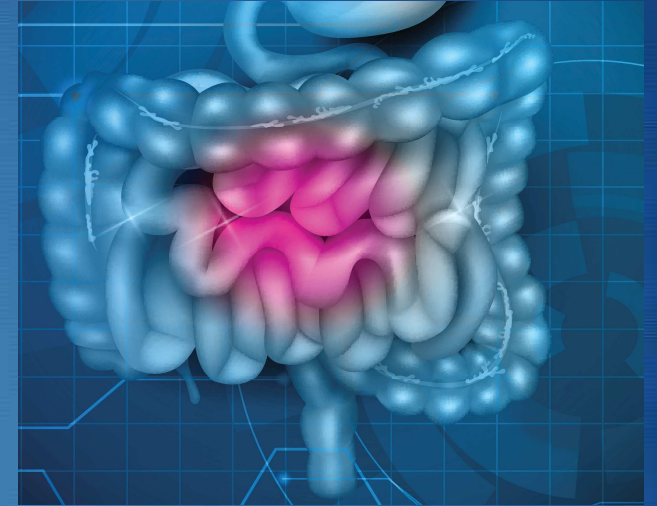
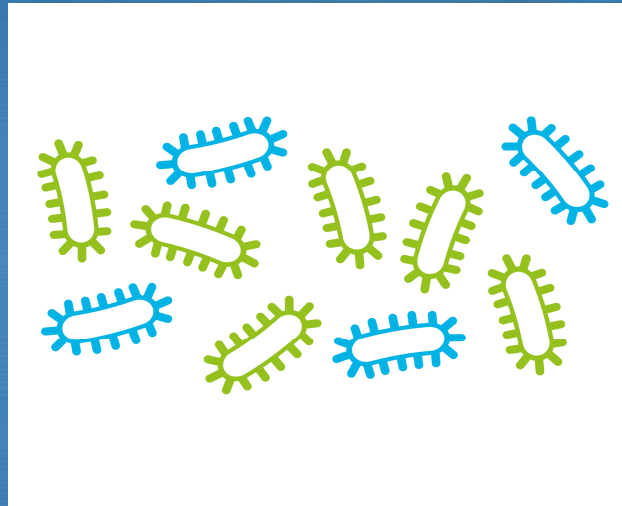


# Peripheral brains-skin microbiome dialogue : a challenge for medicine



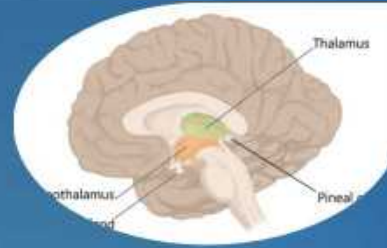
Patrizia d'Alessio MD PhD



What are we going to talk about?



