

# top ten

in gastroenterologia

**14<sup>^</sup> EDIZIONE**

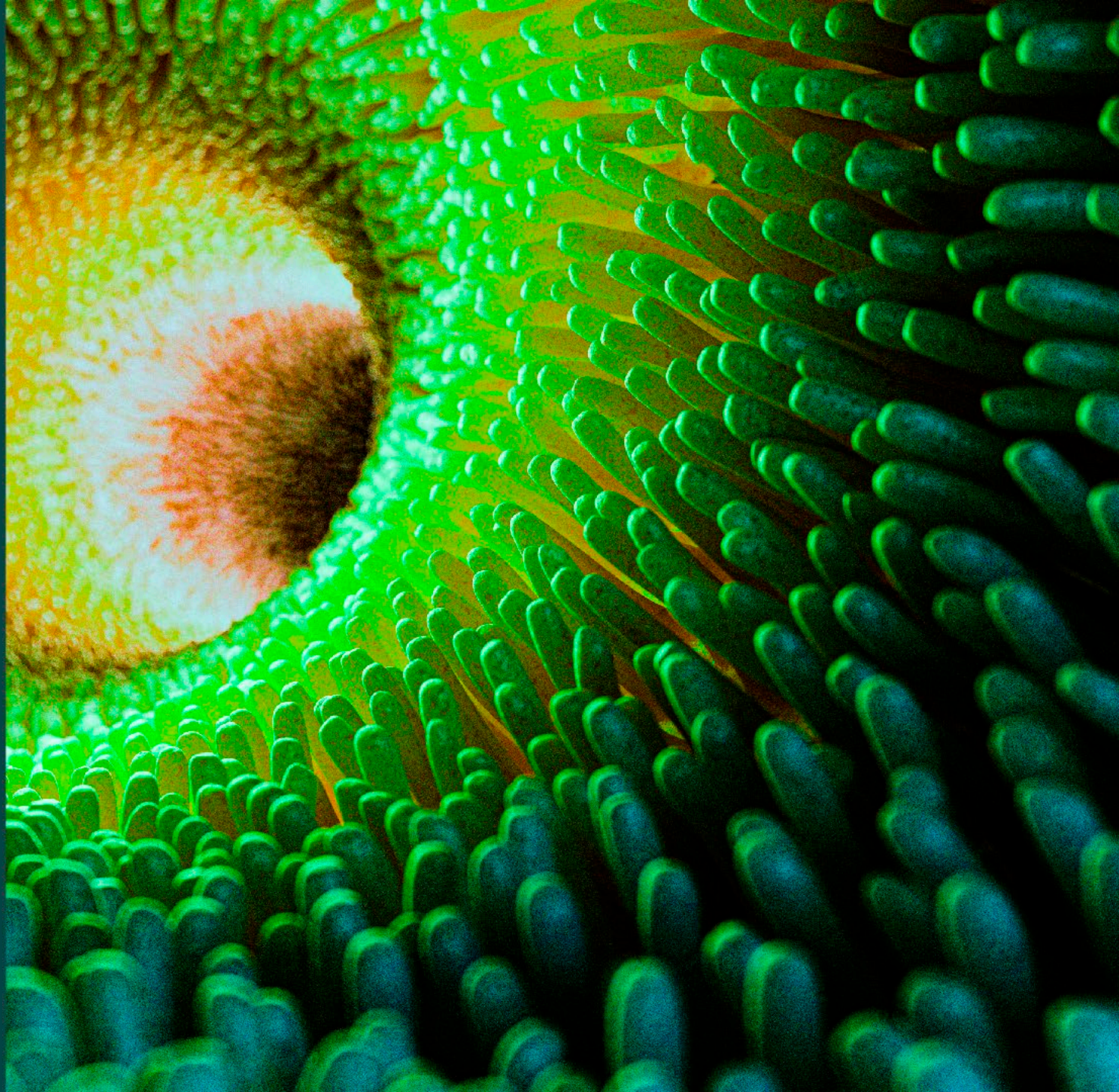
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**24-25 NOVEMBRE 2023**

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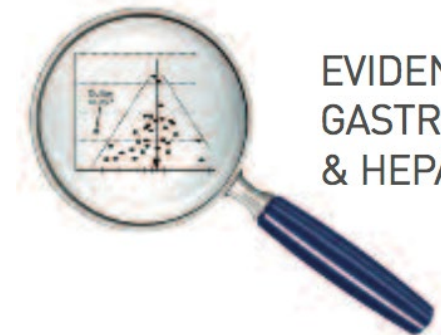
BERGAMO

HOTEL EXCELSIOR SAN MARCO  
Piazza della Repubblica, 6



# MECCANISMO D'AZIONE DEI PROBIOTICI

Maurizio Koch MD



EVIDENCE BASED  
GASTROENTEROLOGY  
& HEPATOLOGY



**EBGH**.IT  
GASTROENTEROLOGIA IN EVIDENZA





I have no disclosures to declare

Maurizio Koch M.D.

[Kochmaurizio@gmail.com](mailto:Kochmaurizio@gmail.com)

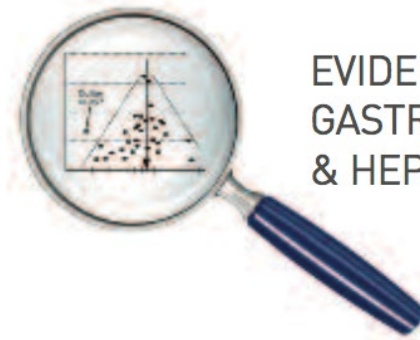
Senior Director

GI & Liver Unit

General Hospital S.Filippo Neri

Club for Evidence Based Gastroenterology & Hepatology ([www.EBGH.it](http://www.EBGH.it))

Rome Italy



EVIDENCE BASED  
GASTROENTEROLOGY  
& HEPATOLOGY



**Exciting times for microbiota research !  
WELCOME BACK AFTER ONE YEAR!**

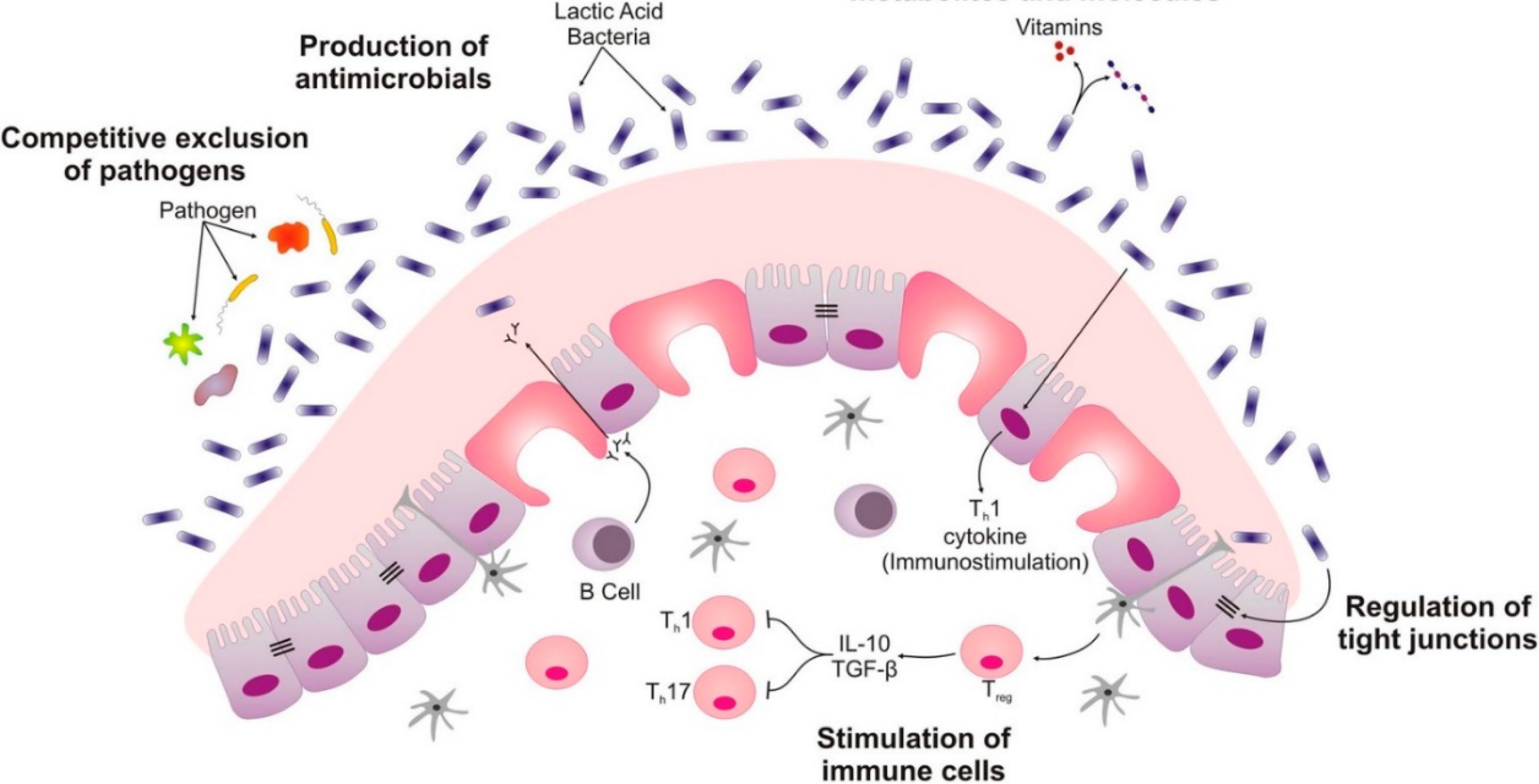


**YOU SHOULD START TAKING PROBIOTICS NOW, BEFORE WE DISCOVER THAT THEY DON'T MAKE ANY DIFFERENCE**

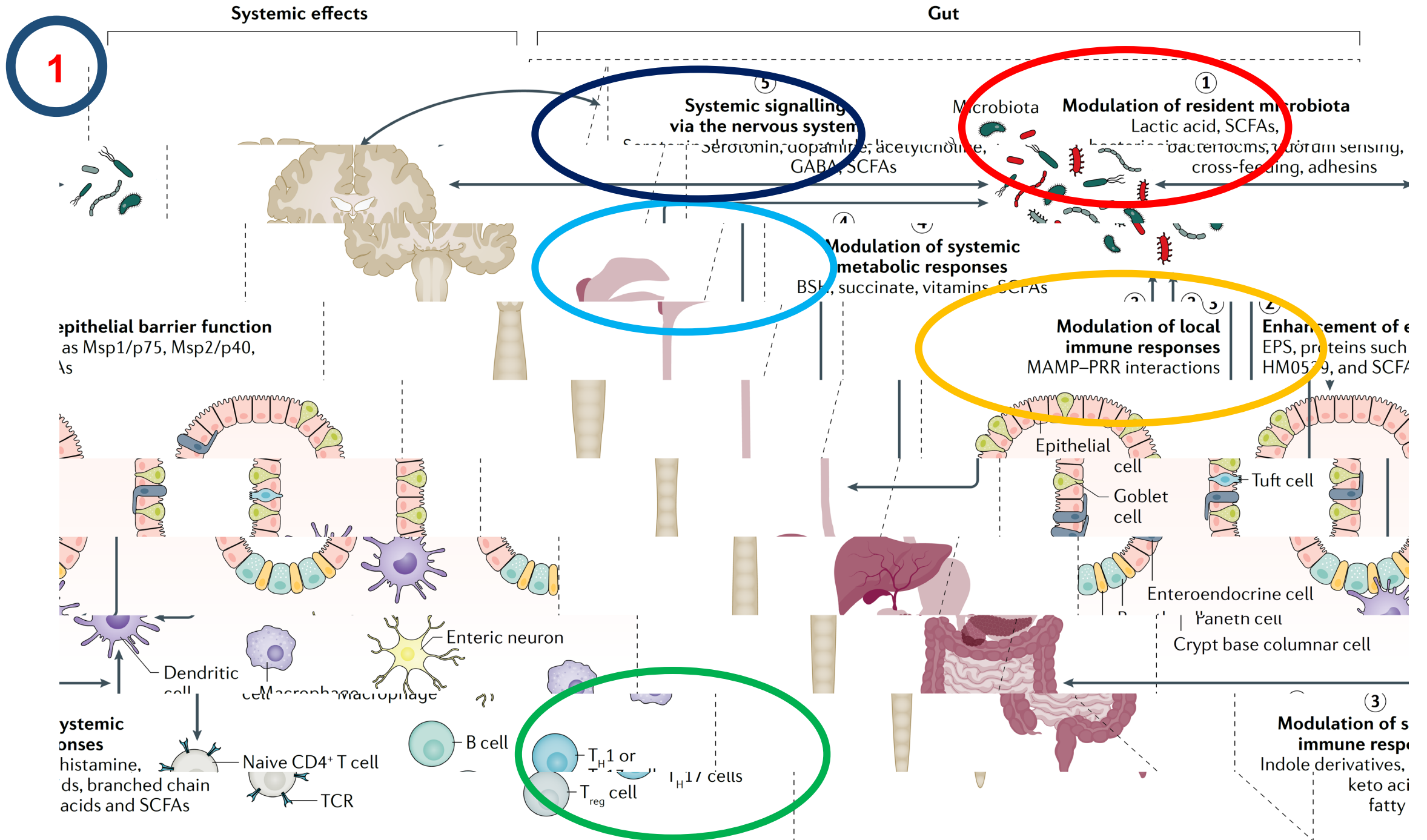
# Production of Important metabolites and molecules

