Napule è...

PEDIATRIA PREVENTIVA E SOCIALE

SIPPS
SOCIETÀ ITALIANA DI PEDIATRIA PREVENTIVA E SOCIALE

Latte formula e Microbiota

Vito Leonardo Miniello

Unità Operativa di Nutrizione

UNIVERSITÀ DEGLI STUDI DI BARI ALDO MORO

Maternal nutrition
- Over/undernutrition
- Vitamin D status
- Dietary methyl donors
- LCPUFA intakes
- Food pollutants

Neonatal and infant nutrition
- Human milk
- Formula milk
- Prebiotics/probiotics

Nutrition

first 1000 days

Microbiome

Epigenome

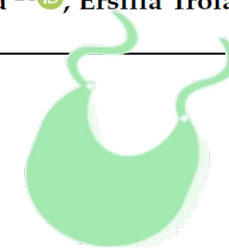
- Maternal microbiota
- Mode of delivery
- Maternal and infant diet
- Antenatal and post-natal antibiotic exposure
- Urban/rural environment

- Human genome
- Environmental factors

Recommendations on Complementary Feeding as a Tool for Prevention of Non-Communicable Diseases (NCDs)—Paper Co-Drafted by the SIPPS, FIMP, SIDOHaD, and SINUPE Joint Working Group

Nutrients **2022**

Margherita Caroli [1,†], Andrea Vania [2,*,†], Maria Carmen Verga [3,†], Giuseppe Di Mauro [4,†], Marcello Bergamini [5], Barbara Cuomo [6], Rosaria D'Anna [7], Giuseppe D'Antonio [8], Iride Dello Iacono [9], Angelica Dessì [10], Mattia Doria [11], Vassilios Fanos [10], Michele Fiore [12], Ruggiero Francavilla [13], Simonetta Genovesi [14], Marco Giussani [14], Antonella Gritti [15], Dario Iafusco [16], Lucia Leonardi [17], Vito Leonardo Miniello [18], Emanuele Miraglia Del Giudice [16], Filomena Palma [19], Francesco Pastore [20], Immacolata Scotese [21], Giovanni Simeone [22], Marco Squicciarini [23], Giovanna Tezza [24], Ersilia Troiano [25] and Giuseppina Rosa Umano [16]



"Noi non veniamo dalle stelle o dai fiori, ma dal latte materno...
Questa è la nostra principale natura."

William Shakespeare

	Oligosac-charides	Bacteria & Metabolites	Fat / LCPUFA	Lactose	Proteins	Hormons	Vitamins	Living Cells	Nucleo-tides	Minerals
Immunity	●	●	●	●	●		●	●	●	
Growth	●	●	●		●	●	●		●	●
Gut Health	●	●	●	●	●	●	●	●	●	●
Other	Microbiota	Microbiota Digestion	Brain Energy	Energy	Signaling	Mood			Brain	Bone & Teeth Blood

Bacco

Guido Reni

(1575 –1642)

Migranti

Hans Baluschek
(1870-1935)

LATTE FORMULA: TRA EVIDENCE-BASED MEDICINE ED EVIDENCE-BASED MARKET

Vito Leonardo Miniello, Lucia Diaferio

LATTI DI CRESCITA

Vito Leonardo Miniello, Lucia Diaferio, Elvira Verduci

LATTI FORMULA "SPECIALI"

Vito Leonardo Miniello, Adima Lamborghini, Alberto Martelli, Diego Peroni

Regolamento (UE) 2016/127 che integra il regolamento (UE) n. 609/2013 per quanto riguarda le prescrizioni specifiche di composizione e di informazione per le formule per lattanti e le formule di proseguimento e per quanto riguarda le prescrizioni relative alle informazioni sull'alimentazione del lattante e del bambino nella prima infanzia