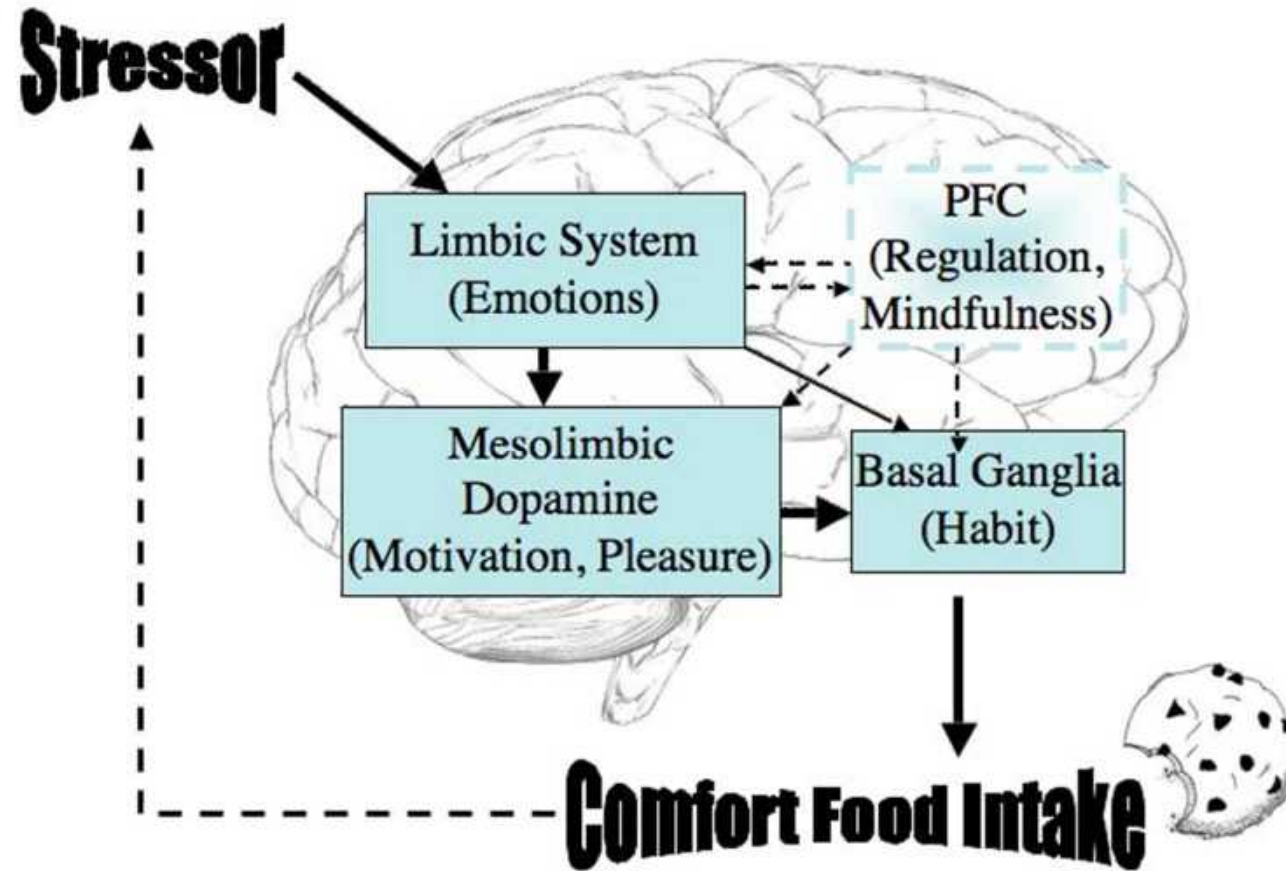
# Brain skin and gut microbiota



- ◆ Brain Central hub
- ◆ Peripheral brains
  - ◆ Skin
  - ◆ Gut

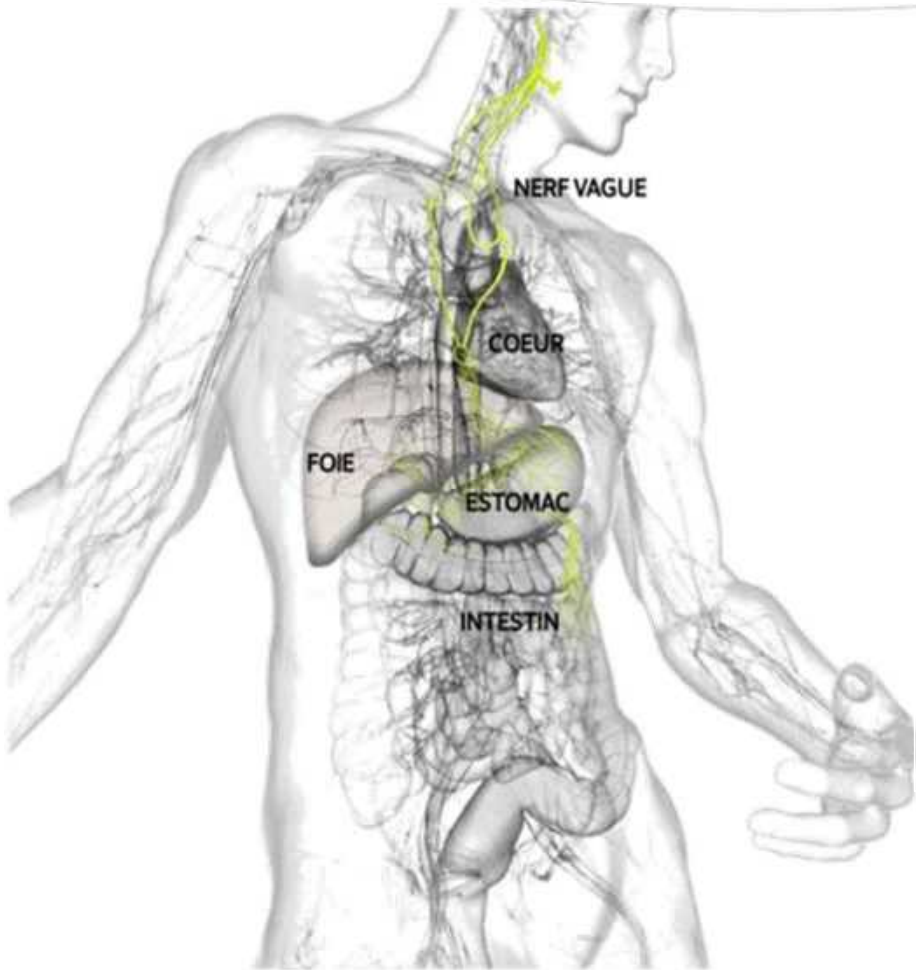


# Brain and Life Stress





# SAM - Sympathetic Adrenal Medullary axis



**Orthosympathetic : Go fast**

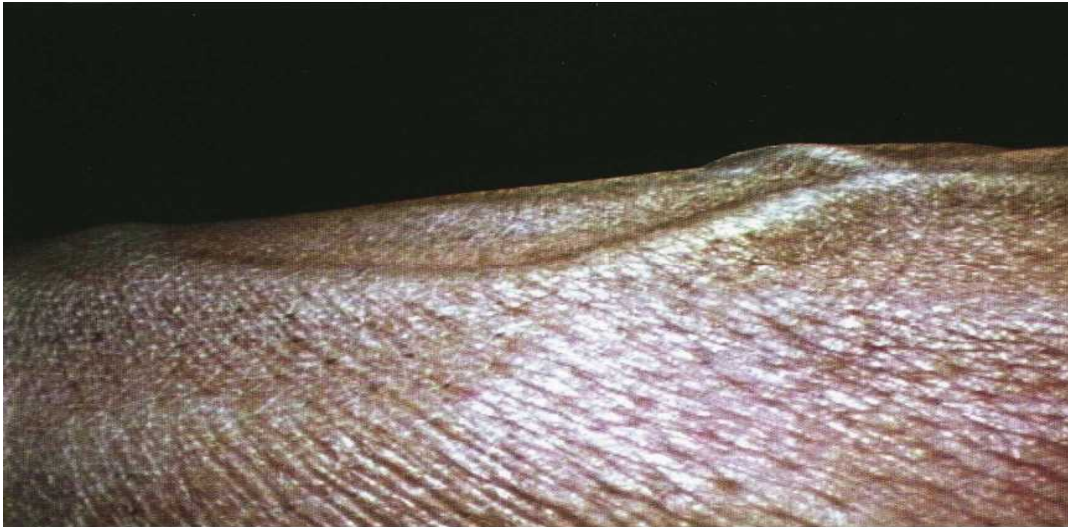
Adrenaline for fight or flight responses.

**Parasympathetic : Slow down**

the cholinergic pathway, a neuro-mechanism that **suppresses the inflammatory response to stress.**

# Skin, our surface integrity policy connected to the body

- 💧 A supple, water-proof envelope...



- 💧 What is special about the skin brain ?

# Which brain ?

- 💧 The skin is provided with hair follicles
- 💧 Hair follicles are the skin localization of a primitive brain



# Once upon a time

- 💧 In the beginning there was the primal soup associated to environmental stress.



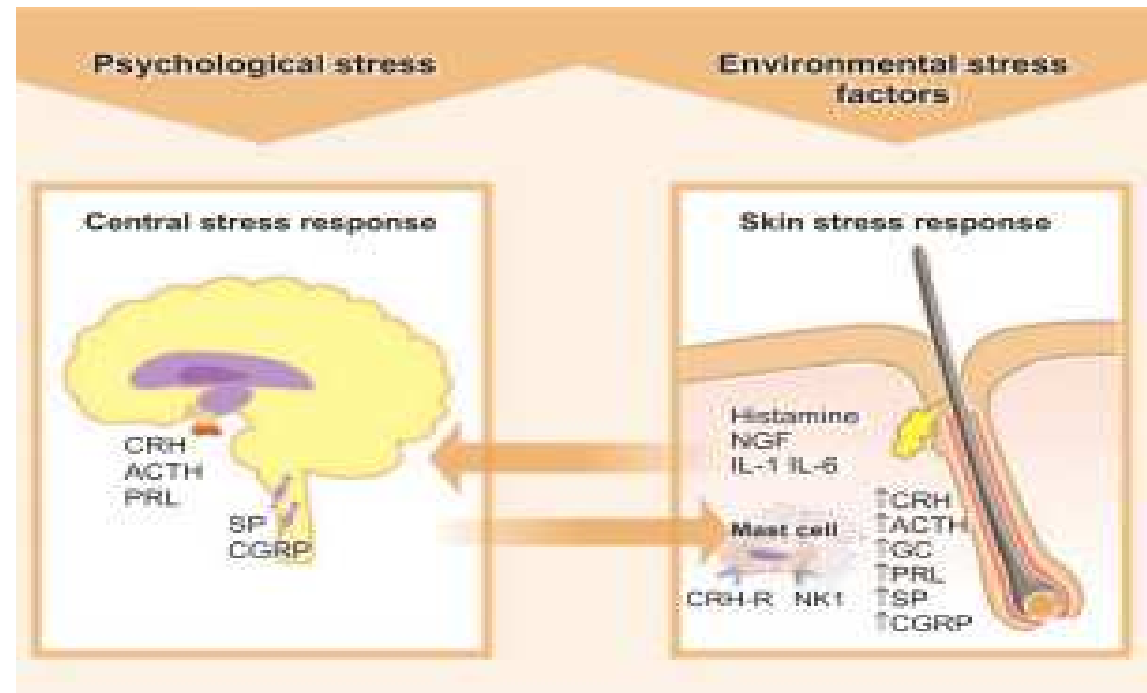
- 💧 **Sponges** neural toolkit including sensory cells, conduction pathways, signaling molecules developed a system to feed, allowing them to ***pump and filter*** the primordial soup, ensuring the essence of life.



Those might be the ancestors of the brain....



# The skin - hair follicle brain displays a fully functional peripheral HPA system



## Neuroimmunology of Stress: Skin Takes Center Stage

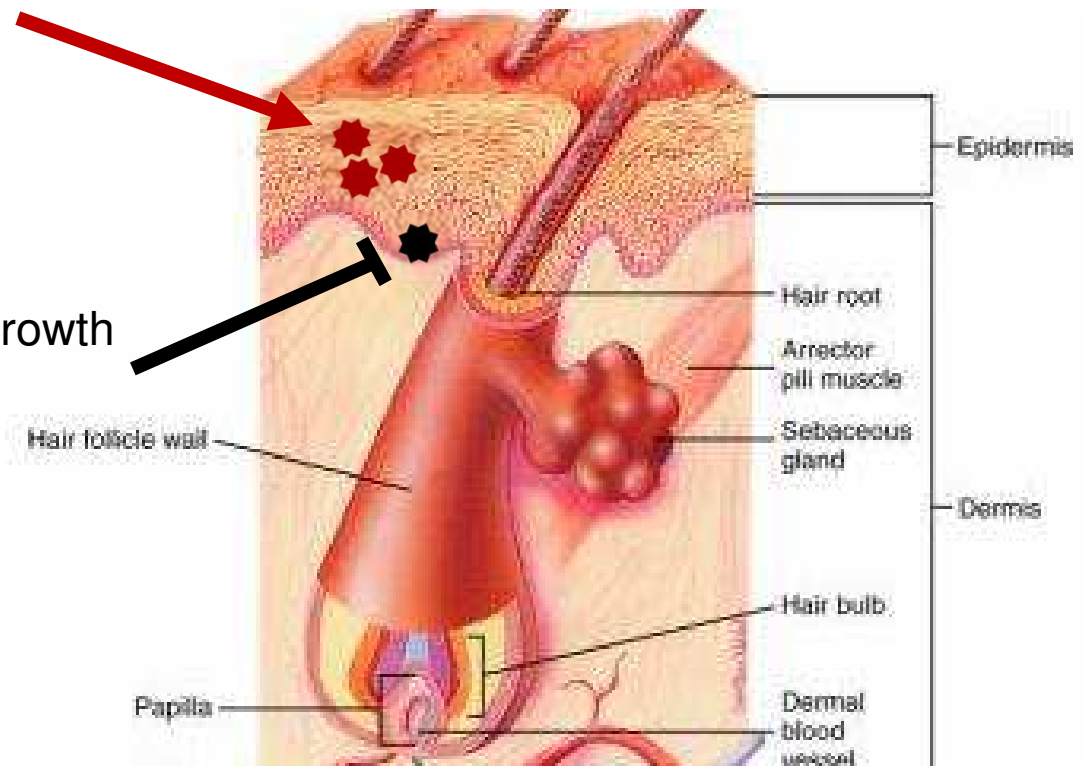
Petra C. Arck<sup>1</sup>, Andrzej Slominski<sup>2</sup>, Theoharis C. Theoharides<sup>3</sup>, Eva M. J. Peters<sup>1</sup> and Ralf Paus<sup>4</sup>

*Journal of Investigative Dermatology* (2006) **126**, 1697–1704. doi:10.1038/sj.jid.5700104

# Upon Stress, CRH...

Stimulates keratinocytes proliferation

Inhibits melanocytes growth



# What is linking skin and gut ?

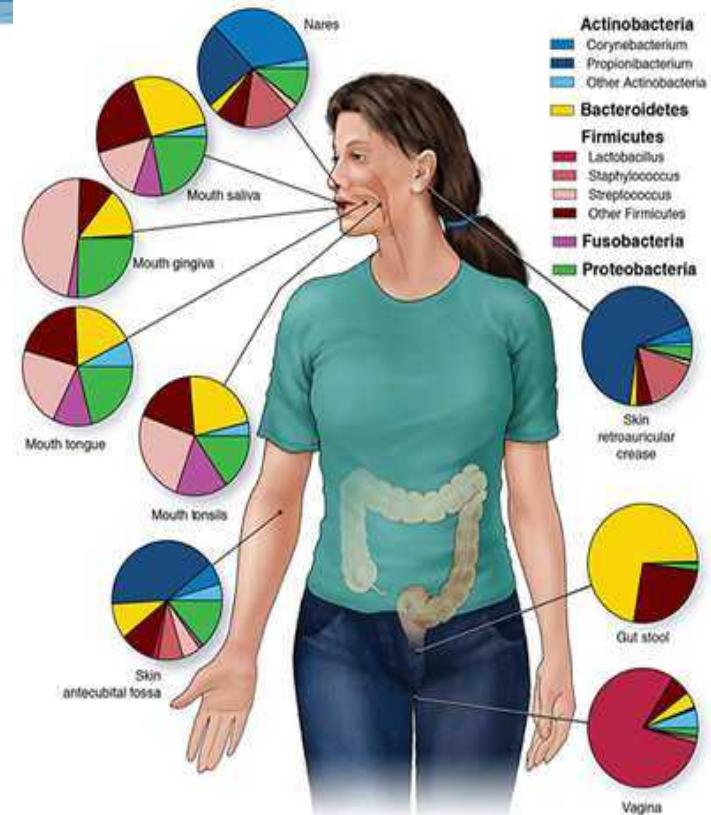
## The microbiota *continuum* of skin and mucosae