## Production of antimicrobials

## Competitive exclusion of pathogens



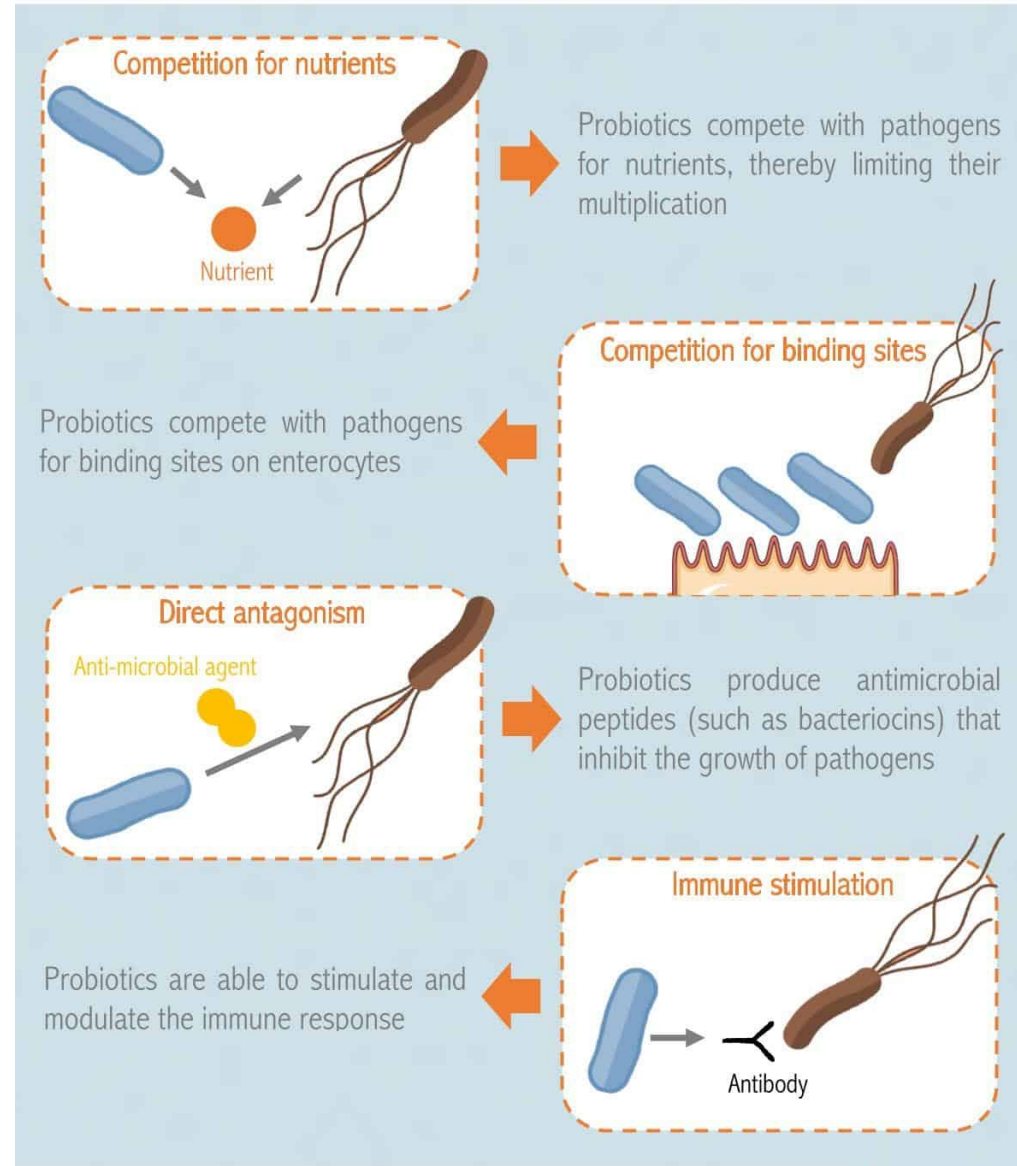




## WHAT ARE THE MECHANISMS OF ACTION OF PROBIOTICS AGAINST PATHOGENS?



## MODULATION OF RESIDENT BACTERIA



### CAPTION:



Probiotic



Pathogen



Enterocyte





2

# **BENEFICIAL MODULATION OF MICROBIOTA**

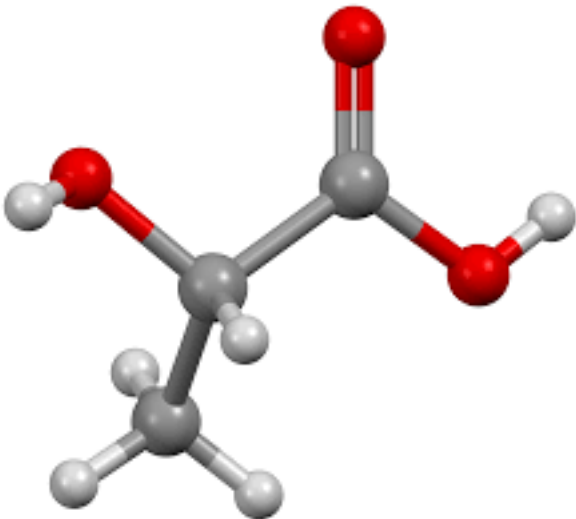
**LACTIC ACID**

**BACTERIOCINS**

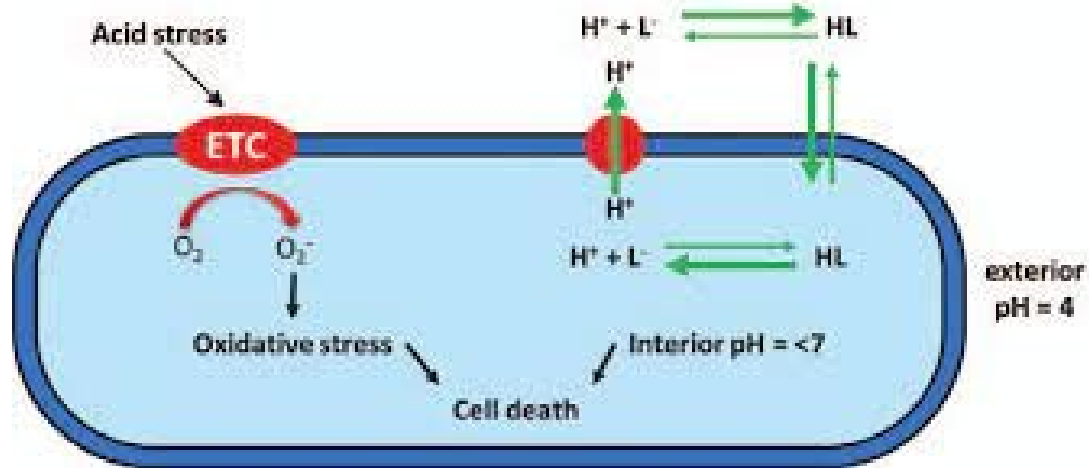
**QUORUM SENSING AND QUORUM QUENCHING MOLECULES**

**SCFAS AND BUTYRATE**

**COMPETE WITH RESIDENT MICROORGANISMS FOR ADHESION  
SITES**

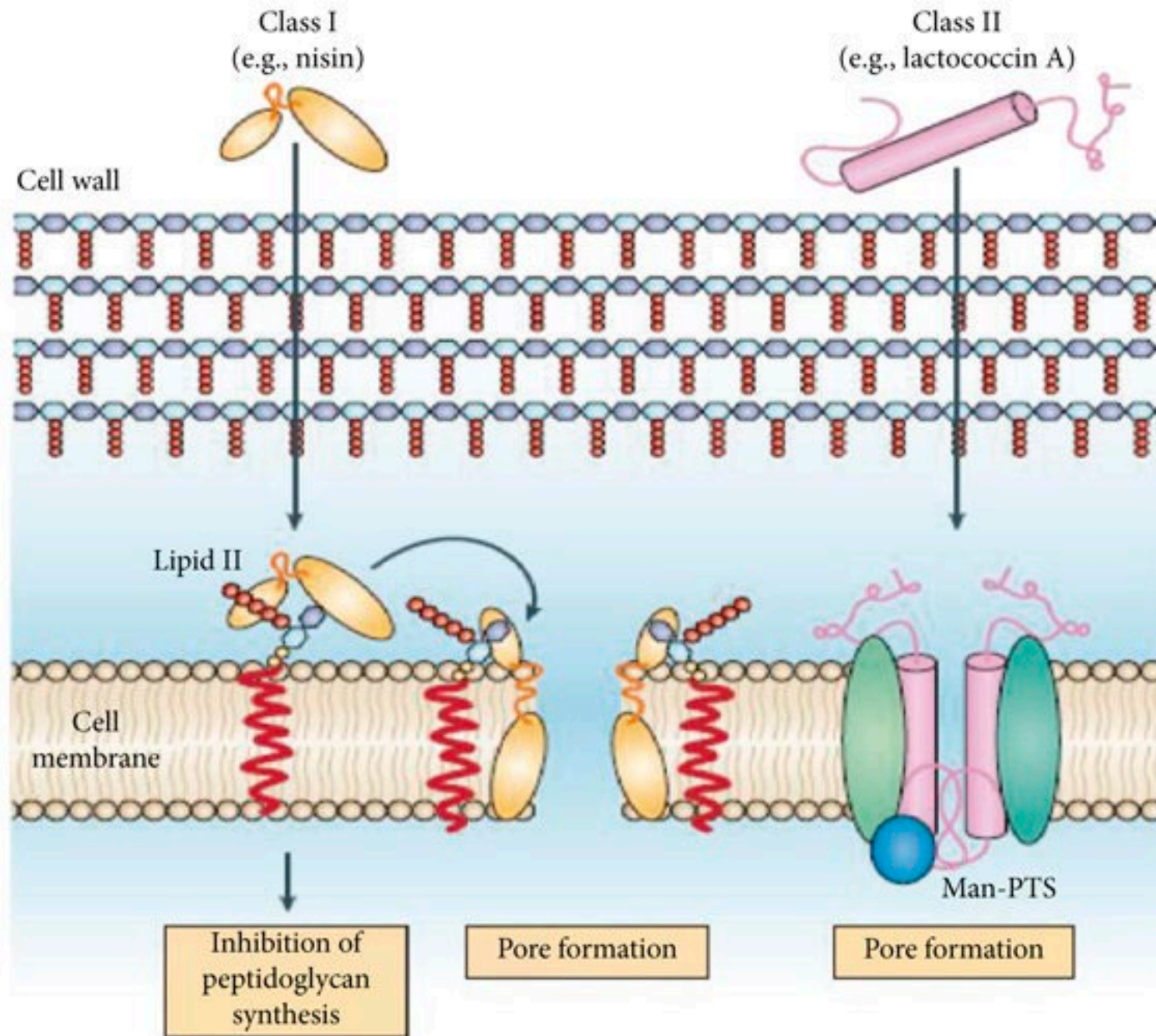


# LACTIC ACID



**bacteriostatic effects by interfering with pathogen cell membrane functions, leading to membrane permeability, loss of cell contents, lysis, and death**

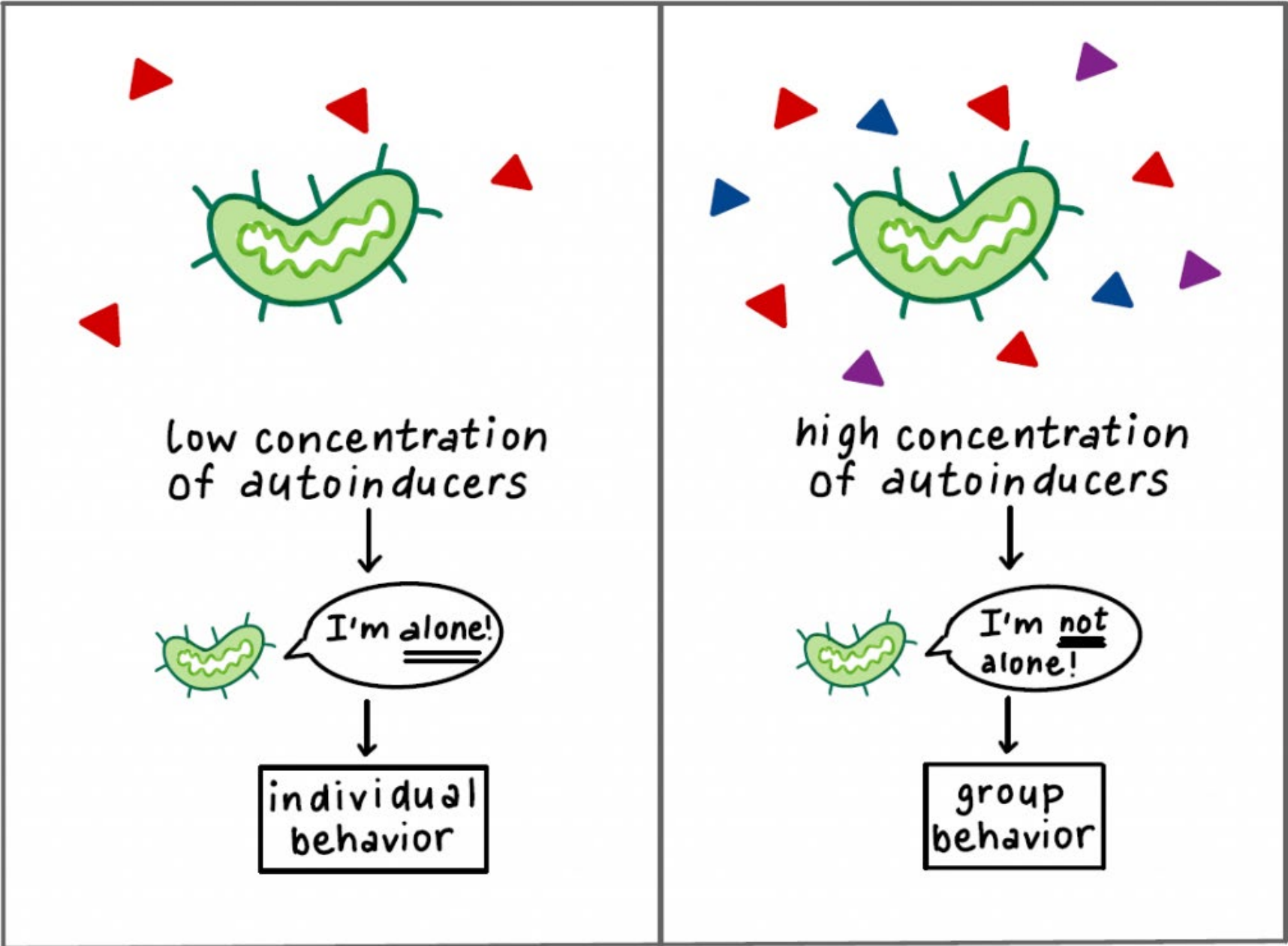
# BACTERIOCINS





# QUORUM SENSING/ quenching

Il quorum-sensing è una forma di comunicazione utilizzata dai batteri per scambiarsi informazioni l'uno con l'altro. Per comunicare, i batteri utilizzano particolari composti chimici (chiamati autoinduttori) che forniscono informazioni sulla popolazione batterica, fra cui informazioni sulle sue dimensioni.