(relativo agli alimenti destinati ai lattanti, ai bambini nella prima infanzia e agli alimenti a fini medici speciali) definiscono **formula per lattanti** *un prodotto alimentare destinato all'alimentazione dei lattanti nei primi mesi di vita, in grado di soddisfare da solo le esigenze nutrizionali dei lattanti fino all'introduzione di un'adeguata alimentazione complementare*

e **formula di proseguimento** *un prodotto alimentare destinato all'alimentazione dei lattanti nel momento in cui viene introdotta un'adeguata alimentazione complementare e che costituisce il principale elemento liquido nell'ambito di un'alimentazione progressivamente diversificata di tali lattanti.*

Ministero della Salute

Oggetto: Indicazioni per gli adeguamenti normativi dei cosiddetti "latti di crescita" e dei prodotti dietetici per sportivi conseguenti all'abrogazione del settore dei prodotti destinati ad una alimentazione con l'applicazione del Regolamento (UE) 609/2013 dal 20 luglio 2016

Ciò premesso, per quanto concerne i cosiddetti **"latti di crescita"**, tenuto conto della loro composizione e della definizione europea (YCF), la denominazione di vendita può contenere termini del tipo "formula", seguiti dalla specifica indicazione del target (i bambini di età compresa tra 1 e 3 anni).

La composizione di nutrienti ed energia delle formule di crescita non è regolamentata su base nazionale o europea

e rappresentano quindi un gruppo eterogeneo di formulazioni, alcune più attente alle necessità nutrizionali specifiche per questa età, altre che appaiono essere solo un espediente commerciale.