Thurnbaugh et al, 2007



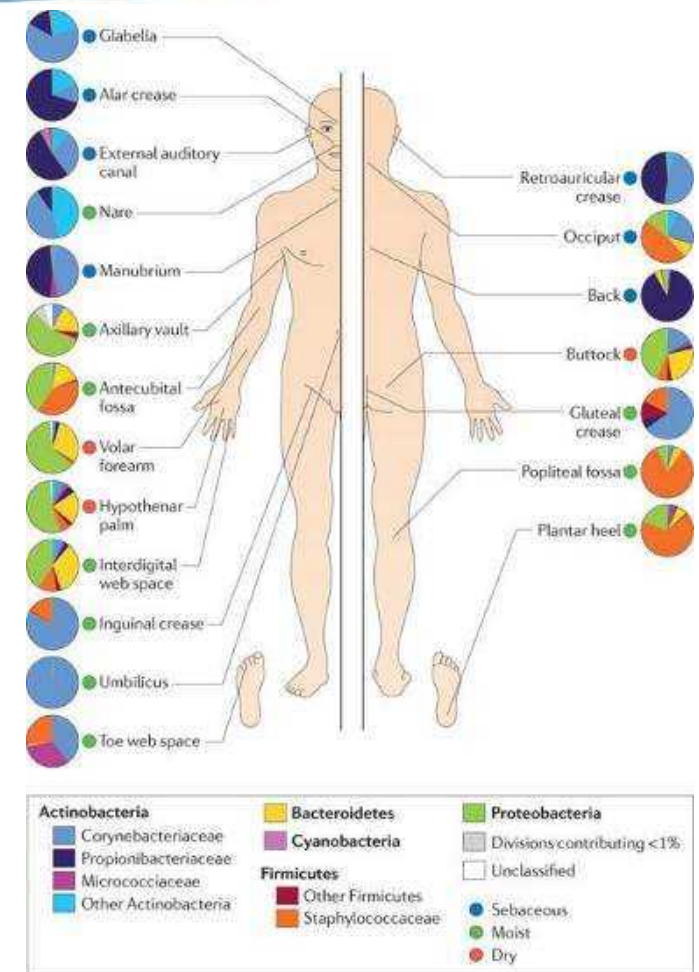
*“The bacterial communities (one hundred trillions microbes) provide us with traits that we had not had to evolve on our own”*

- ◆ Limit the proliferation of pathogens
- ◆ Produce microbial antibiotics
- ◆ Limit the access of antigens to epithelial cells
- ◆ Participate to food degradation and assimilation
- ◆ **Intra-familial & Intra-generational** transmissions are shaping biological features



# SKIN microbiota

A balanced protective microbiota limits the proliferation of pathogens and contributes to the barrier function





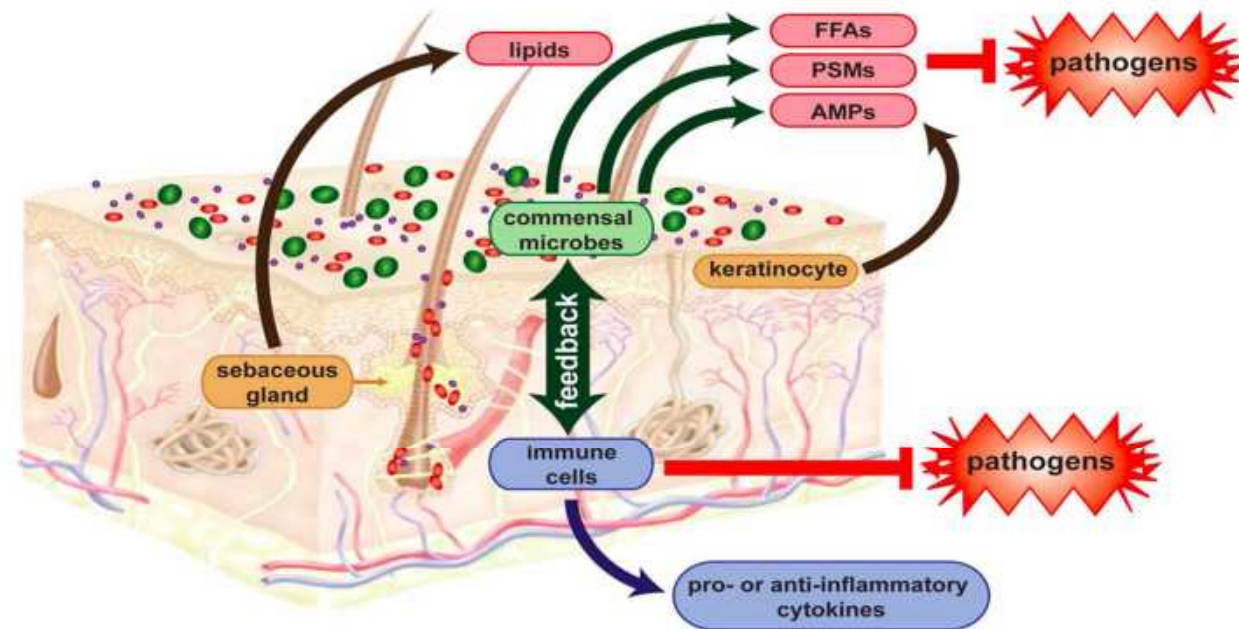
# 1. Impact on the barrier function

## ◆ Resident microbes

*Propionibacteria, Staphylococci, Micrococci, Acinetobacter*

## ◆ Transient microbial species

*Staphylococcus aureus, Pseudomonas Aeruginosa, Escherichia coli,*



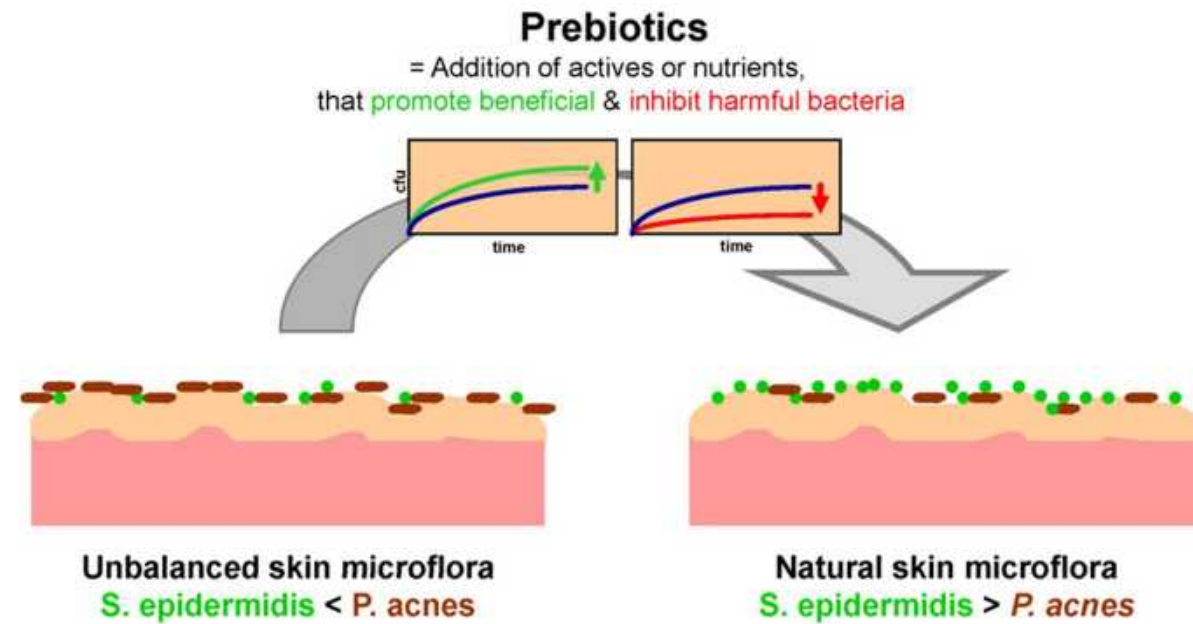
• = viruses	FFAs = free fatty acids
• = bacteria	PSMs = pheno-soluble modulins
• = fungi	AMPs = antimicrobial peptides

*J Am Acad Dermatol.* 2013 July ; 69(1): 143–155.e3. doi:10.1016/j.jaad.2013.01.016.

