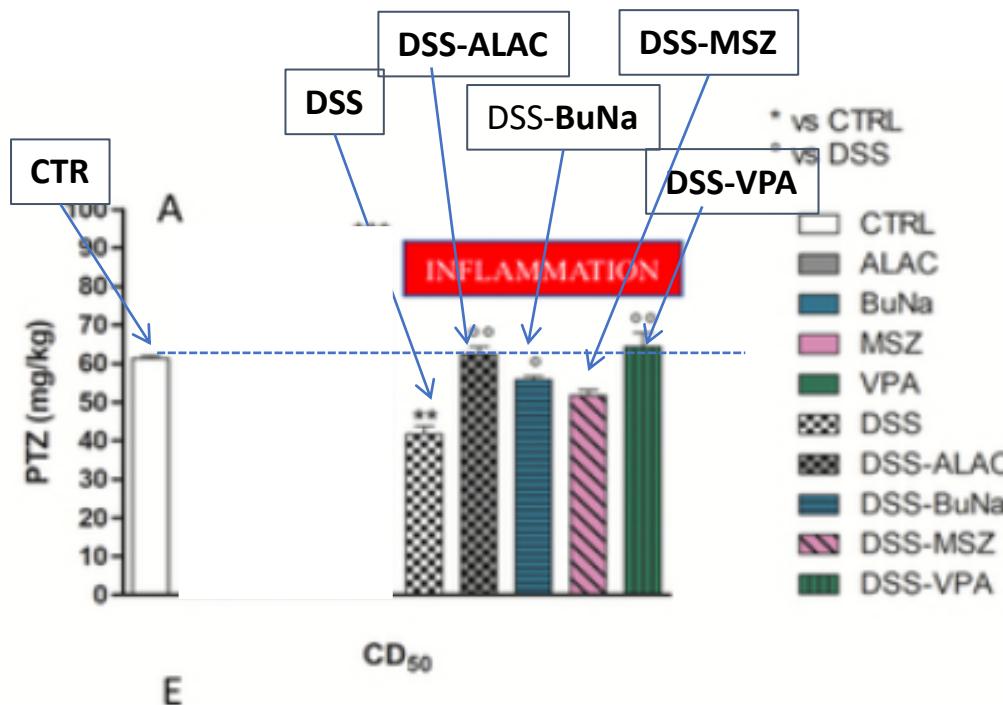
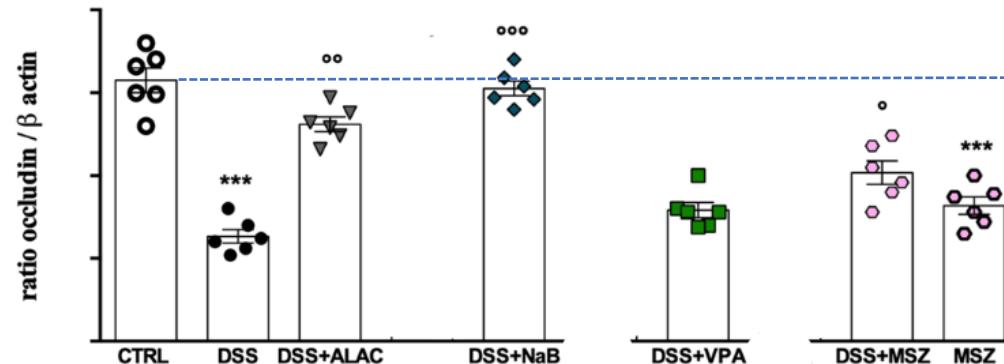


Intestinal inflammation increases convulsant activity and reduces antiepileptic drug efficacy in a mouse model of epilepsy.

De Caro C, Leo A, Nesci V, Ghelardini C, di Cesare Mannelli L, Striano P, Avagliano C, Calignano A, Mainardi P, Constanti A, Citraro R, De Sarro G, Russo E. Intestinal inflammation increases convulsant activity and reduces antiepileptic drug efficacy in a mouse model of epilepsy. Sci Rep. 2019 Sep 27;9(1):13983.