**Forma  
Planctonica**

**Biofilm**

4. Distacco e reversione a crescita planctonica  
cominciando un nuovo ciclo

1. Attaccamento alla  
superficie

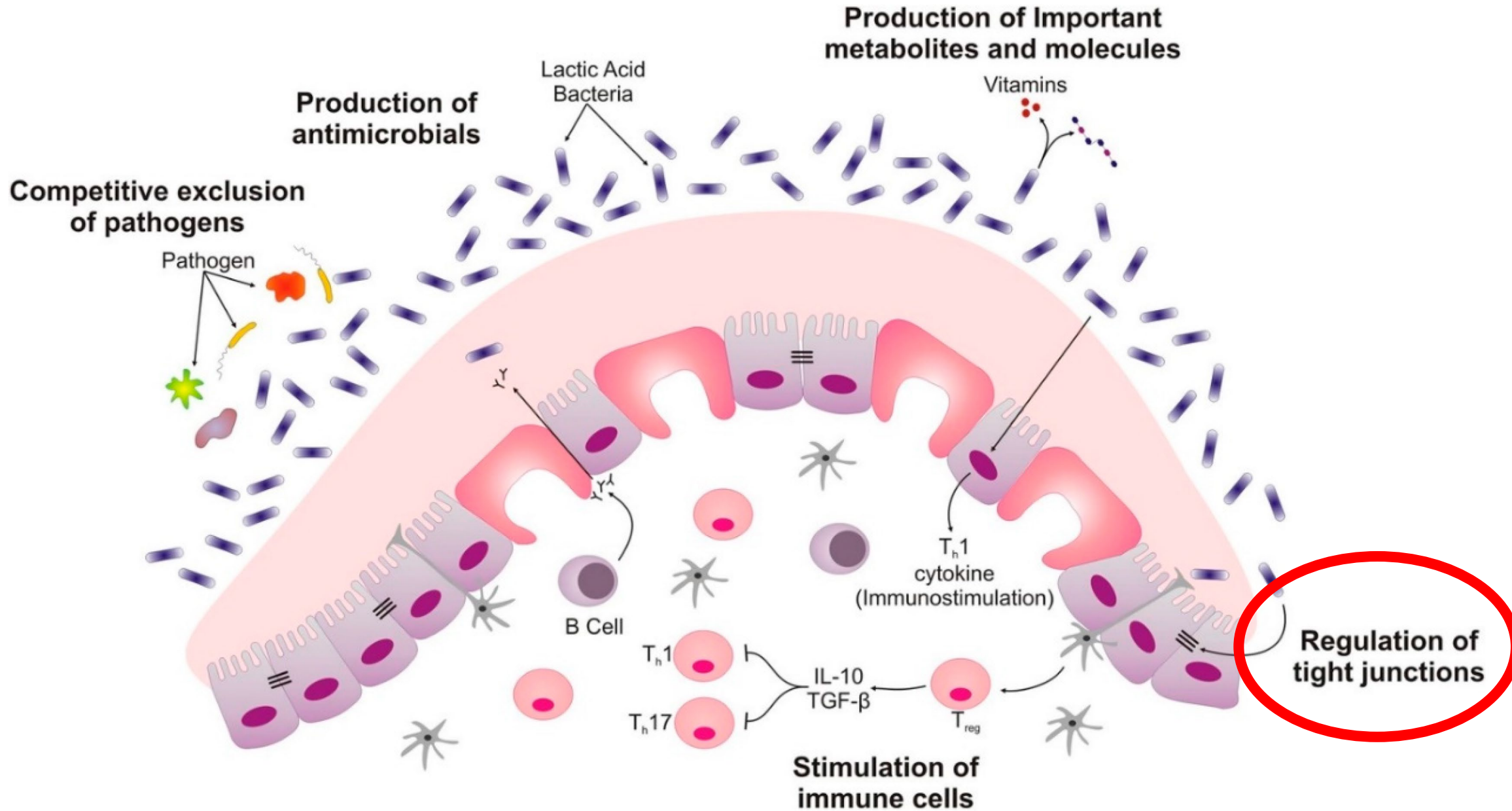
2. Formazione del mono-  
strato e produzione di  
matrice

3. Formazione di micro-  
colonia, multistrato

5. Biofilm maturo, presenza di matrice  
extracellulare formata da polisaccaridi

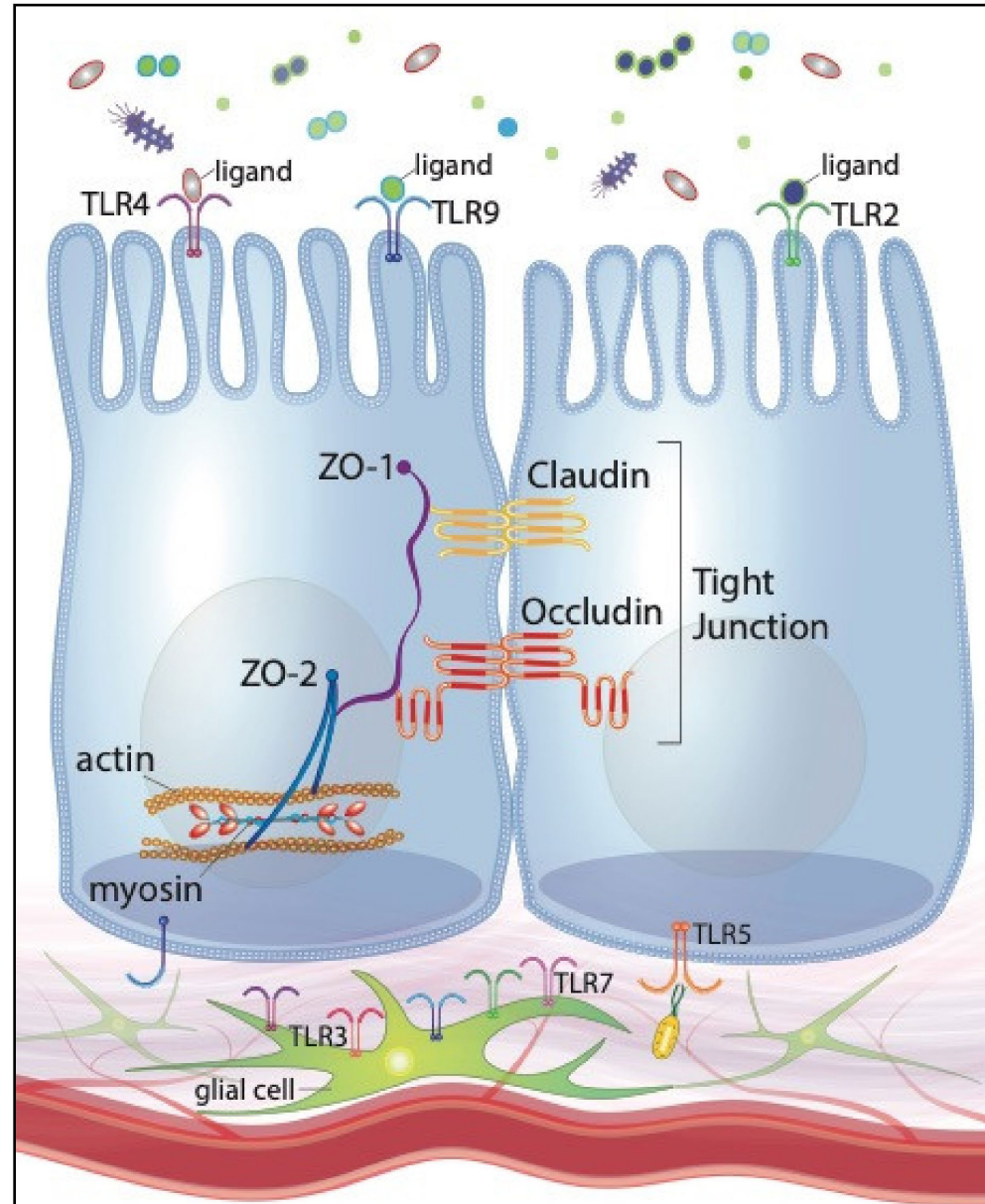


# ENHANCEMENT OF EPITHELIAL BARRIER FUNCTION





# ENHANCEMENT OF EPITHELIAL BARRIER FUNCTION



## **SECRETED PROTEINS**

**MSP1/P75**

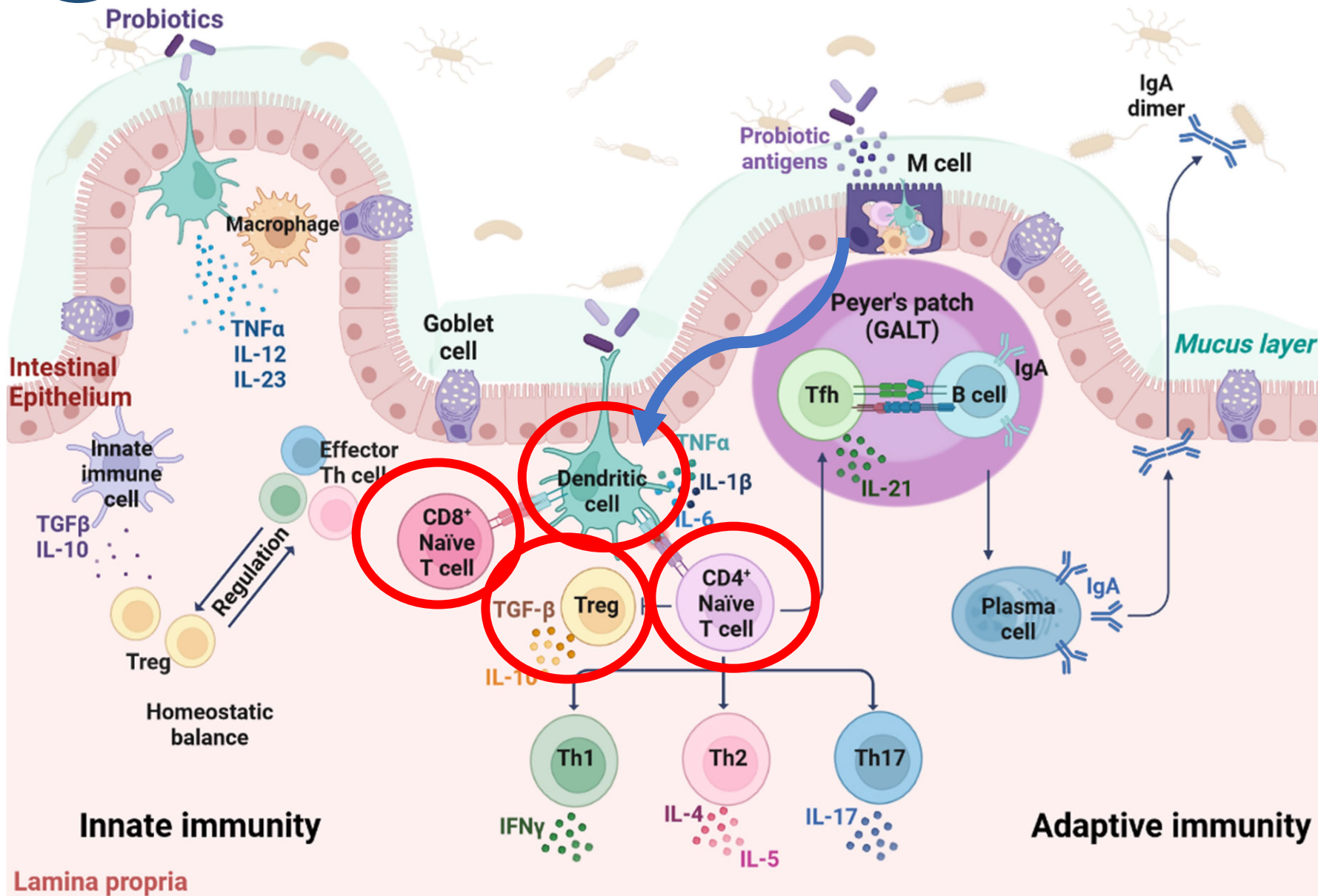
**MSP1/P40**

**HM0539**

**EXOPOLYSACCHARIDES**

**SHORT CHAIN FATTY ACID !**

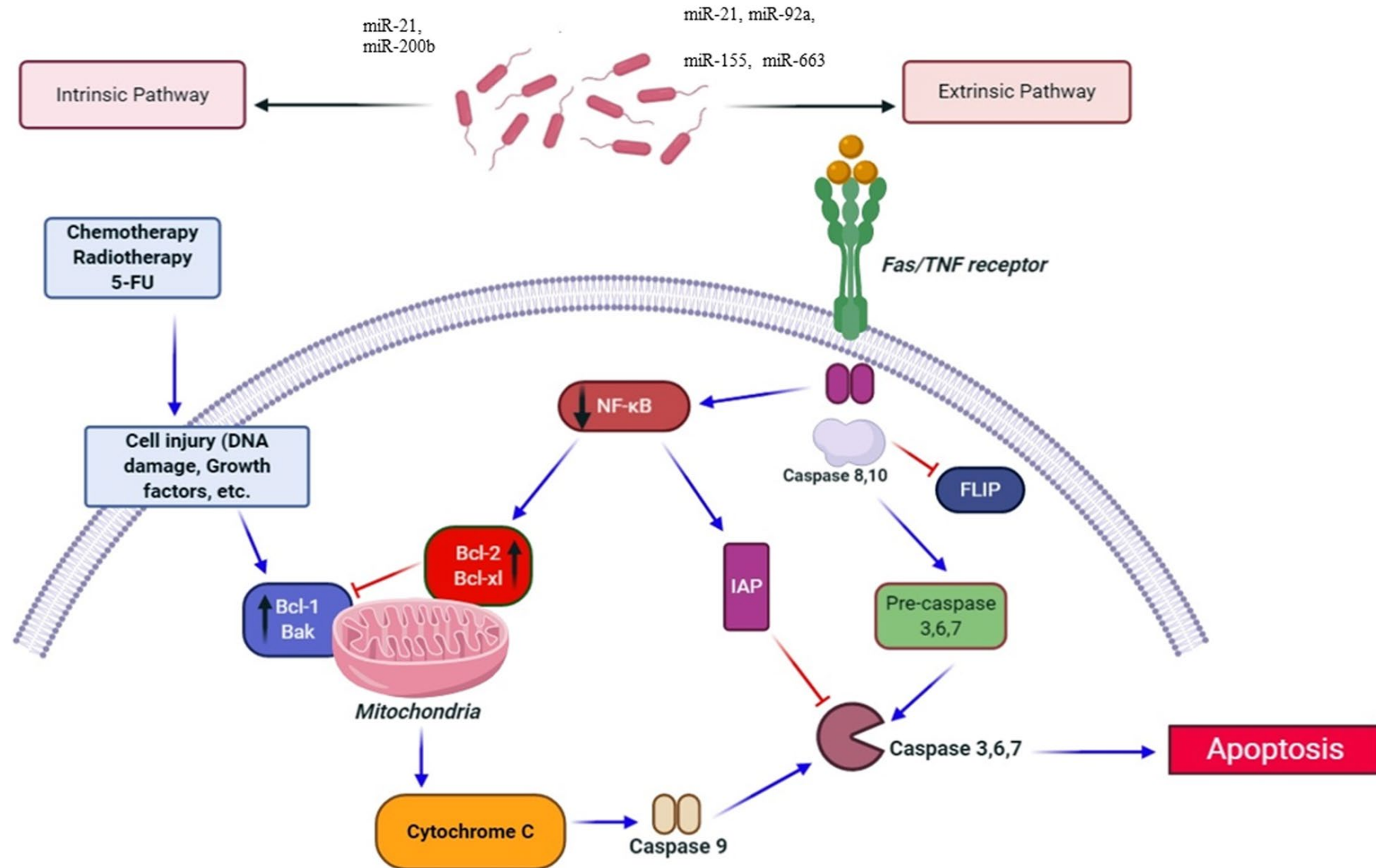
# MODULATION OF IMMUNE RESPONSES





- A. ENHANCE SIGNALING IN HOST CELLS TO REDUCE INFLAMMATORY RESPONSE.**
- B. SWITCH IN IMMUNE RESPONSE TO REDUCE ALLERGY.**
- C. PROBIOTICS AS VEHICLES TO DELIVER ANTI-INFLAMMATORY MOLECULES TO THE INTESTINE.**
- D. REDUCE THE PRODUCTION OF INFLAMMATORY SUBSTANCES.**