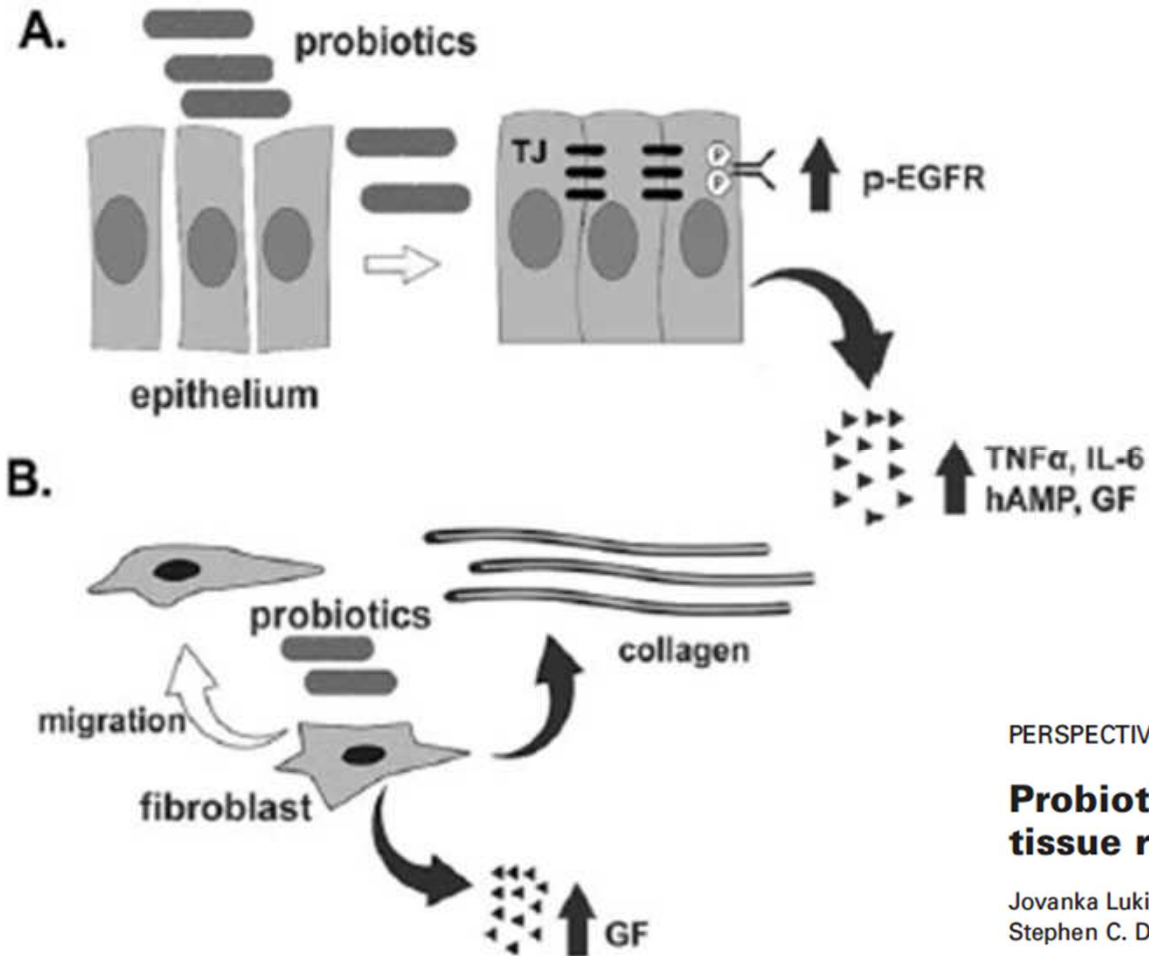
**The skin microbiome: current perspectives and future challenges**

Yiyin Erin Chen, PhD<sup>1</sup> and Hensin Tsao, MD, PhD<sup>\*,2,3</sup>

## 2. Re-establishment of the barrier function




### 3. Anti-infectious role of probiotics



#### PERSPECTIVE ARTICLE

#### Probiotics or pro-healers: the role of beneficial bacteria in tissue repair

Jovanka Lukic, PhD<sup>1</sup>; Vivien Chen, BS<sup>2</sup>; Ivana Strahinic, PhD<sup>1</sup>; Jelena Begovic, PhD<sup>1</sup>; Hadar Lev-Tov, MD<sup>2</sup>; Stephen C. Davis, BS<sup>2</sup>; Marjana Tomic-Canic, PhD<sup>2</sup>; Irena Pastar, PhD <sup>2</sup>

## 4. Prevention of biofilm formation

- ❑ Limited ability to prevent adhesion of some potential skin pathogens.
- ❑ Most of the tested topic probiotics successfully prevent biofilm formation.

Journal of  
Applied Microbiology



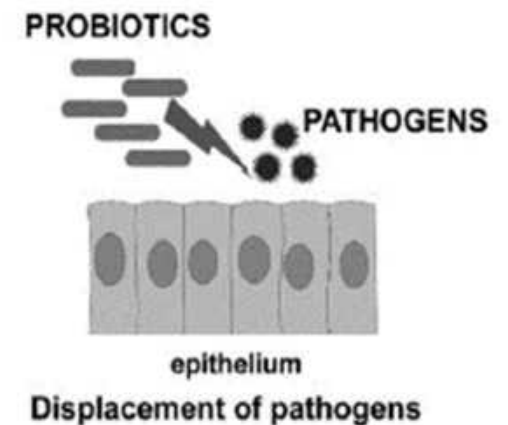
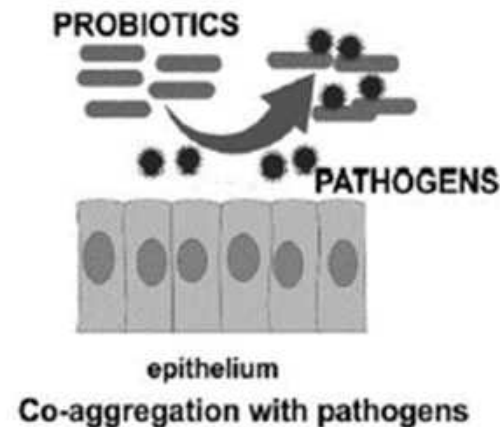
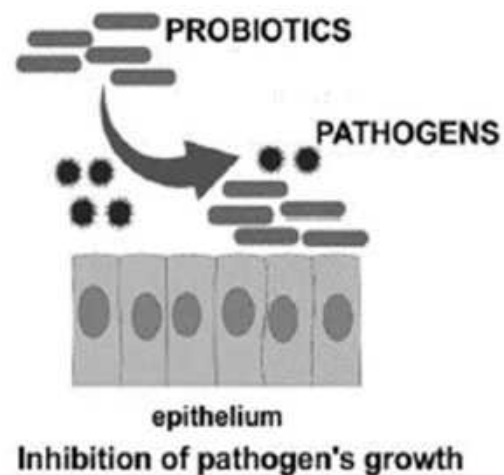
Journal of Applied Microbiology ISSN 1364-5072

ORIGINAL ARTICLE

**Topical application of probiotics in skin: adhesion, antimicrobial and antibiofilm *in vitro* assays**

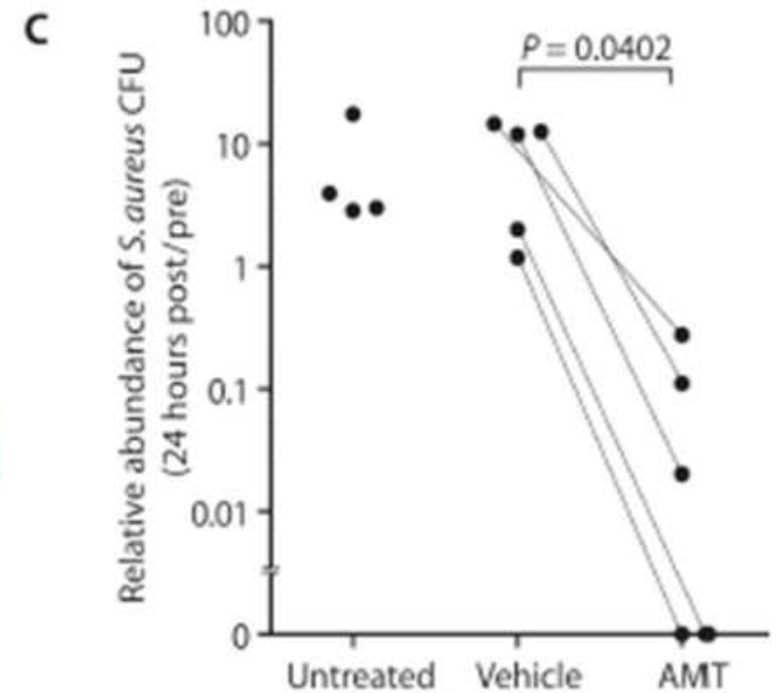
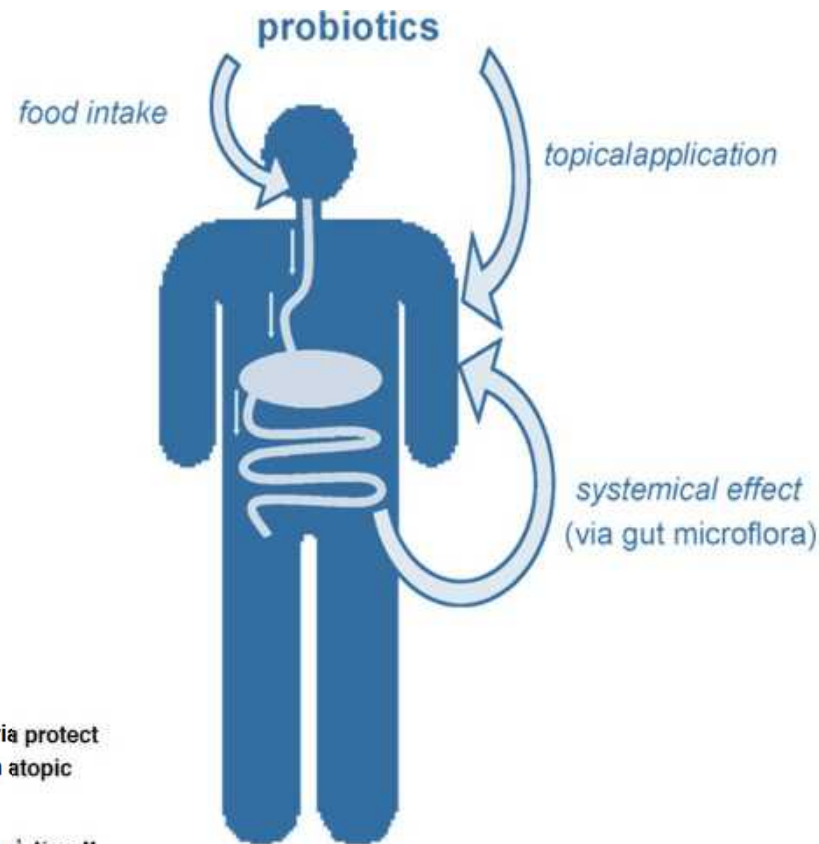
E.G. Lopes, D.A. Moreira, P. Guillón, B. Guillón, A. Cardelle-Cobas and F.K. Távora