Latti speciali

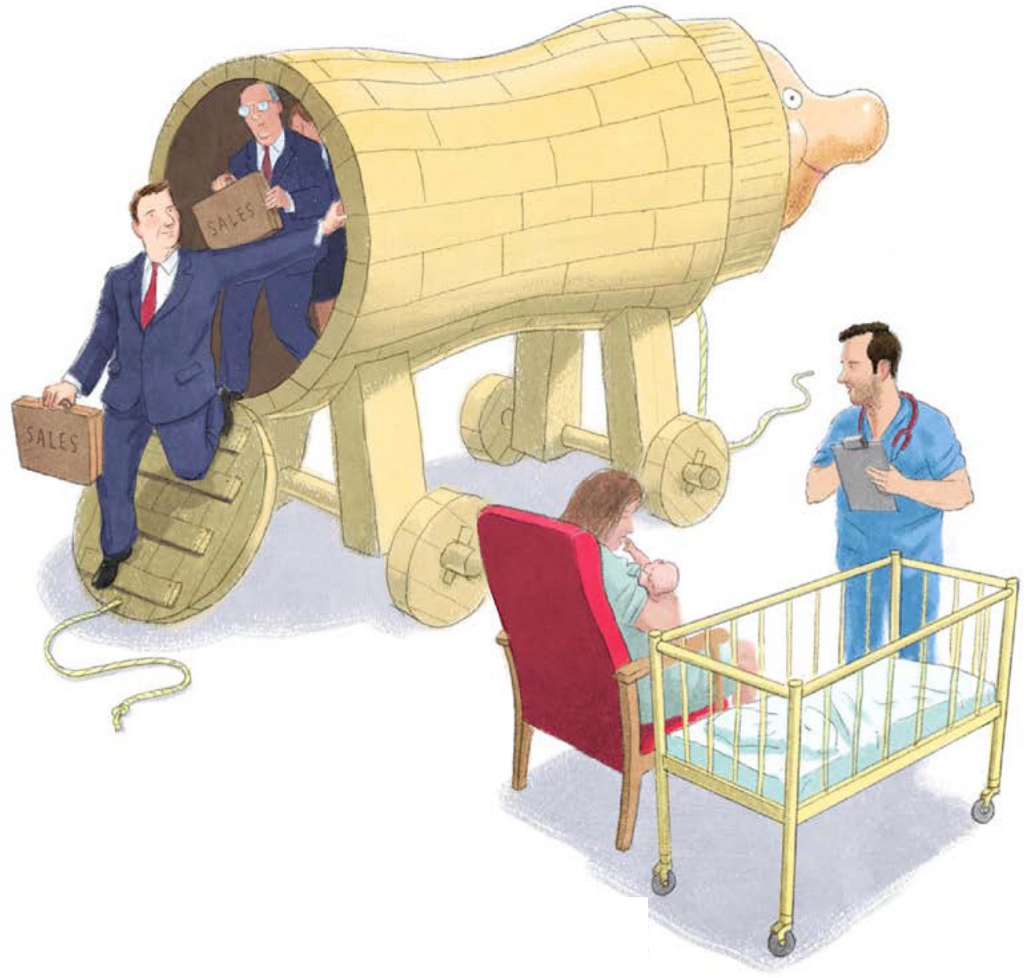
Dalla clinica alla formula

Vito Leonardo Miniello
Lucia Diaferio

Sintesi InfoMedica

Between 2006 and 2016, prescriptions of specialist formula milks for infants with cow's milk protein allergy (CMPA) increased by nearly 500% from 105 029 to over 600 000 a year.

BMJ



a Trojan horse for the formula industry

Chris van Tulleken *BMJ* 2018


1865
JUSTUS VON LIEBIG
MILK POWDER

Thomas Morgan ROTCH

Latte "Formula"

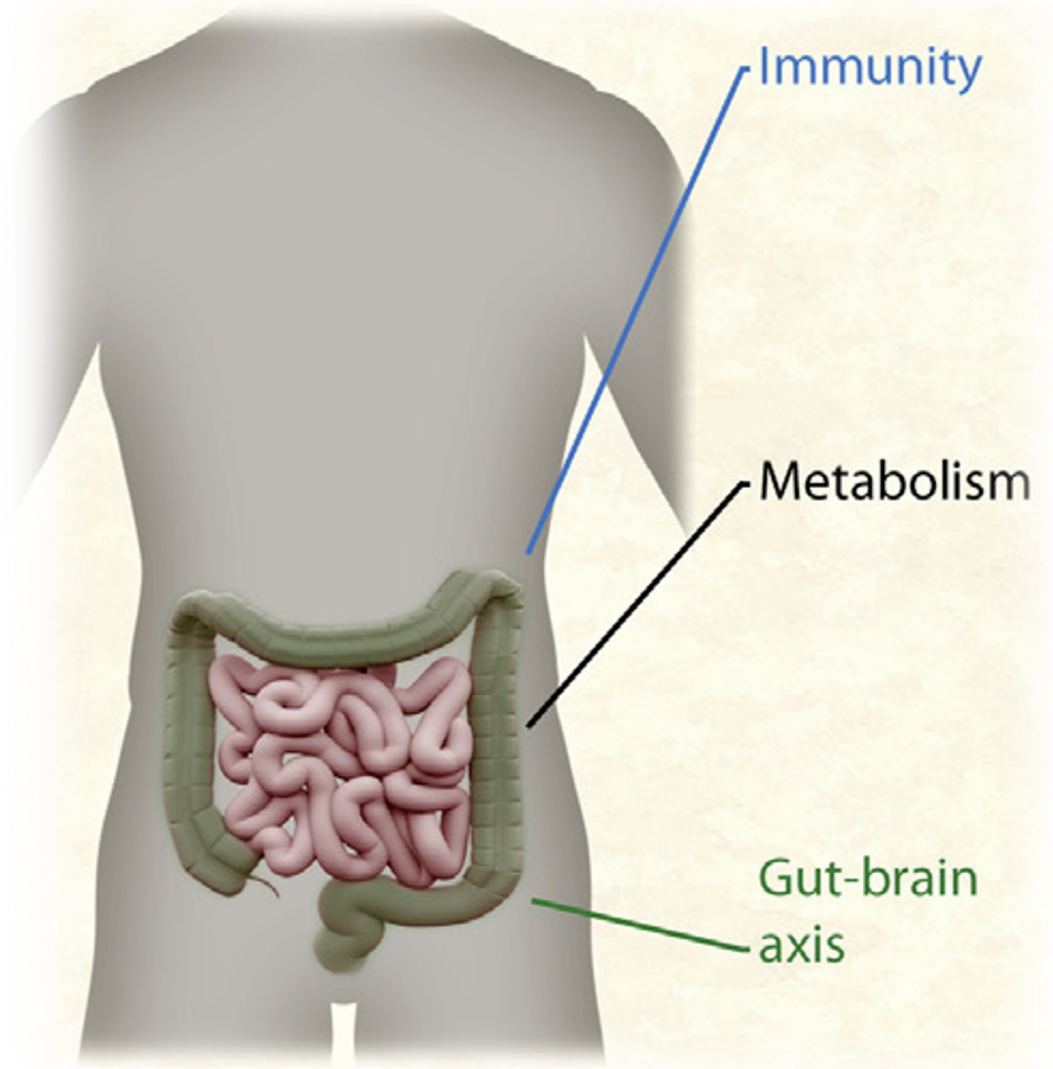
Journal of the American Medical Association 1903; 41: 416-421.