## EFFECTS OF THERAPEUTIC PROBIOTICS ON MODULATION OF MICRORNAS



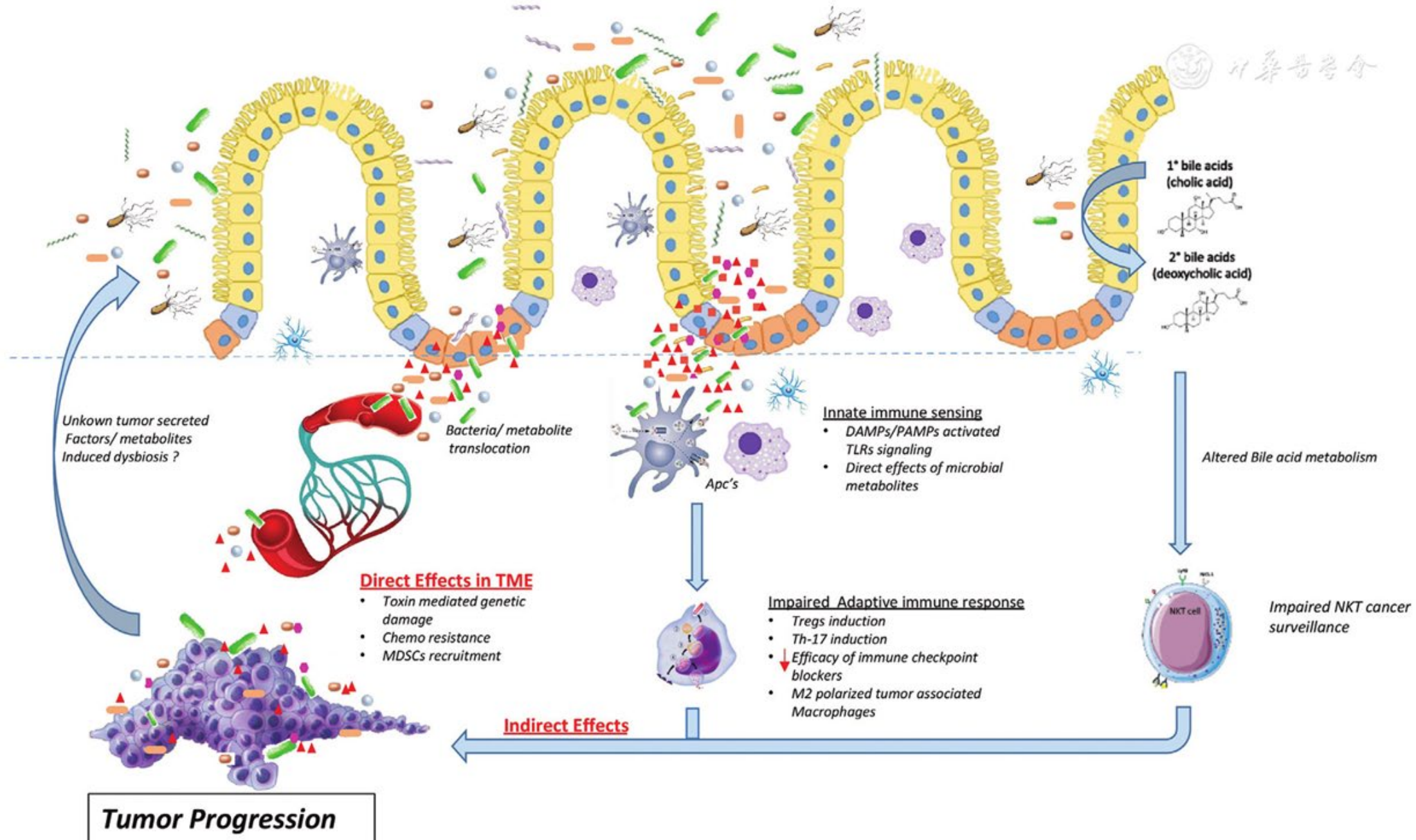
A schema of anti- apoptotic effects of probiotics. Various microRNAs i.e., miR-21, miR-200b and miR-21 can indirectly affect on apoptosis pathways

# EFFECTS OF THERAPEUTIC PROBIOTICS ON MODULATION OF MICRORNAS

MicroRNA	Probiotics	Probiotic concentrations	Expression	Target gene	Effects	Model	Sample (n)
miR-215-5p, miR-10b-5p, miR-21-5p, miR-26a-5p, miR-22-3p, miR-10a-5p, miR-148a-3p, miR-194, miR-92-3p, miR-30d, miR-181a-5p, miR-429-3p, let-7f-5p, miR-30a-5p, miR-133a-3p, miR-199-3p, miR-30c-5p, miR-200a-3p, miR-126-5p, miR-27b-3p	<i>Lactobacillus plantarum</i> Z01 (LPZ01)	$1 \times 10^8$ CFU/mL	Down-regulation of miR-215-5p, miR-3525, miR-122-5p and up regulation of miR-193a-5p, miR-375 and miR-215-5p	cAMP-dependent protein kinase activity, stress-activated MAPK cascade, MAPK and Wnt signaling pathways.	Decrease inflammation in <i>S. typhimurium</i> infection in neonatal broiler chicks	<i>In vivo</i> (Newly hatched chicks)	-
miR-135b, miR-155, miR-26b and miR-18a	<i>Lactobacillus acidophilus</i> and <i>Bifidobacterium bifidum</i> (Bla/016P/M)	$1 \times 10^9$ CFU/g and $1 \times 10^9$ CFU/g	Up regulation of miR-135b, miR-155 and down regulation of miR-26b, miR-18a	APC, PTEN, KRAS, and PU.1	-.	<i>In vivo</i> (Mice)	-
miR-423-5p	<i>Enterococcus faecium</i> NCIMB 10415	$3.6 \times 10^6$ CFU/g	Up regulation of miR-423-5p	Immunoglobulin lambda light C region (IGLC) and immunoglobulin kappa constant (IGKC)	-	<i>In vivo</i> (Landrace pigs)	-
	<i>Lactobacillus rhamnosus</i> GG, <i>Bifidobacterium animalis</i> subsp. <i>lactis</i> Bb-12 and <i>L. acidophilus</i> La-5	$5 \times 10^{10}$ CFU, $5 \times 10^{10}$ CFU and $5 \times 10^9$ CFU				Human	54
miR-122a	<i>Lactobacillus rhamnosus</i> GG	$1 \times 10^9$ CFU	Down-regulation of miR-122a	?	Decrease ethanol-elevated miR122a levels and attenuate ethanol-induced liver injury	<i>In vivo</i> (Mice)	-

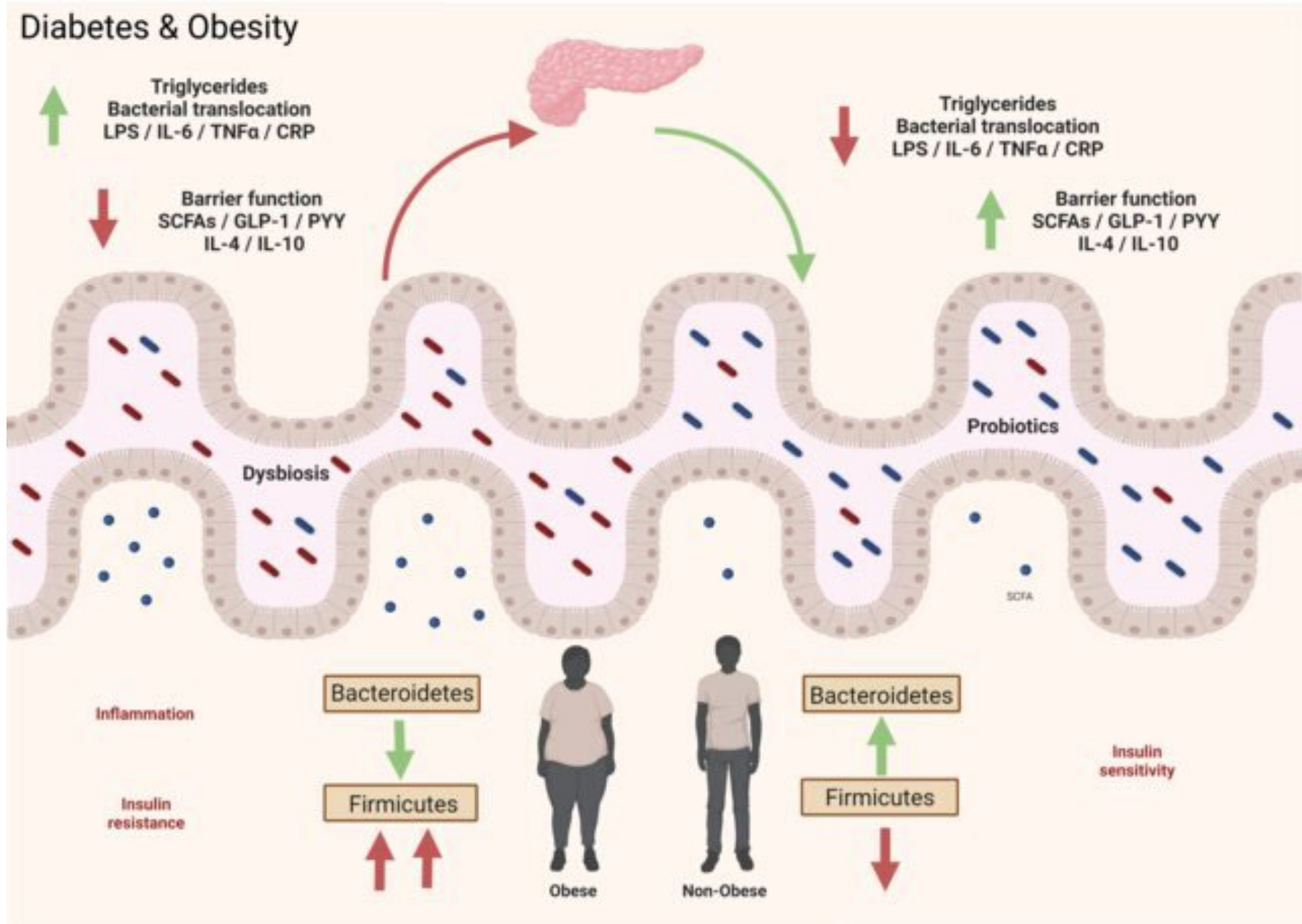
Etc, etc, etc....

# PROBIOTIC ANTI CANCER EFFECTS ?





# MODULATION OF SYSTEMIC METABOLIC RESPONSES



## MODULATION OF SYSTEMIC METABOLIC RESPONSES

BILE SALT HYDROLASE



Glucose, lipid, energy metab  
(loss : *Clostridium Difficile*)

SUCCINATE



Intestinal gluconeogenesis

SCFA



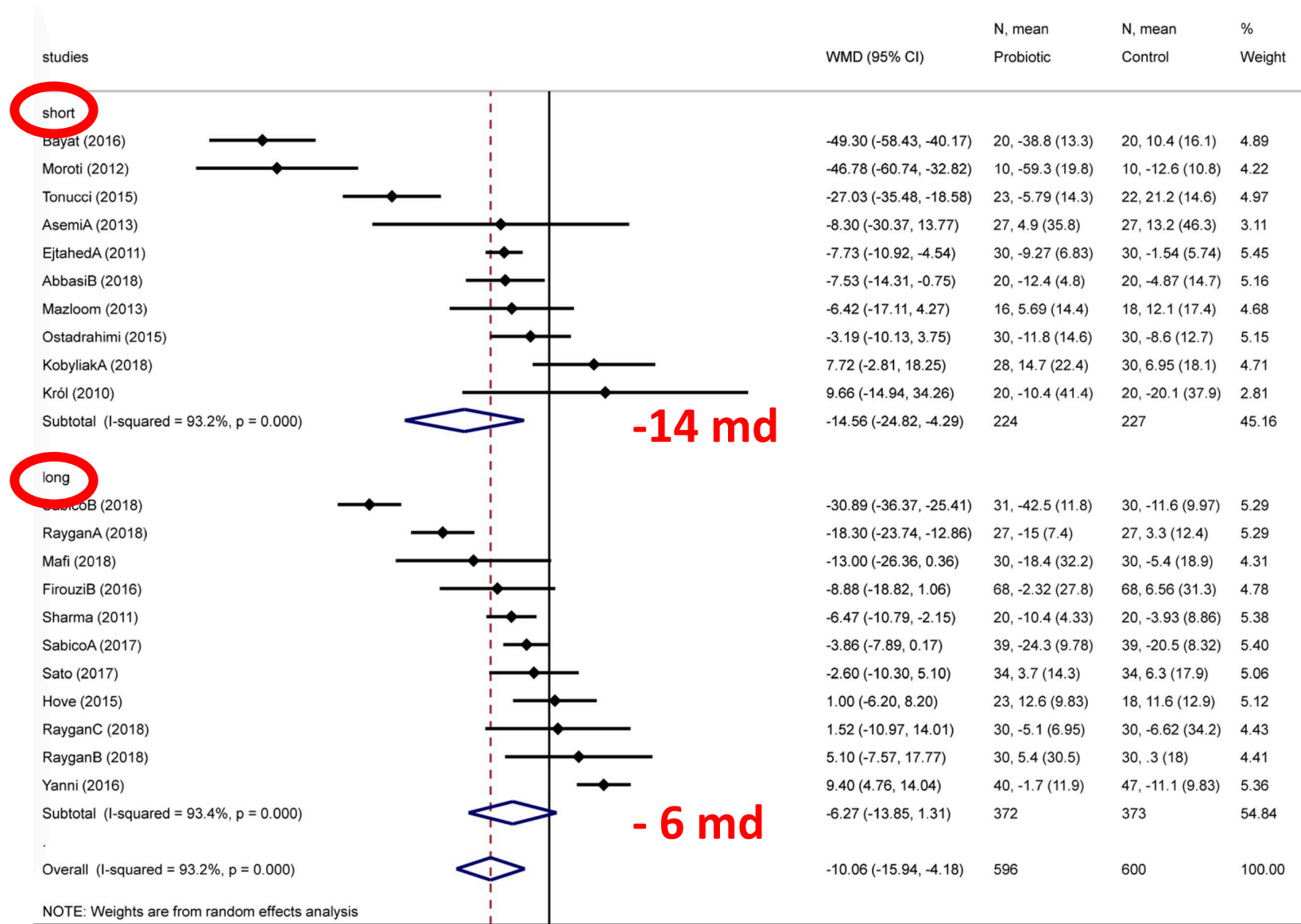
Insulin sensitivity, glucose  
tolerance; lipid metab.;  
Oxidative stress