CBQ<sup>†</sup> – Centro de Biotecnologia e Química Fina – Laboratório Associado, Escola Superior de Biotecnologia, Universidade Católica Portuguesa<sup>†</sup>, Porto, Rua Arquêdo Lobo Vial, Porto, Portugal





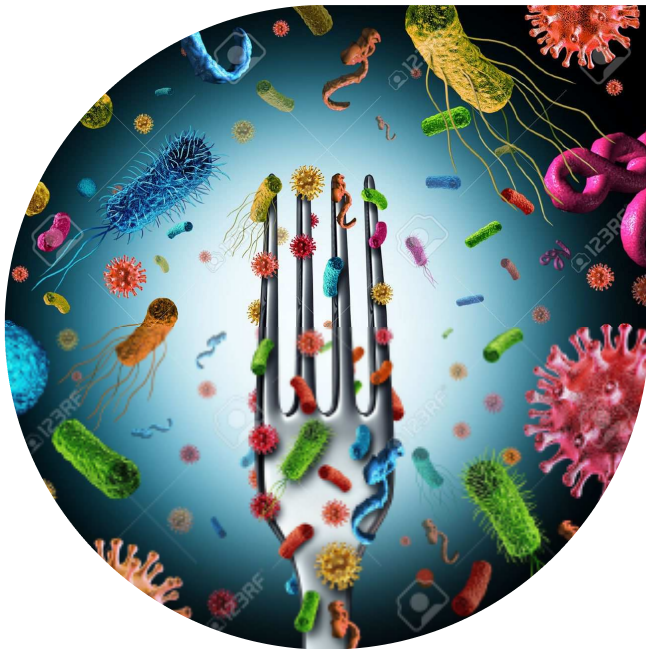
## 5. Transplantation of antimicrobial CoNS\* reduces the survival of *S. aureus* in atopic dermatitis



\*Coagulase-negative staphylococci

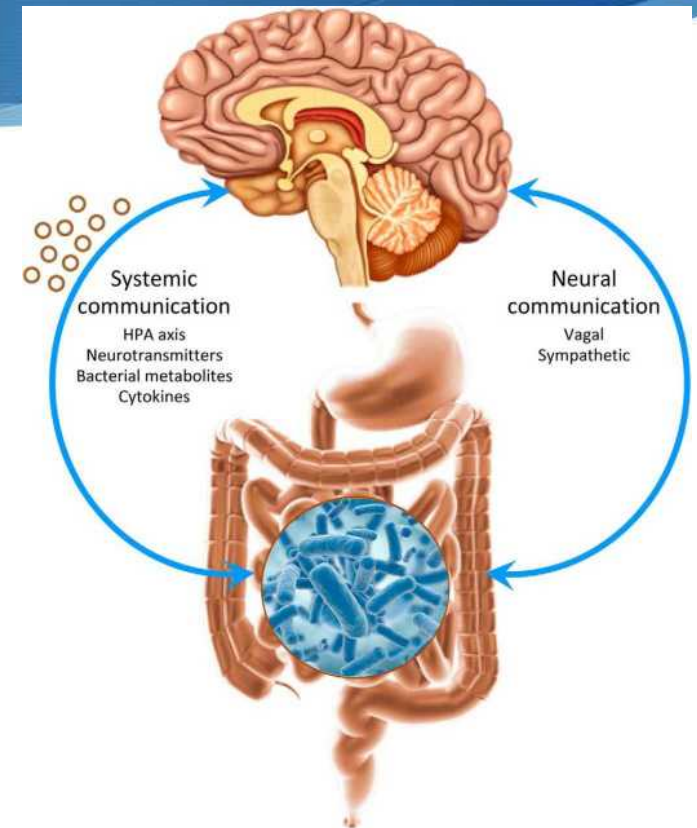
Gut, our friendly...

part of self...

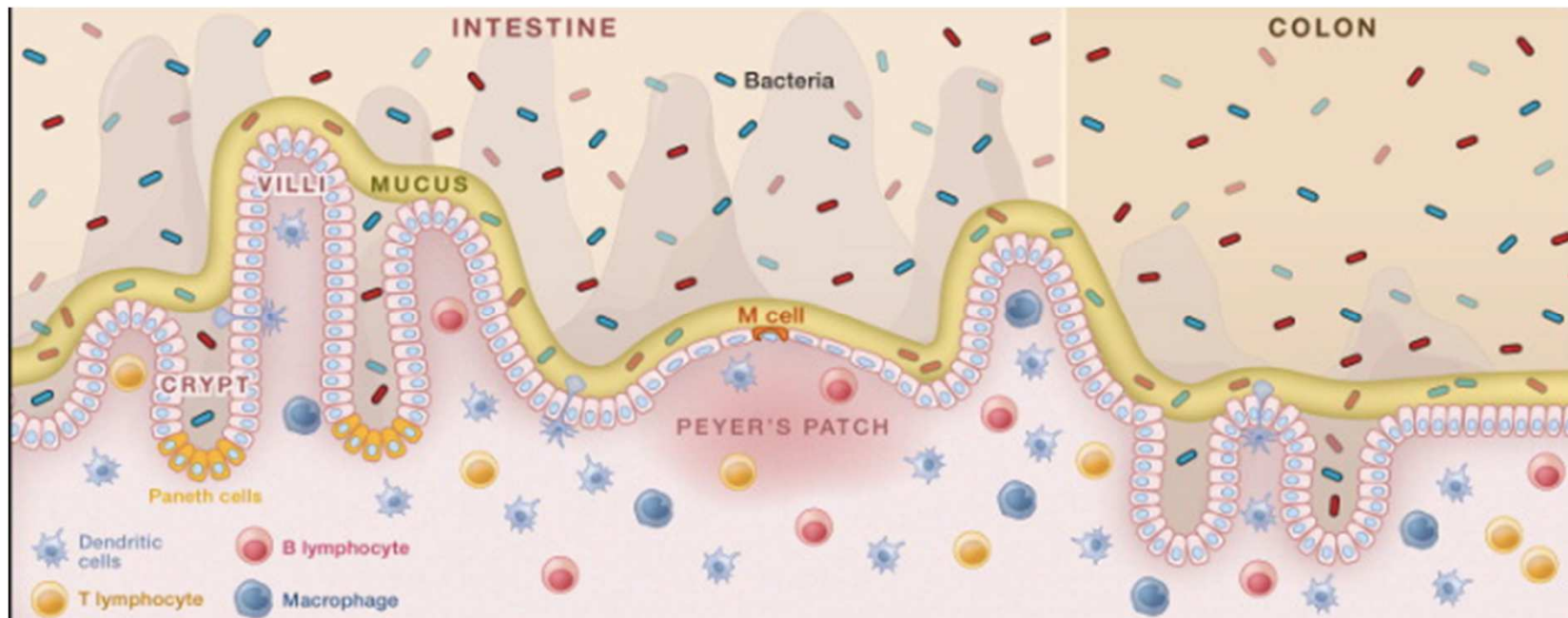


# Functional gut – brain link : the microbiota

- ◆ Bidirectional communication channels between the gut microbiome, the gut, and the brain.
- ◆ Endocrine-, neurocrine- and inflammation-related signals generated by the gut microbiota and specialized cells within the gut affect the brain.
- ◆ In turn, **the brain can influence the microbial composition** and function via endocrine and neural mechanisms
- ◆ Dopamine, serotonin, leptin, adiponectin...