Infiammazione intestinale:

1. BuNa
2. ALAC
3. MSZ
4. VPA



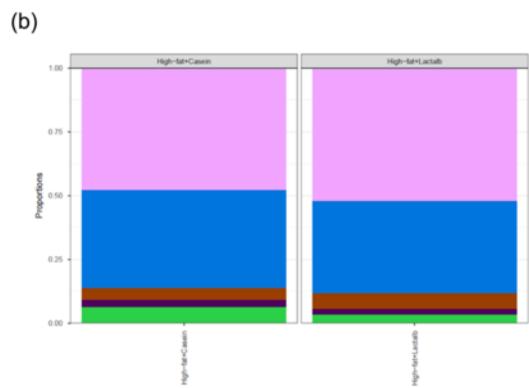
Soglia convulsiva:

1. ALAC=VPA
2. BuNa
3. MSZ

Dietary α -lactalbumin alters energy balance, gut microbiota composition and intestinal nutrient transporter expression in high-fat diet-fed mice

Serena Boscaini^{1,2,3}, Raul Cabrera-Rubio^{1,2}, John R. Speakman^{4,5}, Paul D. Cotter^{1,2}, John F. Cryan^{2,3} and Kanishka N. Nilaweera^{1,2*}

Modifica microbiota

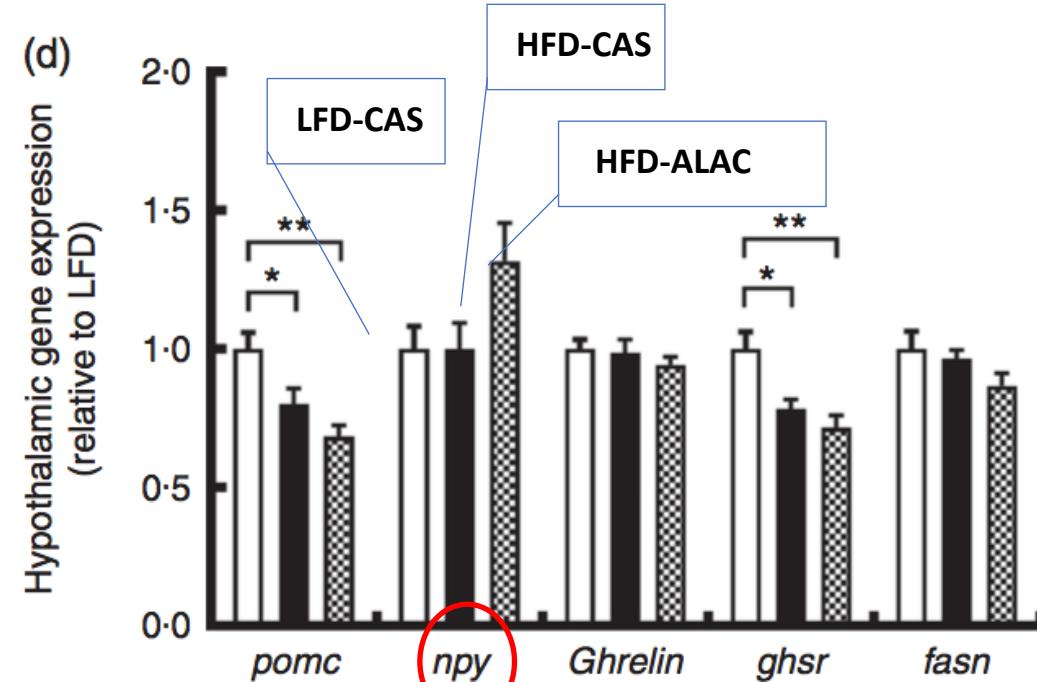


NPY: Endogenous Anticonvulsant

NPY system as a potential therapeutic target in neurodegenerative diseases.

Alfa-lattoalbumina modifica il microbiota e stimola la sintesi di NPY, responsabile della plasticità del SNC.