# Probiotics have beneficial metabolic effects in patients with type 2 diabetes mellitus: a meta-analysis of randomized clinical trials

Tícia Kocsis<sup>1</sup>, Bálint Molnár<sup>1</sup>, Dávid Németh<sup>1</sup>, Péter Hegyi<sup>1,2</sup>, Zsolt Szakács<sup>1,3</sup>,  
Alexandra Bálint<sup>1,4</sup>, András Garami<sup>1</sup>, Alexandra Soós<sup>1</sup>, Katalin Márta<sup>1</sup> & Margit Solymár<sup>1</sup>✉

**32 TRIALS vs PLACEBO**

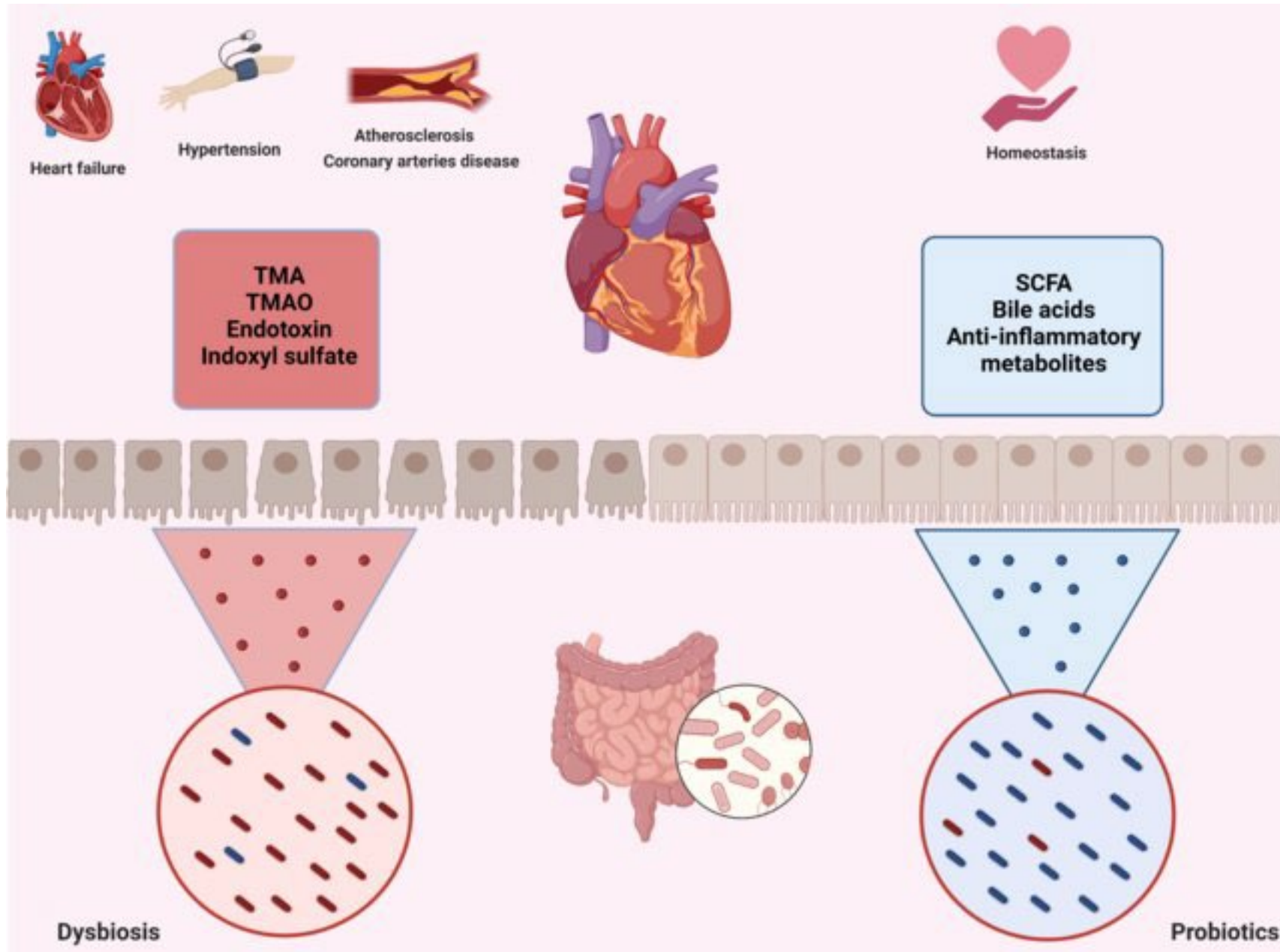
# TOTAL CHOLESTEROL: SHORT vs LONG Tx > 8w





**PROBIOTICS  
COULD INFLUENCE  
BLOOD TESTS,  
STRONGLY CORRELATED  
TO CLINICAL OUTCOMES**

# HEART



THE PRESENT AND FUTURE

2023

JACC REVIEW TOPIC OF THE WEEK

# Gut Microbiome-Based Management of Patients With Heart Failure

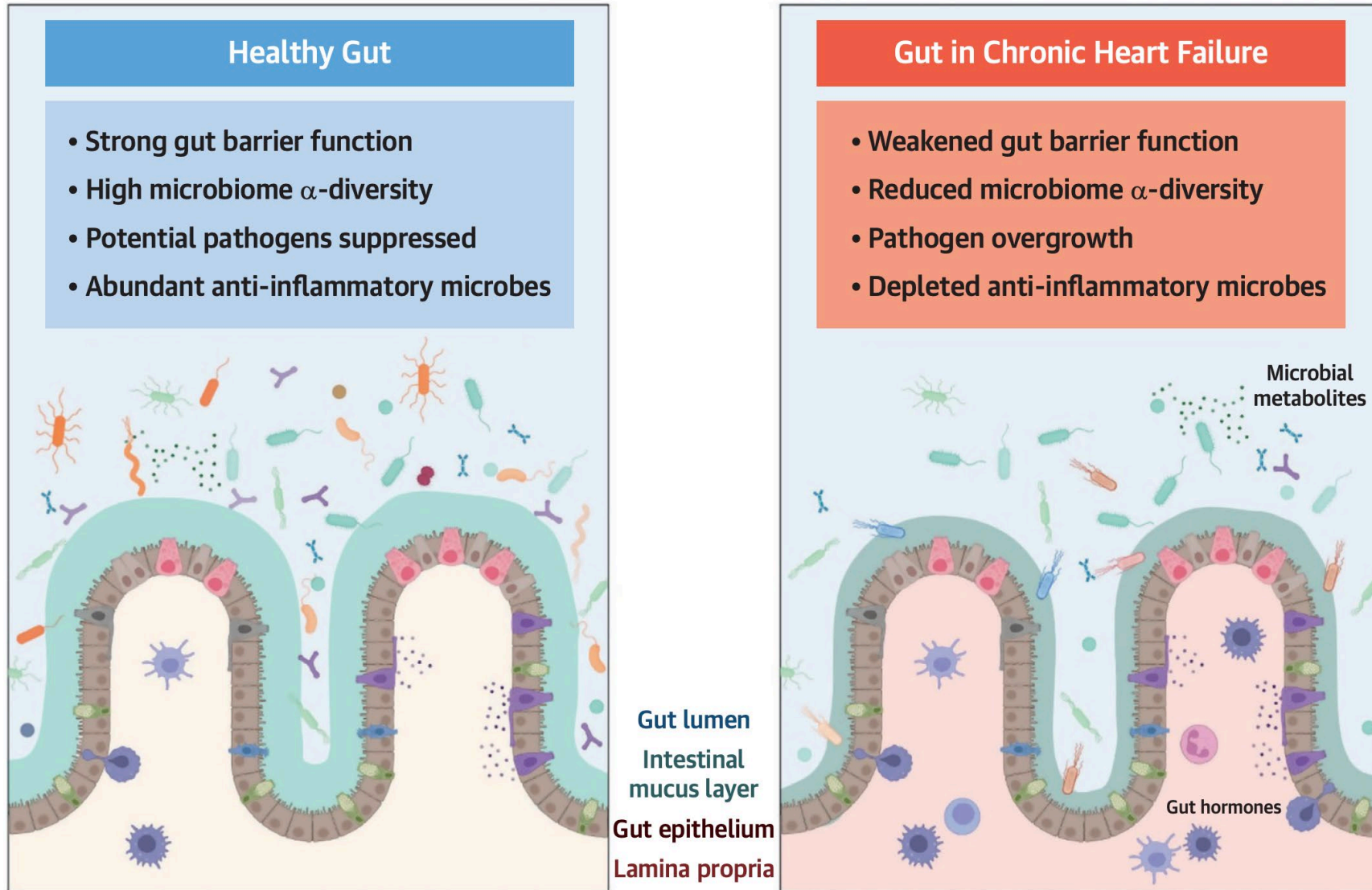
JACC Review Topic of the Week

Petra Mamic, MD,<sup>a,b</sup> Michael Snyder, PhD,<sup>b</sup> W.H. Wilson Tang, MD<sup>c</sup>

## ABSTRACT

Despite therapeutic advances, chronic heart failure (HF) is still associated with significant risk of morbidity and mortality. The course of disease and responses to therapies vary widely among individuals with HF, highlighting the need for precision medicine approaches. Gut microbiome stands to be an important aspect of precision medicine in HF. Exploratory clinical studies have revealed shared patterns of gut microbiome dysregulation in this disease, with mechanistic animal studies providing evidence for active involvement of the gut microbiome in development and pathophysiology of HF. Deeper insights into gut microbiome-host interactions in patients with HF promise to deliver novel disease biomarkers, preventative and therapeutic targets, and improve disease risk stratification. This knowledge may enable a paradigm shift in how we care for patients with HF, and pave the path toward improved clinical outcomes through personalized HF care. (J Am Coll Cardiol 2023;81:1729-1739) © 2023 by the American College of Cardiology Foundation.

**FIGURE 2** Chronic Heart Failure-Associated Gut Microbiome Differs From Healthy Microbiome



Key features of the heart failure-associated gut milieu and microbiome compared with healthy microbiome include impaired intestinal barrier function, reduced microbiome  $\alpha$ -diversity, pathogen overgrowth, and loss of anti-inflammatory gut microbes.



## HIGHLIGHTS

- Gut microbiome modulates HF pathophysiology, contributes to disease progression and therapeutic responses, and holds promise as a novel biomarker.
- Interactions among the gut microbiome, diet, and medications offer potentially innovative modalities for management of patients with HF.
- Interdisciplinary collaboration will facilitate translation of precision gut microbiomics to the clinical evaluation and management of patients with HF.