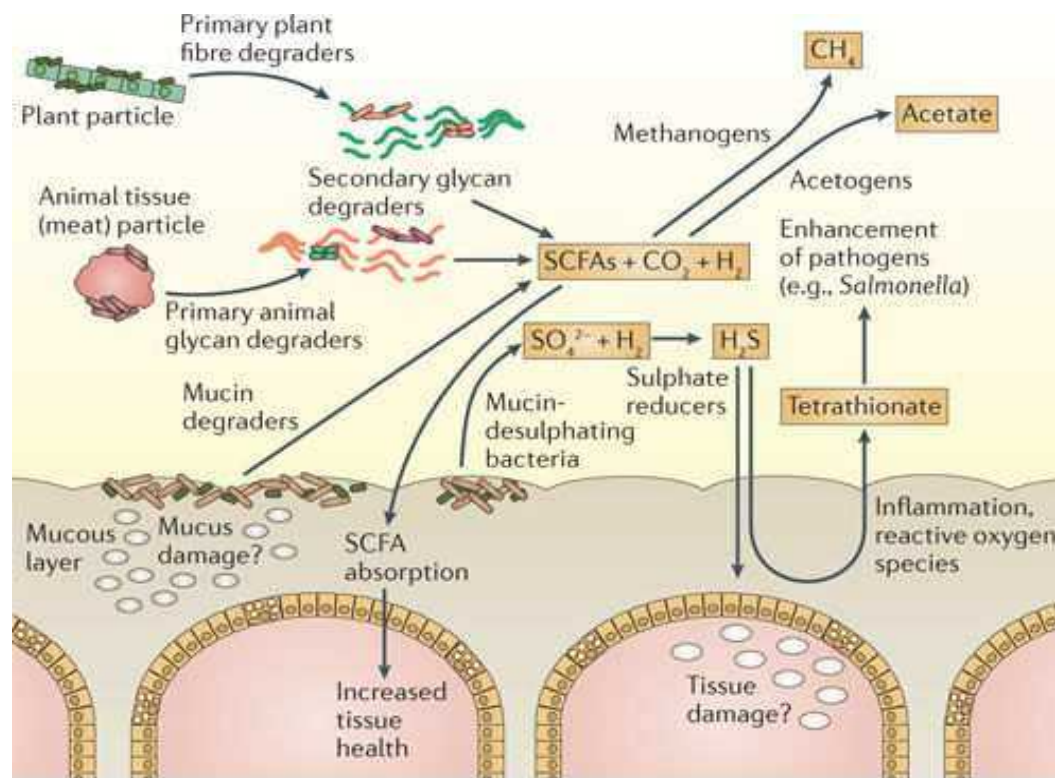
# A continuously perfused peristaltic bioreactor



Garrett WS, Gordon JI Glimcher LH. Homeostasis and Inflammation in the Intestine. Cell REVIEW 140,6:859-870;201



# Strategic role of the gut microbiota : synthesis of SCFA\*



Butyrate, Folate,  
Propionate by:

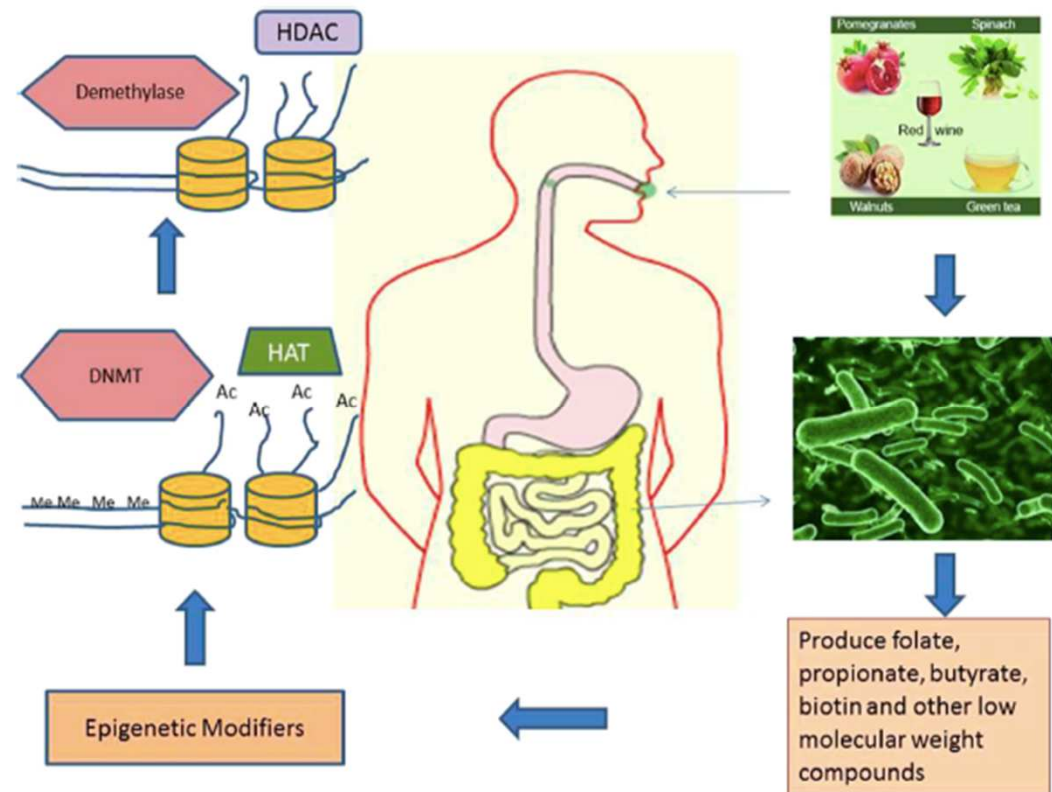
*Bifidobacteria*  
*Clostridii*  
*Enterocaterium*  
*Enterococcus*  
*Ruminococcus*  
*Roseburia*

Nature Reviews | Microbiology

\* Short chain fatty acids

# Bacterial metabolism of dietary fibers impacts epigenetics

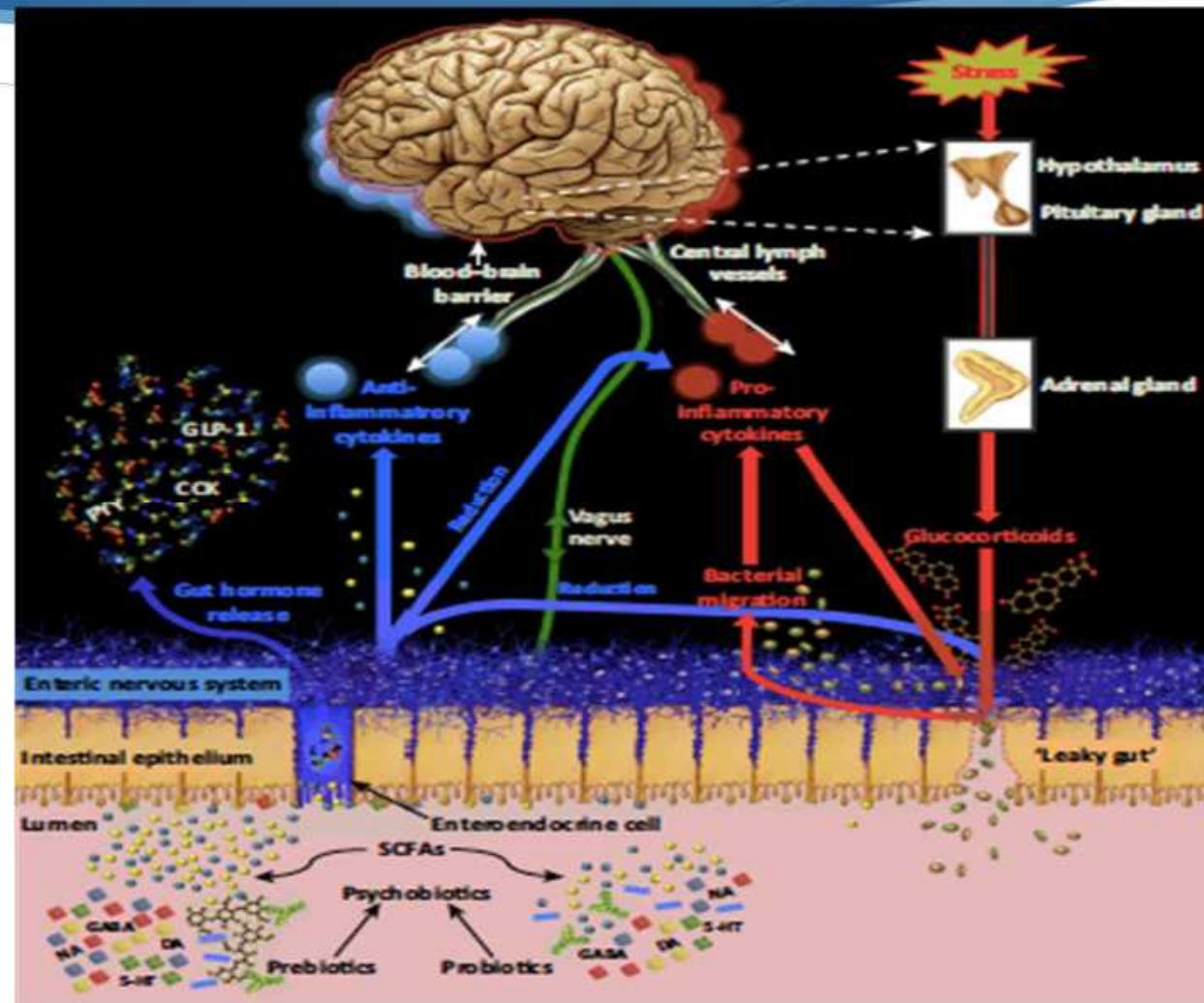
Acetate, **butyrate**,  
propionate (SCFA) and  
folates, produced following  
dietary intake of  
phytochemicals,  
are epigenetic modifiers.