The essential principles of infant feeding and
the modern methods of applying them

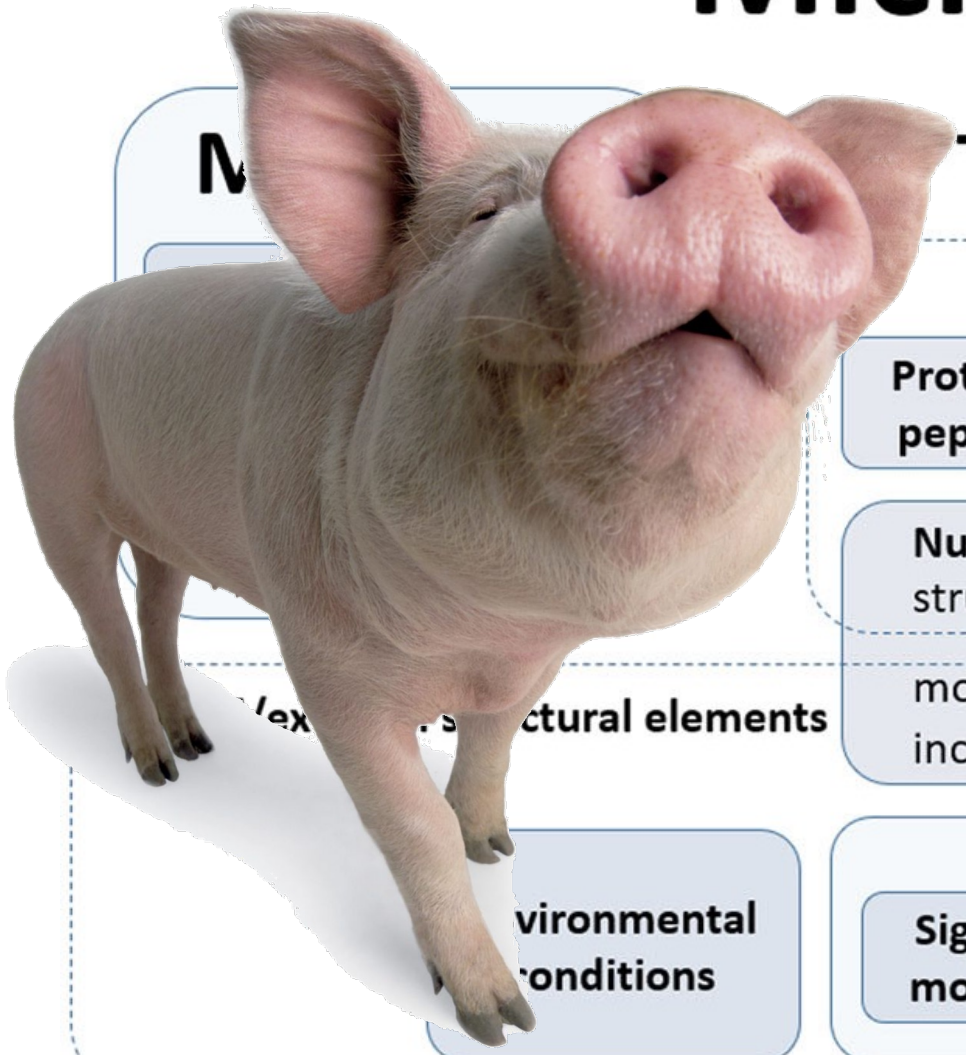
"Modified ***milk formula***, carefully prepared at milk laboratories,
are far superior to even breast feeding,
and will result in a decided reduction in their mortality "