# Microbiome-derived metabolites comprise about 10% of all circulating metabolites among humans.

- The review highlighted particular metabolites that affect HF:
  - **Lipopolysaccharides** promote production of inflammatory cytokines and induce insulin resistance and atherothrombosis, leading to cardiac dysfunction
  - In contrast, **short-chain fatty acids** reduce systemic inflammation and augment the intestinal barrier. These molecules are also associated with benefits in cardiac remodeling; however, the concentration of short-chain fatty acids is reduced in cases of HF
  - **TMAO** is a metabolite related to the consumption of dietary L-carnitine and (phosphatidyl) choline, which are commonly found in animal products. TMAO has atherogenic and thrombotic effects, as well as negative effects on cardiac remodeling in mouse models.
  - **Phenacetylglutamine** reduces cardiomyocyte contractility and induces natriuretic gene expression, and adults with HF have higher mean levels of this metabolite as well

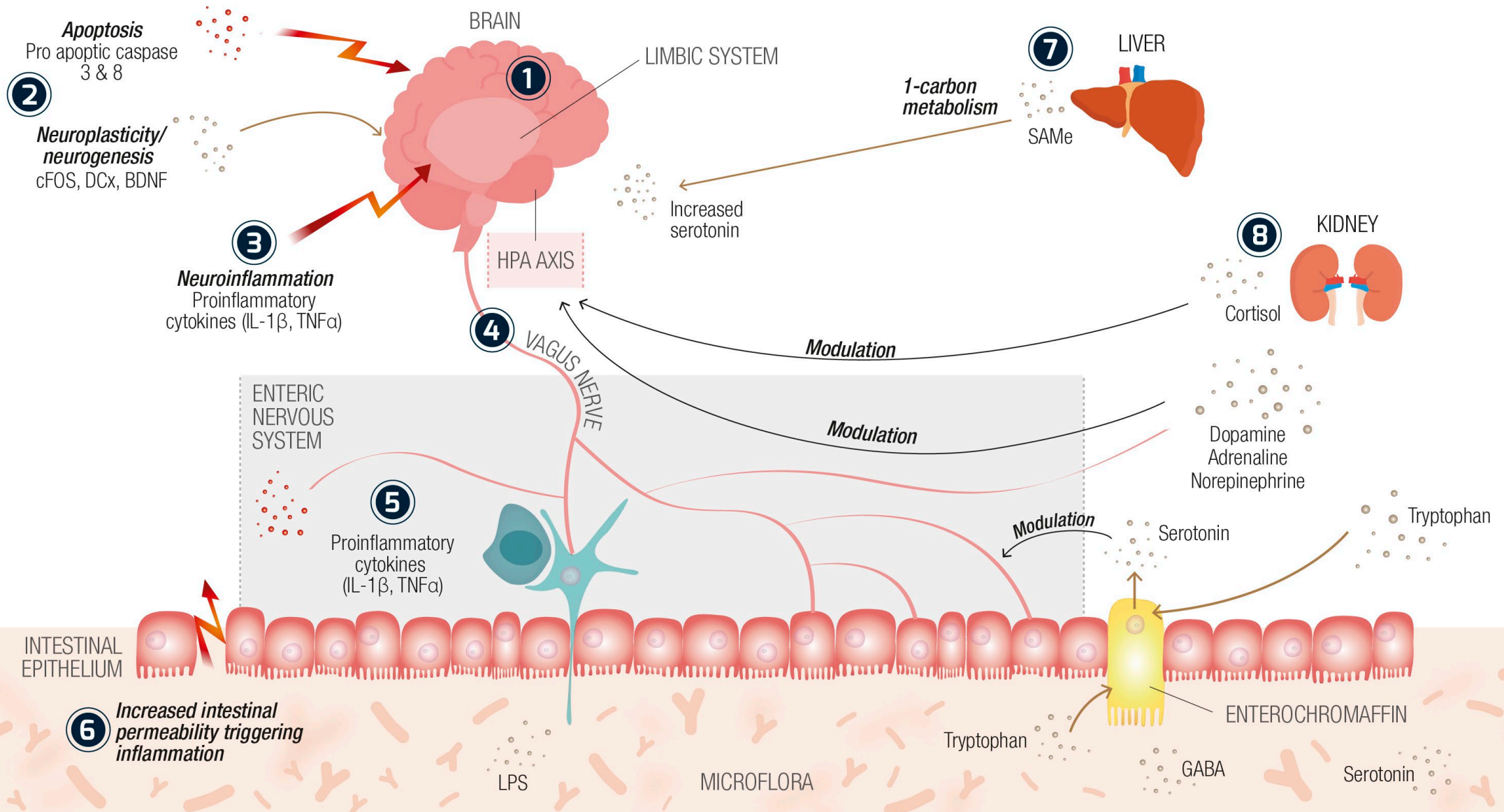
**TABLE 2** Design of Future HF Microbiome Studies

Study Feature	Rationale
General study design	Combining population-based and N-of-1 approach (in which each person serves as his or her own control) enables both group- and individual-level analyses, which is necessary to gain insights into highly personalized systems such as microbiome

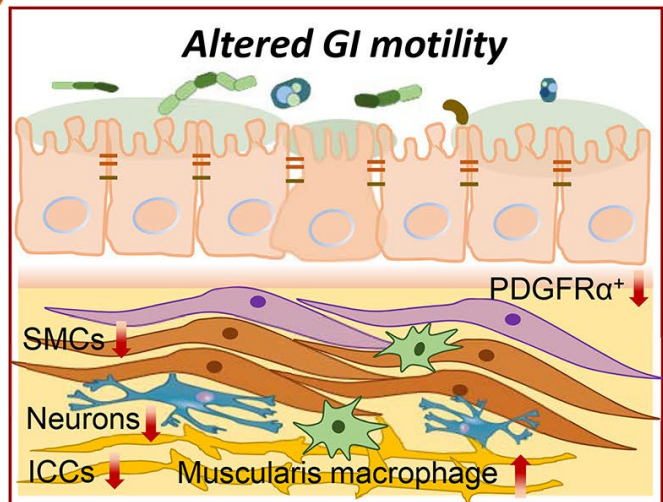
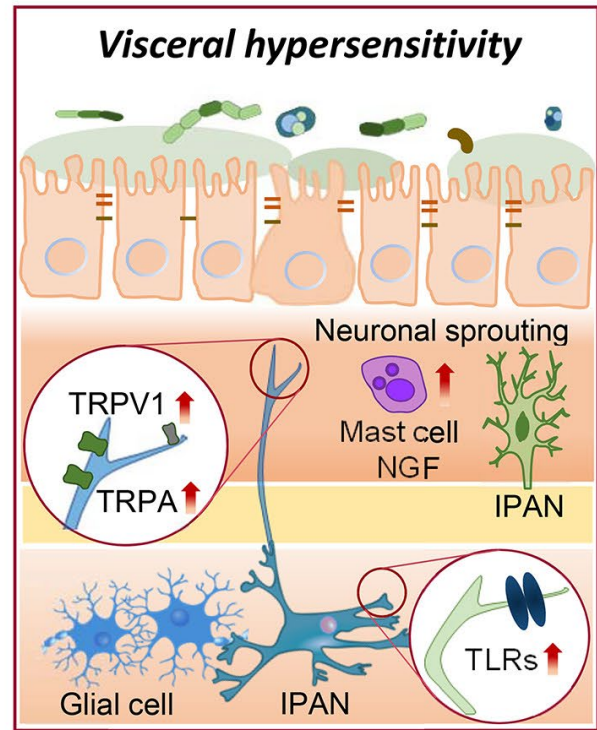
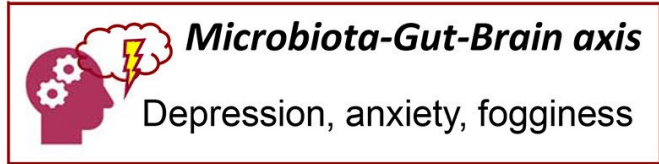
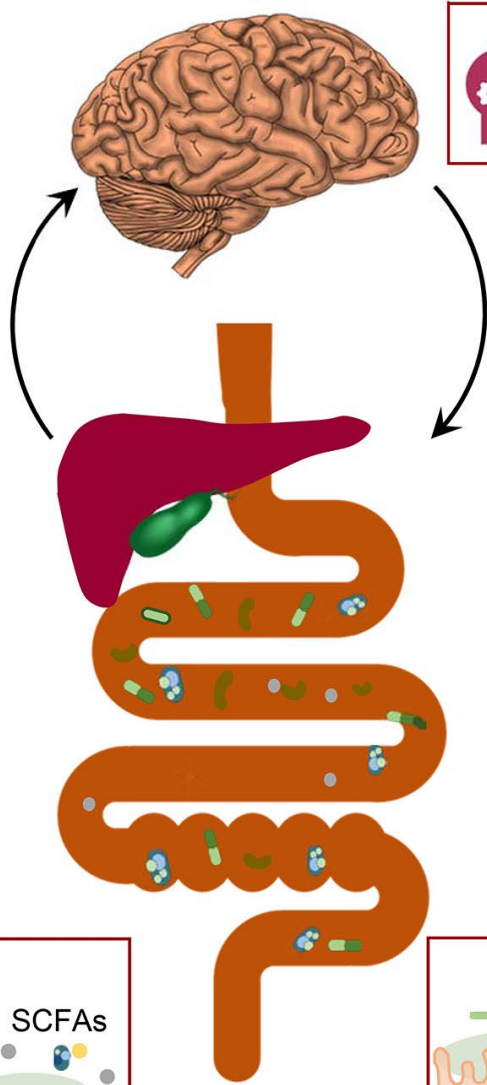
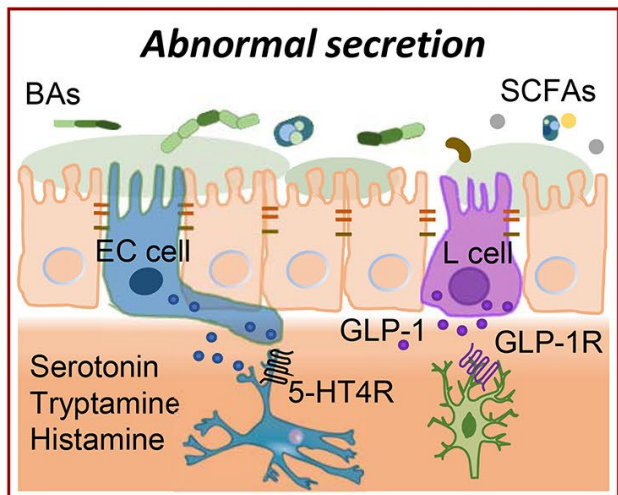
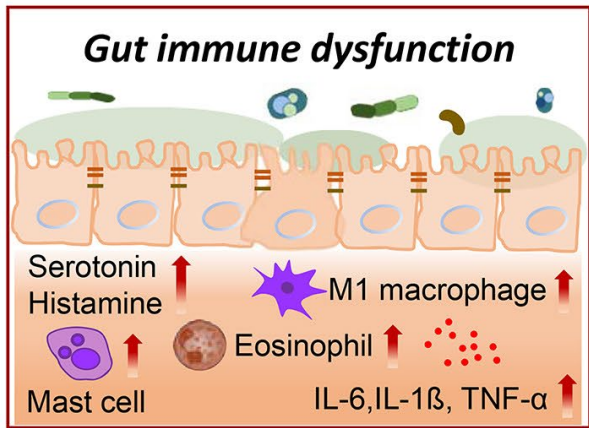
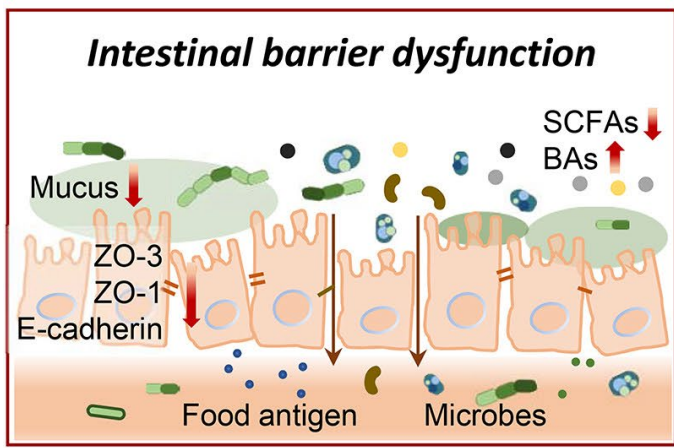
Combining population-based and N-of-1 approach (in which each person serves as his or her own control) enables both group- and individual-level analyses, which is necessary to gain insights into highly personalized systems such as microbiome.

	through multiomic approaches. Simultaneous clinical assessments—including HF functional status, cardiac imaging, biomarkers, and data on outcomes—are equally important to accurately relate microbiome activity to HF physiology.
Confounders	Given their impact on the microbiome community, relevant microbiome confounders—including comorbidities, medications, dietary, and lifestyle habits—need to be catalogued carefully to interpret study findings correctly.
Feasibility	To scale HF-microbiome research efforts, existing HF biobanks, consortia, and clinical trials could be leveraged.
HF = heart failure.	

# SYSTEMATIC SIGNALLING VIA THE NERVOUS SYSTEM







## **“Most diseases are characterized by a pathobiome”**

This term is unfortunately overly simplistic and inherently flawed. **Microorganisms and their metabolites are neither ‘good’ nor ‘bad’, they merely exist. Their impacts on us as hosts are heavily dependent on context. Microorganisms or metabolites that are deleterious in one context may cause no harm in another.** As examples, *Clostridioides difficile* can be carried asymptotically throughout life, and only cause problems in older age when the host is immunocompromised and treated with antibiotics. Similarly, a strain of *E. coli* may be relatively harmless in the colon, but cause a urinary tract infection if it invades the urethra.

**It is true, however, that numerous human conditions have been shown to correlate with alterations in microbiota composition. This is sometimes referred to as ‘dysbiosis’, which is also a vague term with limited clinical applicability.**

to disease progression in some conditions, including inflammatory bowel diseases: **however, such alterations are rarely consistent and the microbiota is hugely variable between individuals, both in health and disease. This makes it extremely difficult to identify gut microbiota configurations with the required specificity and reproducibility for clinical practice**

## REPLICABILITY

Developing a new conceptual framework and applying it to the human microbiome will require much more collaboration between investigators working across disparate fields, including evolution, ecology, microbiology, biomedicine and computational biology. It will also demand significant changes in how data and other resources are distributed between scientists, and in how currently disparate areas of microbiome research inter-relate.

**Data standards. Microbiome researchers have not yet broadly embraced quality-control practices for their data in a way that would make results more reproducible, and that would facilitate the analysis and interpretation of data across multiple studies.**

Studies based on characterizing genetic material, proteins or metabolites using high-throughput analyses will remain the norm for the foreseeable future. To produce useful results, however, researchers must adopt better data-sharing practices.

## MEDICINA DEI PROBIOTICI

HOME / AREE TEMATICHE / MEDICINA DEI PROBIOTICI

**ATTENZIONE  
RICERCATORI: OCCHIO  
ALLA REPLICABILITA'  
COME RENDERLA PIU'  
SISTEMATICA E  
MIGLIORARE LE  
EVIDENZE! DA "NATURE"  
(FREE)**

GASTROENTEROLOGIA,  
LINEE GUIDA EBM,  
MEDICINA DEI PROBIOTICI,  
METODOLOGIA, NEWSLETTER  
Di Redazione • 27 Settembre 2023

Replication games: how to make  
reproducibility research more  
systematic Abel Brodeur, Anna  
Dreber, Fernando Hoces de la  
Guardia & Edward Miguel...

Approfondisci... ▶

**PROBIOTICI E COLON  
IRRITABILE.  
ULTIMISSIMA META-  
ANALISI DA  
"GASTROENTEROLOGY"  
(FREE). PECCATO CHE  
NON SI DISTINGUA TRA  
FORME STIPSI E  
DIARREA!**

GASTROENTEROLOGIA, IBS,  
MALATTIA DIVERTICOLARE,  
MEDICI DI FAMIGLIA,  
MEDICINA DEI PROBIOTICI,  
MEDICINA INTERNA, NEWSLETTER  
Di Redazione • 5 Agosto 2023

Efficacy of Probiotics in Irritable  
Bowel Syndrome: Systematic  
Review and Meta-analysis Vivek  
C. Goodyer et al.  
BACKGROUND & AIMS: Some...