# Psychobiotic Action of Food Components

Prebiotics =  
Non digestible fibers

Probiotics =  
Live micro-organisms



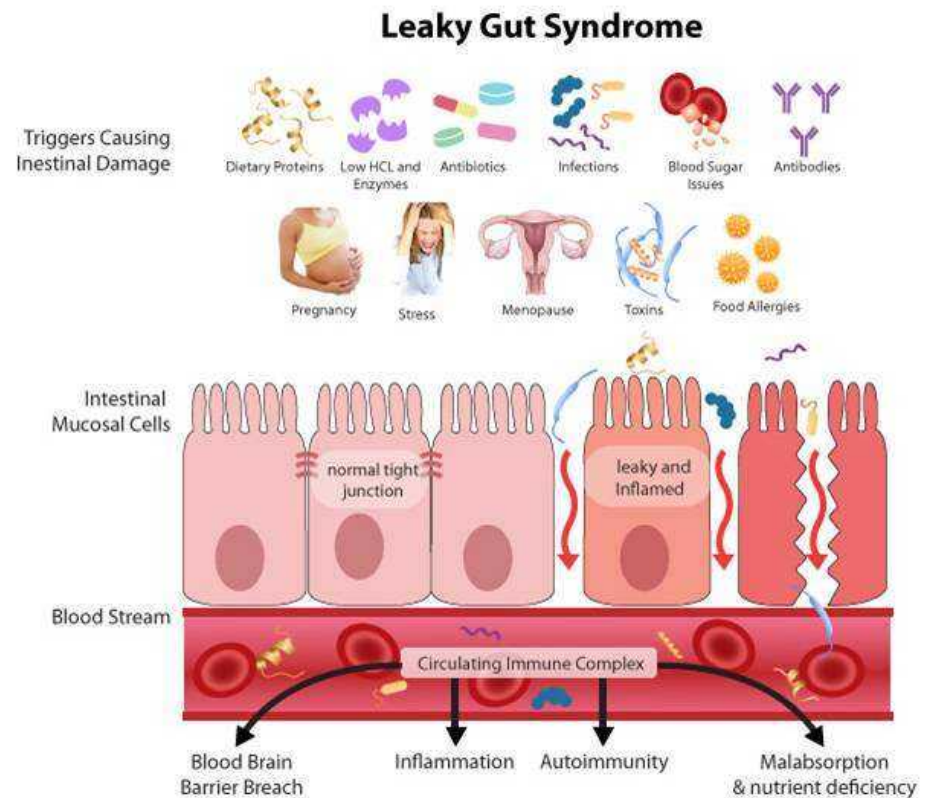
A. Sarkar et al Trends in Neurosciences Cell Press 11 : 763-781, 2016.



# BARRIER DYSFUNCTION = LEAKY GUT SYNDROME = DYSBIOSIS

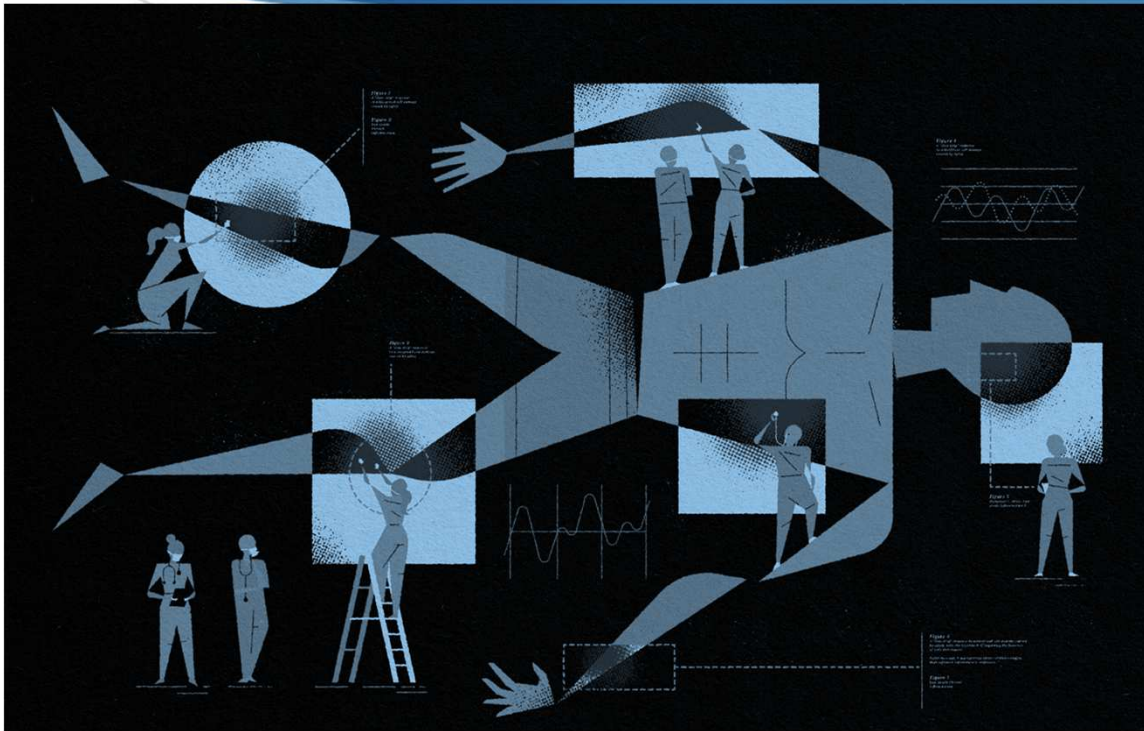
Cortisol

Mood





# BARRIER DYSFUNCTION AND « SICKNESS DISEASE »

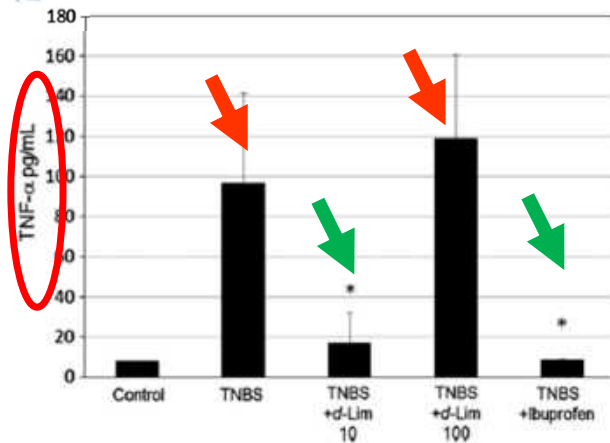


loss of memory,  
anxiety,  
refusal to meet social events,  
obsessional thoughts,  
difficulty to concentrate,  
depression,  
chronic fatigue syndrome,  
sleeplessness,  
loss of interest,  
obsessional neurosis

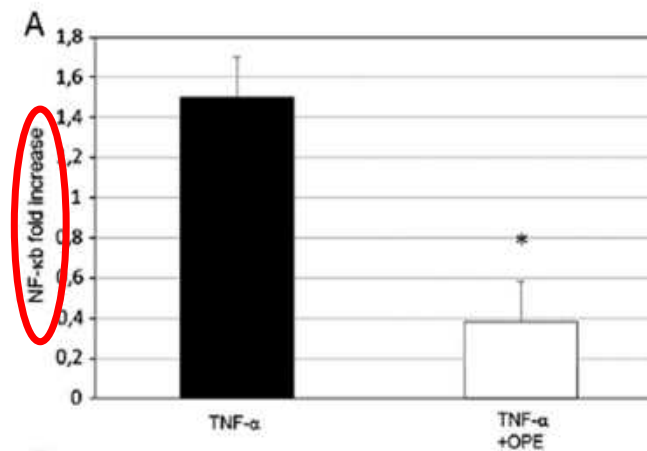
# Mechanisms of gut de-inflammation



## Anti-TNF effect - Inhibition of NF- $\kappa$ B



Same effect as ibuprofen  
for low-dose *d*-Lim



# Control of chronic inflammation in humans

The European project RISTOMED FP7 “Healthy aging by nutrition”  
Capacity program 2222-30 : 2009-2012

Positive effects of oral administration of AISA small mono-terpens from  
Orange Peel Extract (OPE) in the course of a controlled diet  
**in healthy volunteers 65-85 years old**

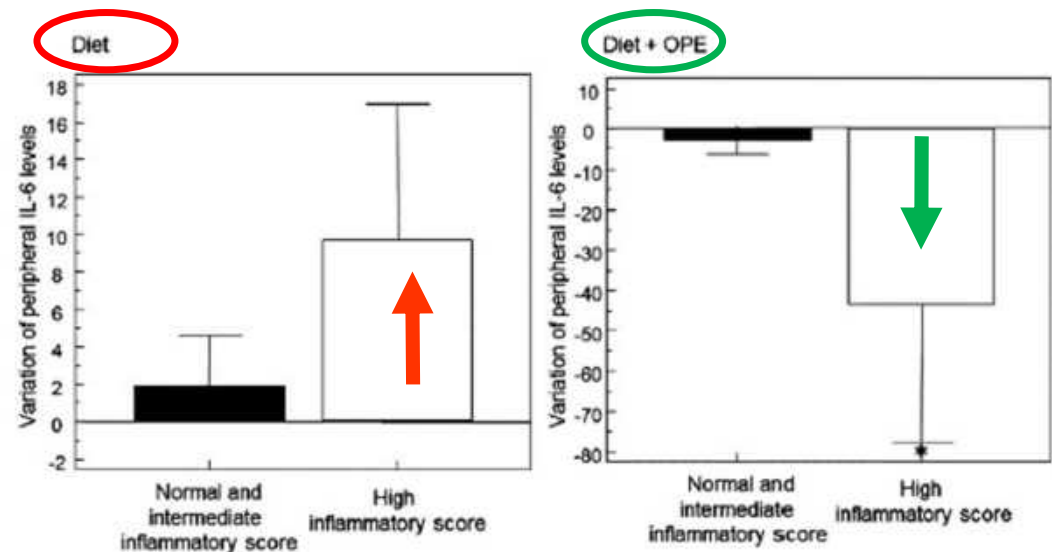


# Anti-Inflammatory effect in humans



Assay of IL-6 as function of the basic inflammatory profile

A controlled diet plus a supplementation by AISA **decreases** the levels of circulating IL-6