alla ricerca del correlato funzionale

Benchè tutti i latti formula commercializzati e normati sul mercato europeo presentino un comune *core compositivo,* le industrie produttrici differenziano i vari brand con componenti (*bioactive ingredients*) analoghi a quelli presenti nel latte umano quali prebiotici, probiotici, sinbiotici, postbiotici, LCPUFA, lattoferrina, nucleotidi, miscele di trigliceridi inter-esterificati enzimaticamente, in grado di riprodurne gli effetti immunitari e/o metabolici e sul **microbiota intestinale**.


Immunity
Metabolism
Gut-brain
axis

Microbiome



M… Theatre of activity”

Microbial structural elements

- **Proteins/ peptides**
- **Lipids**
- **Poly-sacharides**

Nucleic acids
structural DNA/RNA

mobile genetic elements
incl. viruses/phages relic DNA

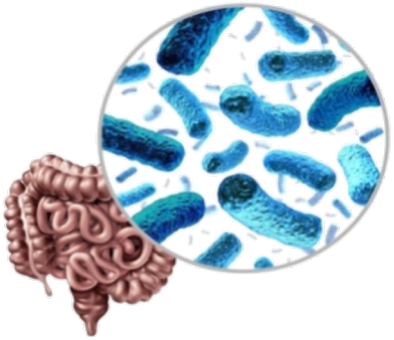
…ctural elements

…vironmental …conditions

Microbial metabolites

- **Signalling molecules**
- **Toxins**
- **(An)organic molecules**

Berg *et al. Microbiome* 2020



Metabolites
primary metabolites
secondary metabolites
"specialized metabolites"