Aumenta NPY



1. De Caro C, Leo A, Nesci V, Ghelardini C, di Cesare Mannelli L, Striano P, Avagliano C, Calignano A, **Mainardi P**, Constanti A, Citraro R, De Sarro G, Russo E. Intestinal inflammation increases convulsant activity and reduces antiepileptic drug efficacy in a mouse model of epilepsy. *Sci Rep.* 2019 Sep 27;9(1):13983
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3. **P.Mainardi, P.Carta, P.Striano.** **How Knowledge on Microbiota may be Helpful to Establish an Optimal Diet for Health Maintenance.** *Int J Nutrition, 2018.*
- 4.
5. **Mainardi P, Carta P, Montinari M, Striano P et al.** **From the Ancient Diets to the Recent Acquisitions on the Role of Brain Inflammation in Epilepsy, Are there Any Links?** *J Neurol Neurophysiol 2015, 6:3*
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15. **Mainardi P, Leonardi A, Albano C.** **Potentiation of brain serotonin activity may inhibit seizures, especially in drug-resistant epilepsy.** *Med Hypotheses.* 2008;70(4):876-9.
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Associazione tra fibromialgia e microbiota.

- Microbiota alterato nei pazienti fibromialgici.
- Curare il microbiota dei fibromialgici può essere una nuova strategia terapeutica?

È un caso o la causa?

BJA

British Journal of Anaesthesia, 123 (5): 637–654 (2019)

doi: [10.1016/j.bja.2019.07.026](https://doi.org/10.1016/j.bja.2019.07.026)

Advance Access Publication Date: 21 September 2019

Review Article

NPY è coinvolto nel dolore cronico

Pain regulation by gut microbiota: molecular mechanisms and therapeutic potential

Ran Guo^{1,†}, Li-Hua Chen^{2,†}, Chungen Xing^{4,*} and Tong Liu^{3,5,*}

Diaz-delCastillo M, Woldbye DPD, Heegaard AM. Neuropeptide Y and its Involvement in Chronic Pain. *Neuroscience*. 2018 Sep 1;387:162-169.

Erdrich S, Hawrelak JA, Myers SP, Harnett JE. Determining the association between fibromyalgia, the gut microbiome and its biomarkers: A systematic review. *BMC Musculoskelet Disord*. 2020;21(1):181. Published 2020 Mar 20. doi:10.1186/s12891-020-03201-9

- Alpha-lactoalbumin increases NPY

- KD increases NPY

- Weinshenker D. Stafstrom CE and Rho JM eds. Humana Press. 2004

- VPA increases NPY

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- Topiramate increases NPY (Chronically administered for 10 days)

- Husum H, et al. Neuropsychopharmacology. 2003 Jul;28(7):1292-9.