**TRAPIANTO FECALE: LA  
PRIMA CONFERENZA  
INTERNAZIONALE PER  
TENTARE LA  
STANDARDIZZAZIONE  
DELLA TECNICA NELLE  
IBD ! FINALMENTE!  
DA "BMJ" (FREE)**

GASTROENTEROLOGIA, IBD,  
MEDICINA DEI PROBIOTICI,  
MEDICINA INTERNA, NEWSLETTER,  
Senza categoria  
Di Redazione • 7 Luglio 2023

The first international Rome  
consensus conference on gut  
microbiota and faecal microbiota  
transplantation in inflammatory  
bowel disease Loris Riccardo...

Approfondisci... ▶

### NEWSLETTER

Iscriviti

### I NOSTRI CORSI



CONTRIBUTI VIDEO - BROCHURE

Notizie da EBGH.it - Gastroenterologia in evidenza

Dante, Paradiso, XXII, 67-69

**Se siete interessati ad un accesso unlimited  
segnalate la vs. email alla Segreteria.  
Riceverete ID e PASSWORD**



**top**  
**ten**

in gastroenterologia

**14<sup>^</sup> EDIZIONE**

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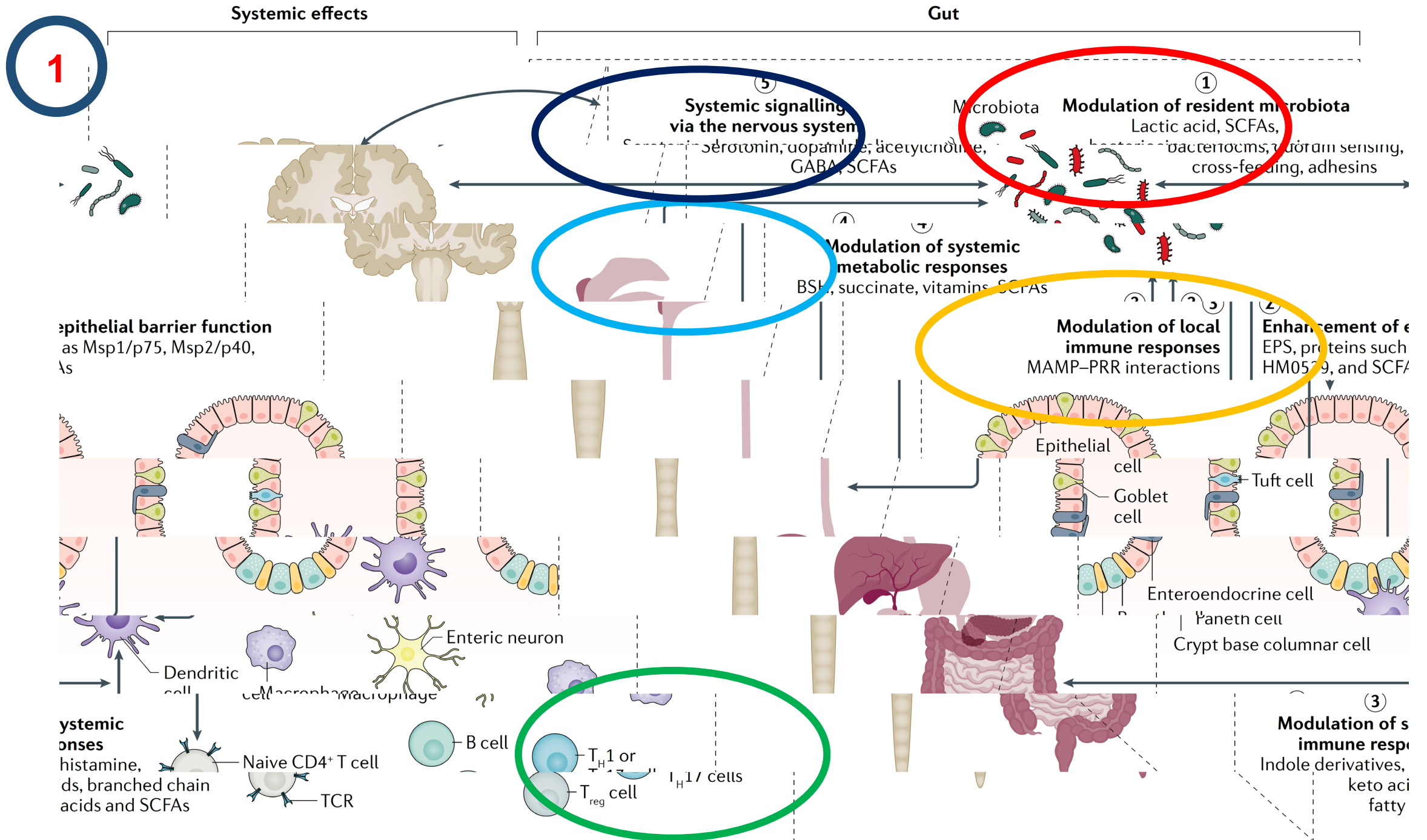
**24-25 NOVEMBRE 2023**

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**BERGAMO**

HOTEL EXCELSIOR SAN MARCO  
Piazza della Repubblica, 6

**TOP TEN Slides**



2

# **BENEFICIAL MODULATION OF MICROBIOTA**

**LACTIC ACID**

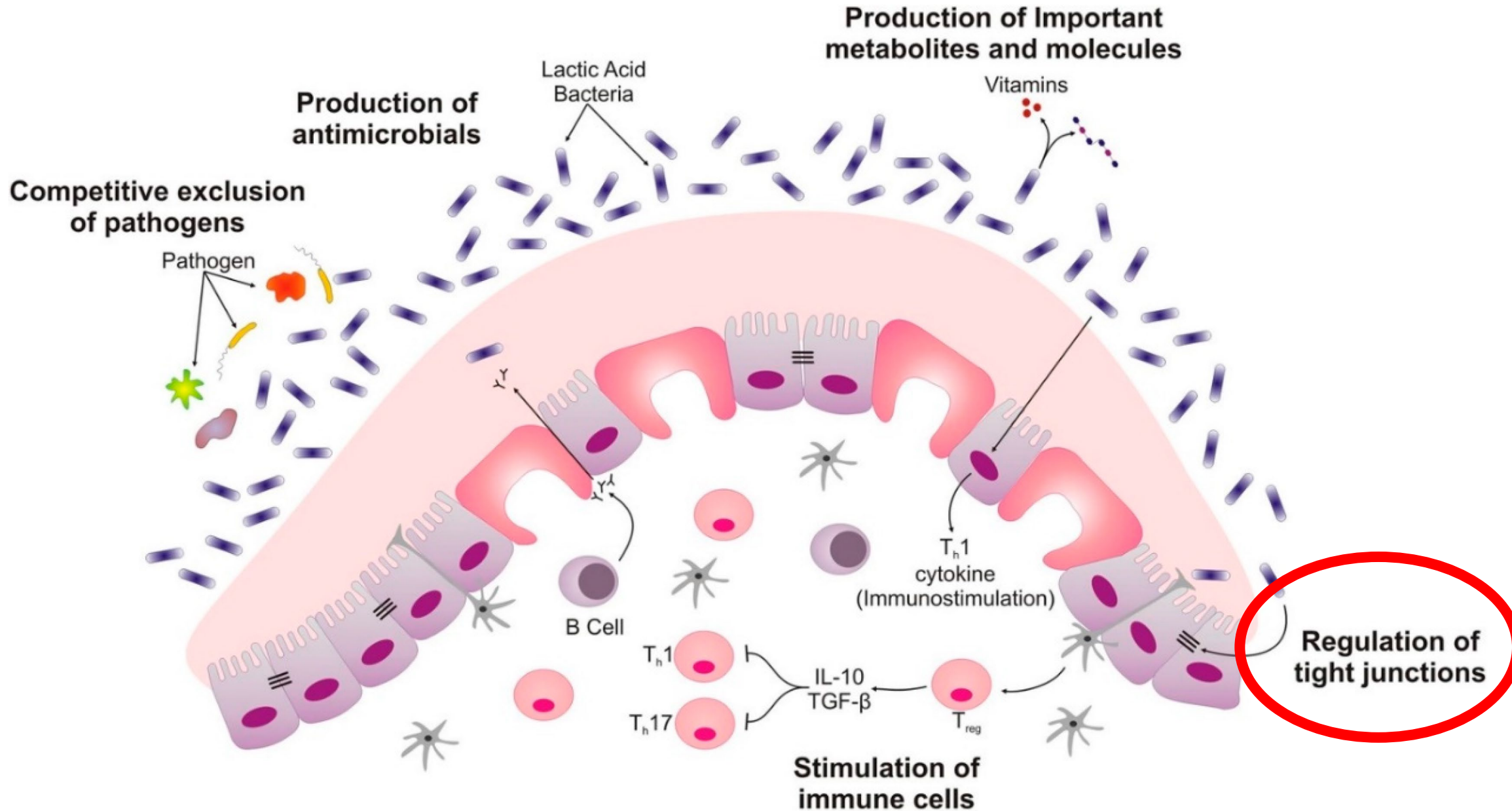
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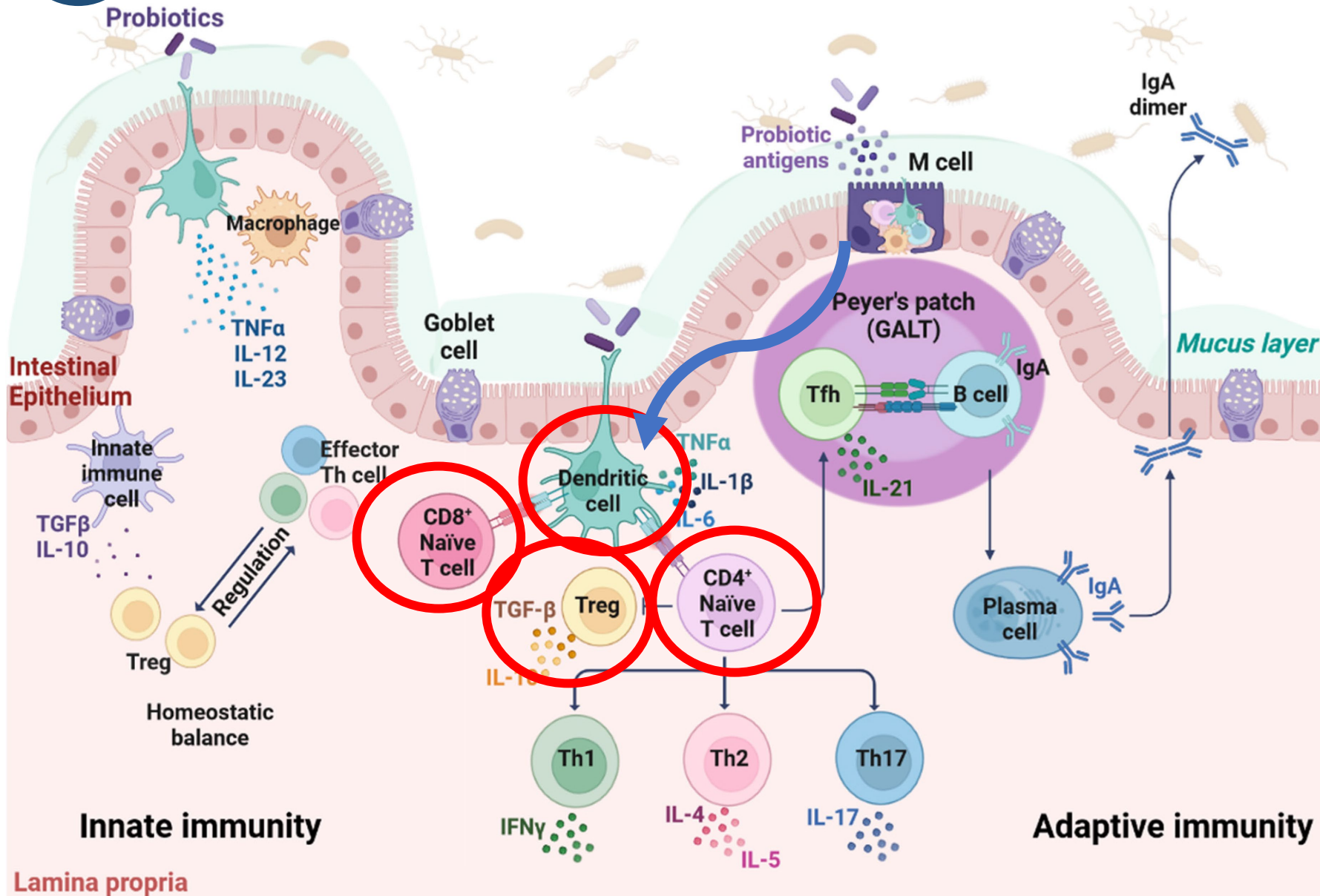
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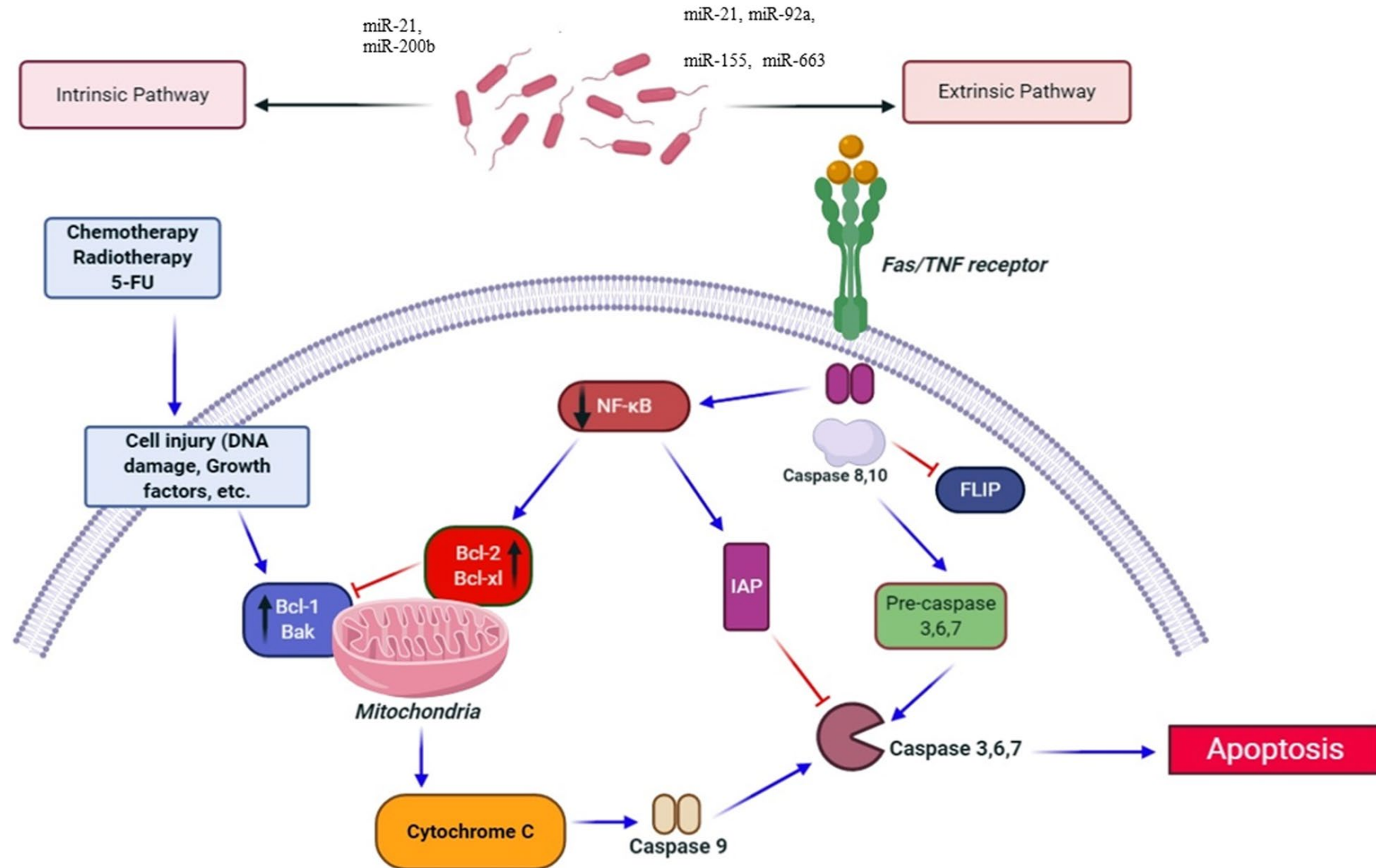