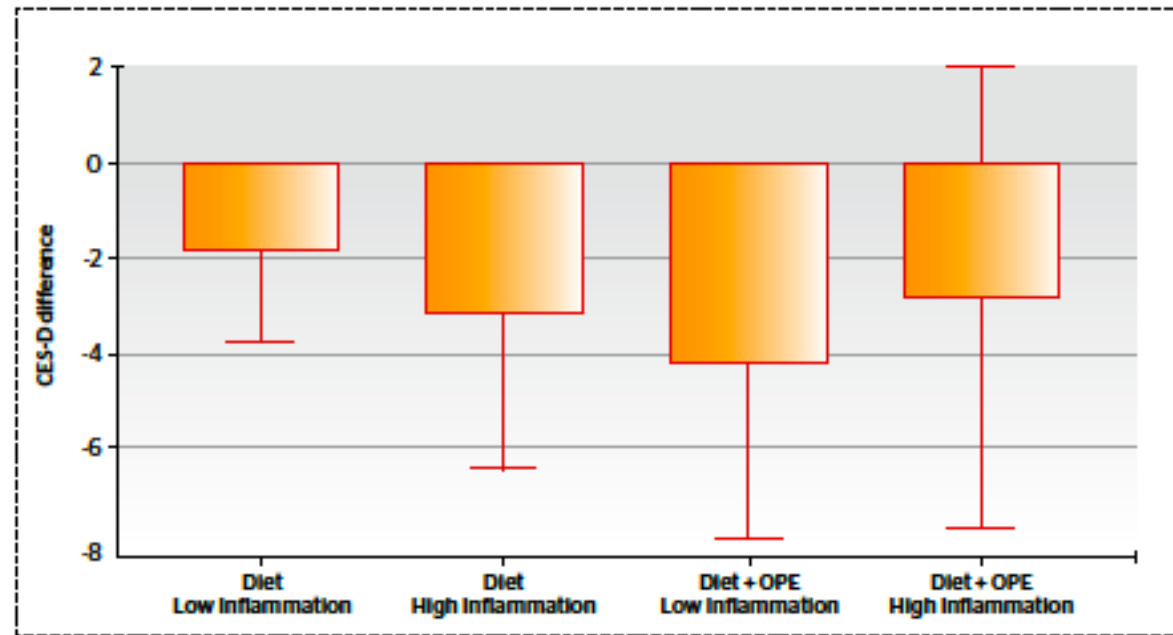




# The CES-D\* score varies according to the inflammatory profile



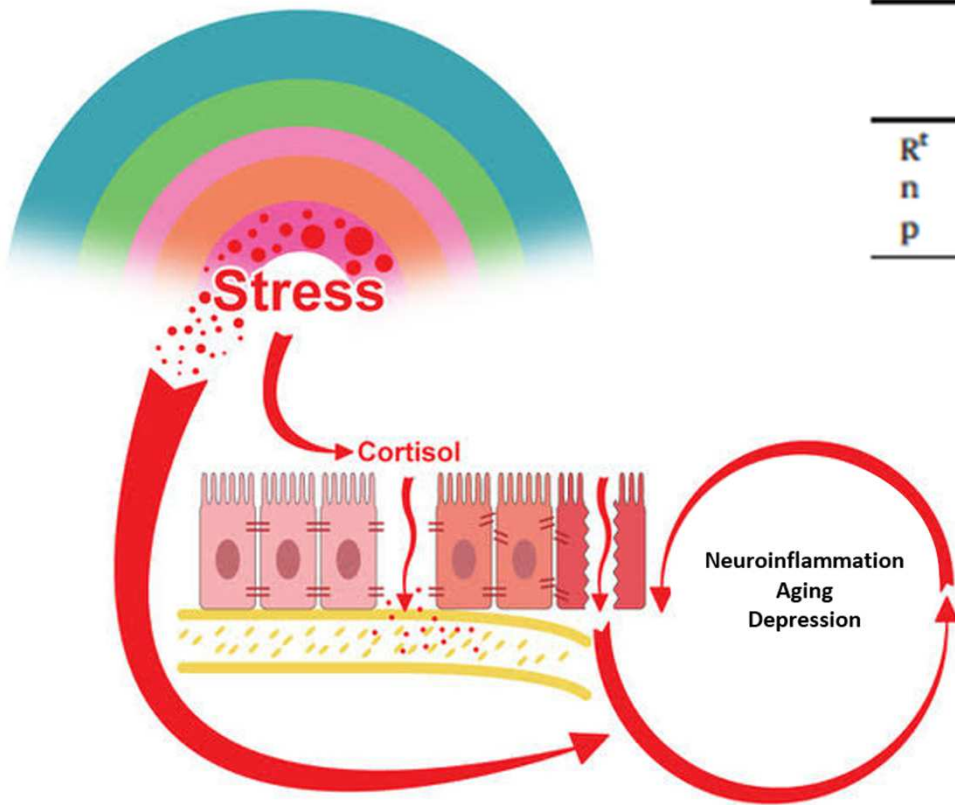
**Significant** decrease of the CES-D by AISA → mood modulation



\* Center for Epidemiological Studies Depression Score

Clin Nutr. 2016;35:812-818.

# BARRIER RESTORATION



**Table 1**

OPE containing 95% of *d*-Limonene: effect on epithelial barrier function.

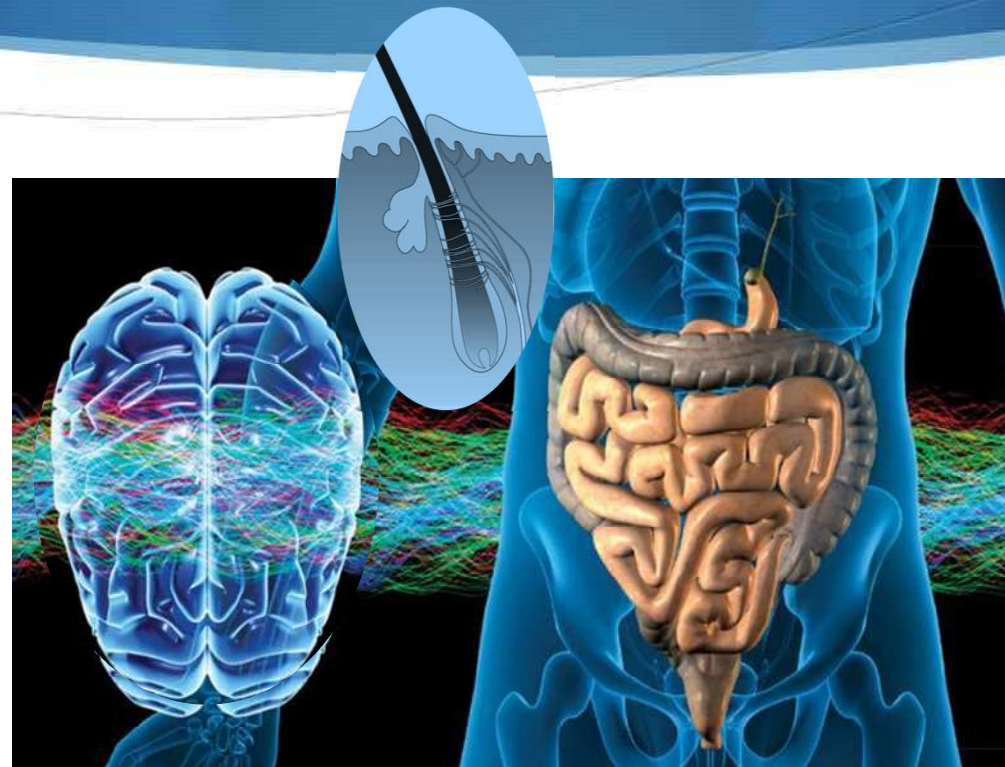
	Control	OPE			
		75 $\mu$ M	150 $\mu$ M	750 $\mu$ M	1500 $\mu$ M
$R^t$	107 $\pm$ 3%	106 $\pm$ 4%	112 $\pm$ 3%	132 $\pm$ 3%	153 $\pm$ 4%
n	9	6	6	6	6
p		n.s.	n.s.	<0.001	<0.001

Measure of the electric ( $\text{in } \Omega \cdot \text{cm}^2$ ) resistance as % of the initial resistance  $R_t$ .

Life Sciences. 2013;92:1151-1156

# Conclusions ....

## 1. A three-headed brain-skin-gut circuitry



## 2. Relieve of stress induced inflammation



With inflammation at the gut level, due to stress, the barrier function is altered.

**Vagal tone** activation induces repair and impairs chronic inflammation.

Balanced microbiota has been documented to be linked to healthspan extension.



# VAGAL ACTIVATION

Breathing – cardiac coherence



Enchanting sounds



Smell of a perfume



Manual pressure





Jean-François Bisson, Chantal Menut, Claudio Franceschi, Valeria M Ursini, Joerg D Schulzke, Marie C Béné, Olivier Herault



# Thank you for your attention



patri4639

[www.aisa-tx.com](http://www.aisa-tx.com)



@PatriziadAless4

[www.aisa-care.com](http://www.aisa-care.com)



European Innovation  
Partnership on Active  
and Healthy Ageing

REFERENCE SITE

[patriz.dalessio@gmail.com](mailto:patriz.dalessio@gmail.com)



**ISOAD** International Society on Aging and Disease