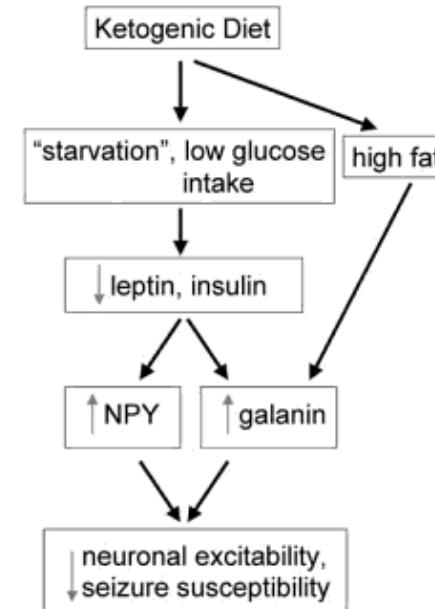
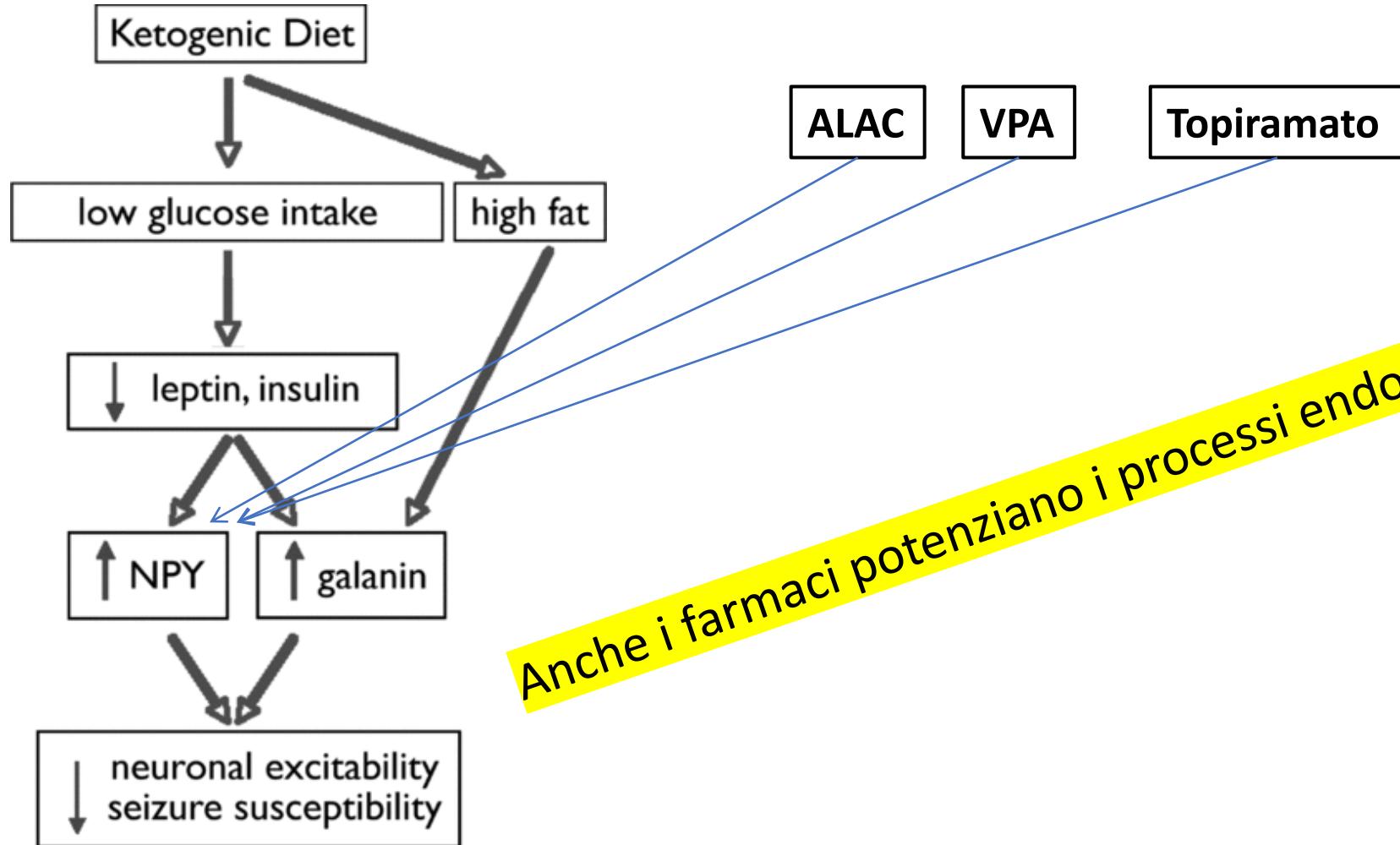


Fig. 1. Model for the mediation of the KD's anticonvulsant effect by NPY and galanin.

Derry S, Wiffen PJ, Moore RA. **Valproic acid and sodium valproate for neuropathic pain and fibromyalgia**. Cochrane Database of Systematic Reviews 2011, Issue 7. Art. No.: CD009183.

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Wiffen PJ, Derry S, Lunn MP, Moore RA. **Topiramate for neuropathic pain and fibromyalgia in adults**. Cochrane Database Syst Rev. 2013 Aug 30;(8):CD008314.



Anche i farmaci potenziano i processi endogeni riparativi?

Weinshenker, D. (2008), The contribution of norepinephrine and orexigenic neuropeptides to the anticonvulsant effect of the ketogenic diet. *Epilepsia*, 49: 104-107.

Looking towards a new medicine:

- MORE POWERFUL THAN ANY DRUGS

restore the powerful and endogenous controller and self-repair mechanisms

Take – home message:

Cure the microbiota to allow it to take care of you.



Università Popolare delle
Scienze dell'Alimentazione e
salute. (UNIPSAS)

 UnaMedicina
di Paolo Mainardi



Looking for the One Medicine

www.unipsas.it

www.unamedicina.it

p.mainardi@unamedicina.it



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