# MODULATION OF IMMUNE RESPONSES

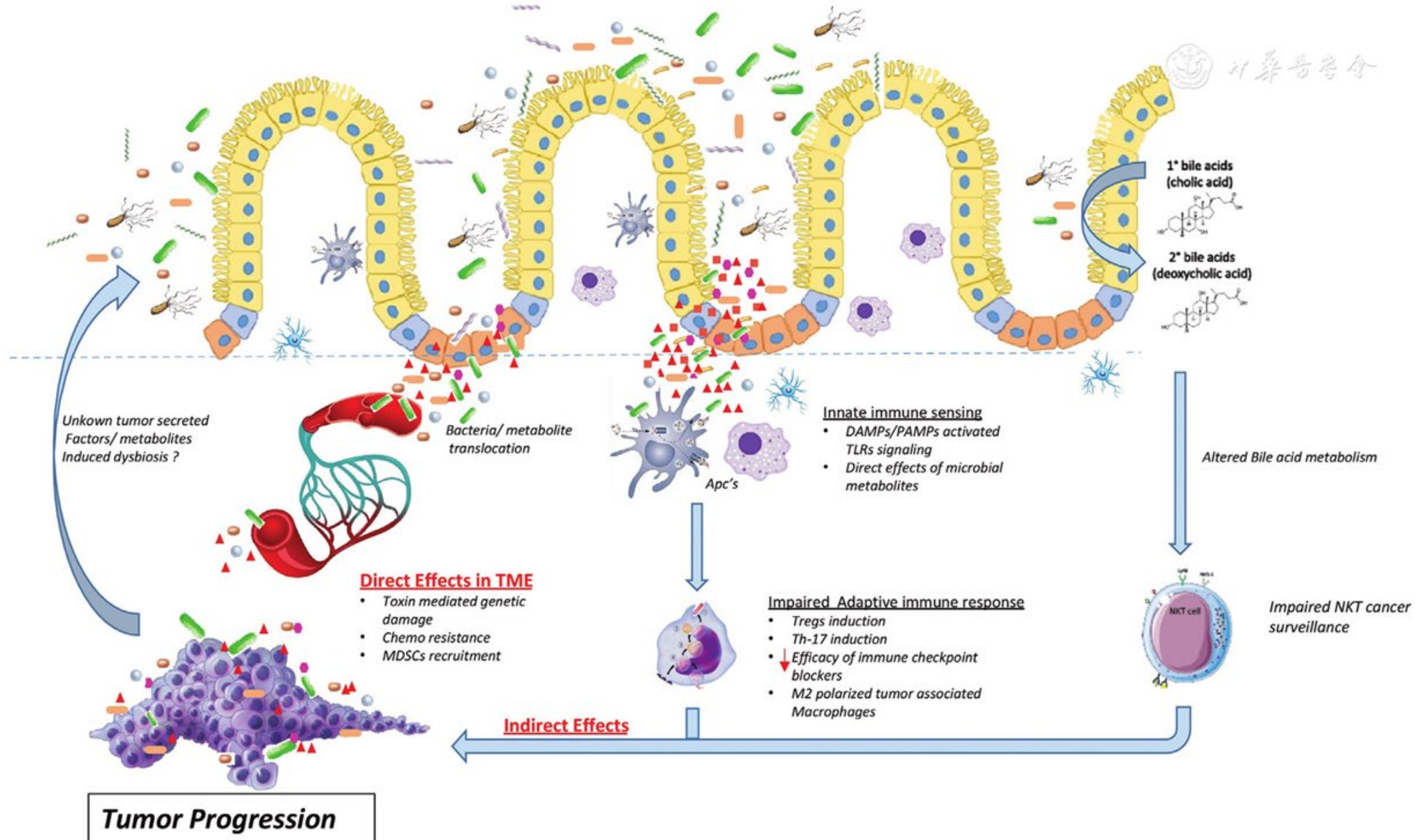


## EFFECTS OF THERAPEUTIC PROBIOTICS ON MODULATION OF MICRORNAS



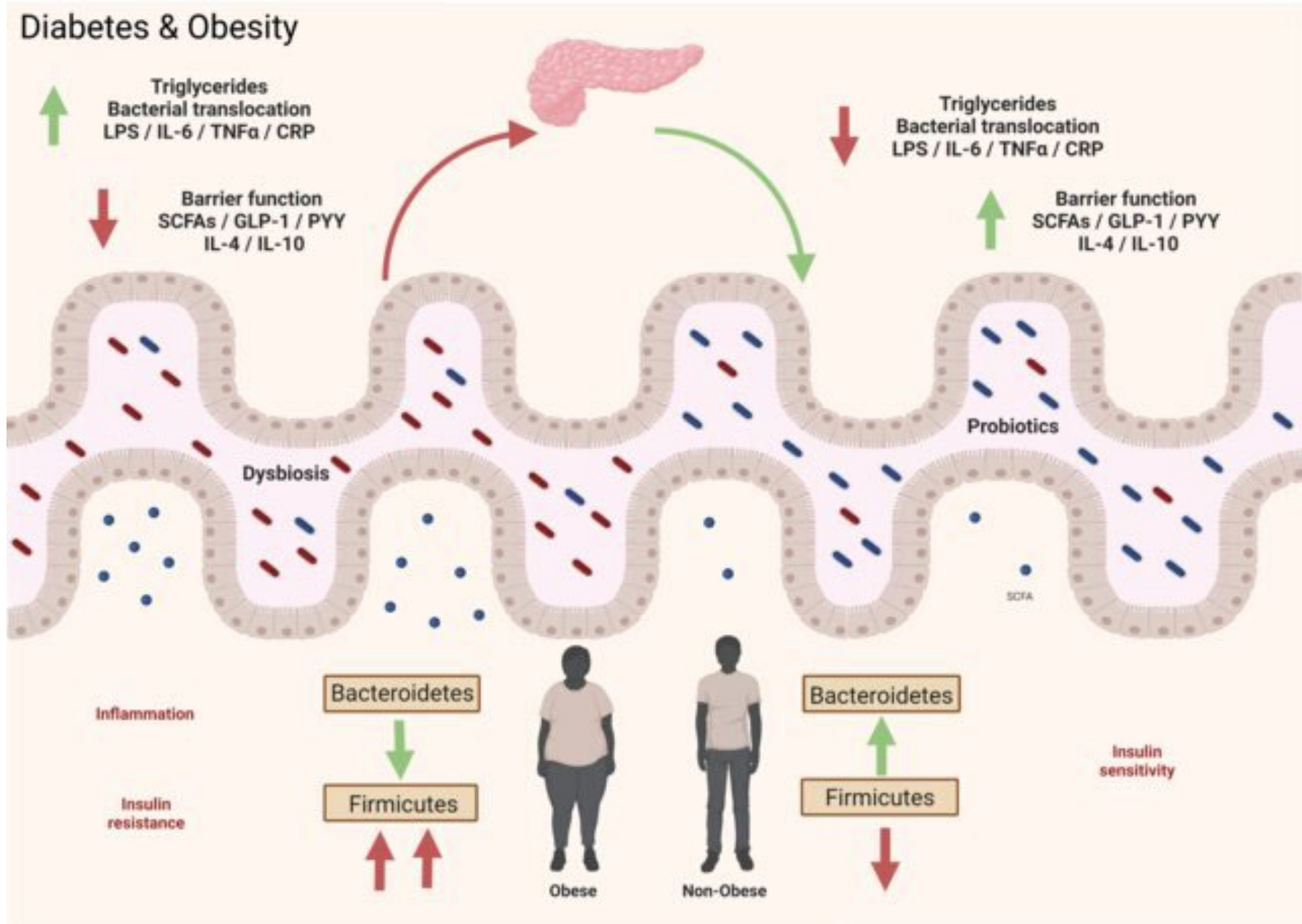
A schema of anti- apoptotic effects of probiotics. Various microRNAs i.e., miR-21, miR-200b and miR-21 can indirectly affect on apoptosis pathways

# PROBIOTIC ANTI CANCER EFFECTS ?





# MODULATION OF SYSTEMIC METABOLIC RESPONSES





THE PRESENT AND FUTURE

2023

JACC REVIEW TOPIC OF THE WEEK

# Gut Microbiome-Based Management of Patients With Heart Failure

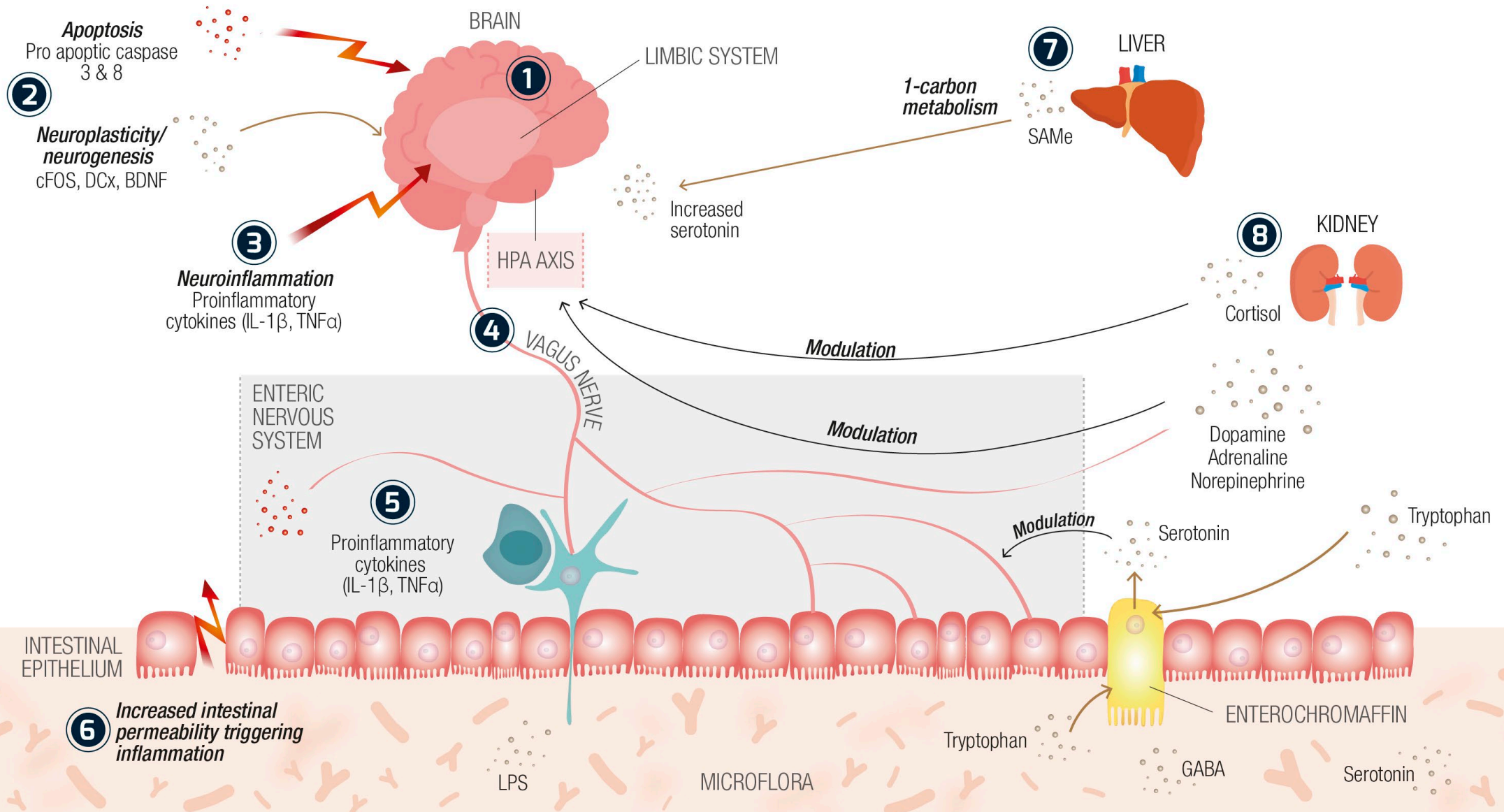
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# SYSTEMATIC SIGNALLING VIA THE NERVOUS SYSTEM



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Studies based on characterizing genetic material, proteins or metabolites using high-throughput analyses will remain the norm for the foreseeable future. To produce useful results, however, researchers must adopt better data-sharing practices.



***MI SONO DIVERTITO UN MONTE CON QUESTA LETTURA.  
E' STATO COME AL PROCESSO DI NORIMBERGA  
Woody Allen***

“

”





**A Través De Mi Ventana** ^^

14 ottobre alle ore 21:38 · 🌐

La pace è l'unica battaglia che vale la pena combattere.  
Albert Camus