- SCFAs
- Bile acids
- TMA(TMAOs)
- GABA

Microbial structural elements

- LPS
- Bacterial DNA
- Bacterial amyloids

Cytokines

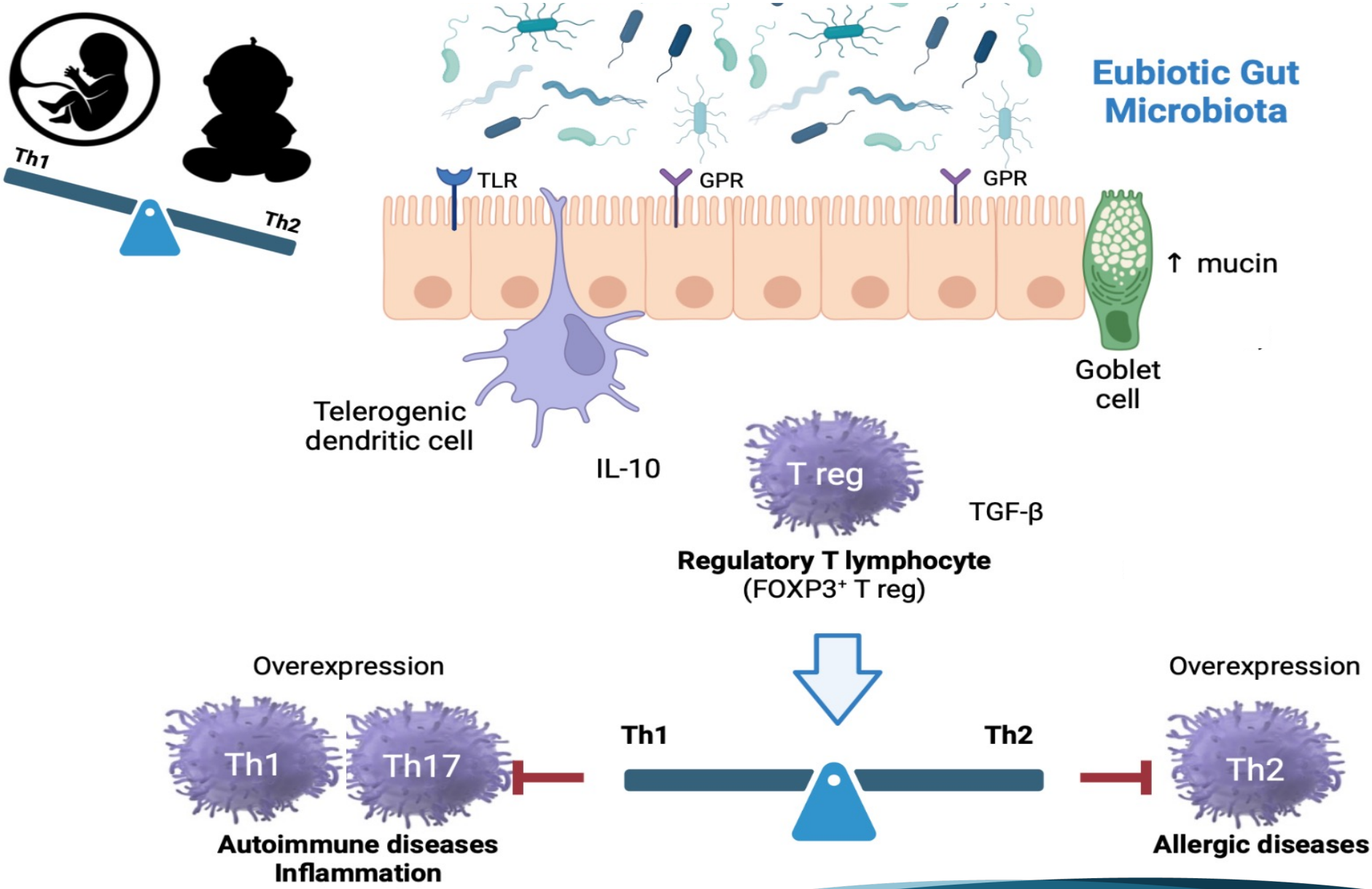
MAMPs

Neurontransmitters

Brain-gut peptides

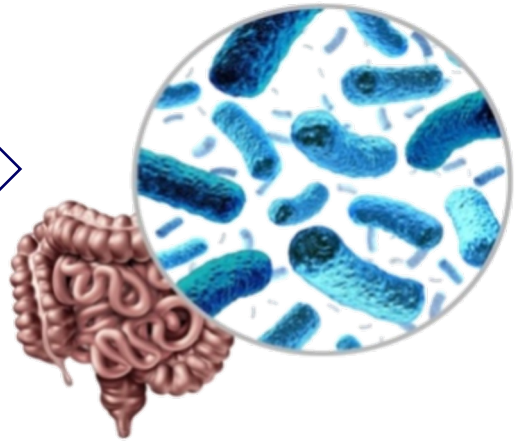
- **Satiety control**
- **Lipid and glucose metabolism**
- **Energy harvest and fat storage**
- **Immune homeostasis and inflammation**
- **Gut barrier function**

C. Jian et al. / EBioMedicine 69 (2021)



V.L. Miniello et al. *Nutrients* **2023**

- ***Roseburia intestinalis***
- ***Faecalibacterium prausnitzii***
- ***Enterobacterium rectale***
- *Clostridia*
- *Bifidobacterium spp*
- *Lactobacillus spp*

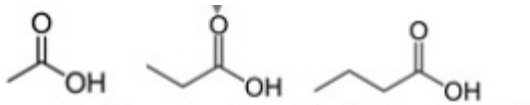


anaerobic fermentation

- ***diet fibers***
- ***resistant starch***

Short Chain Fatty Acids

(SCFA)

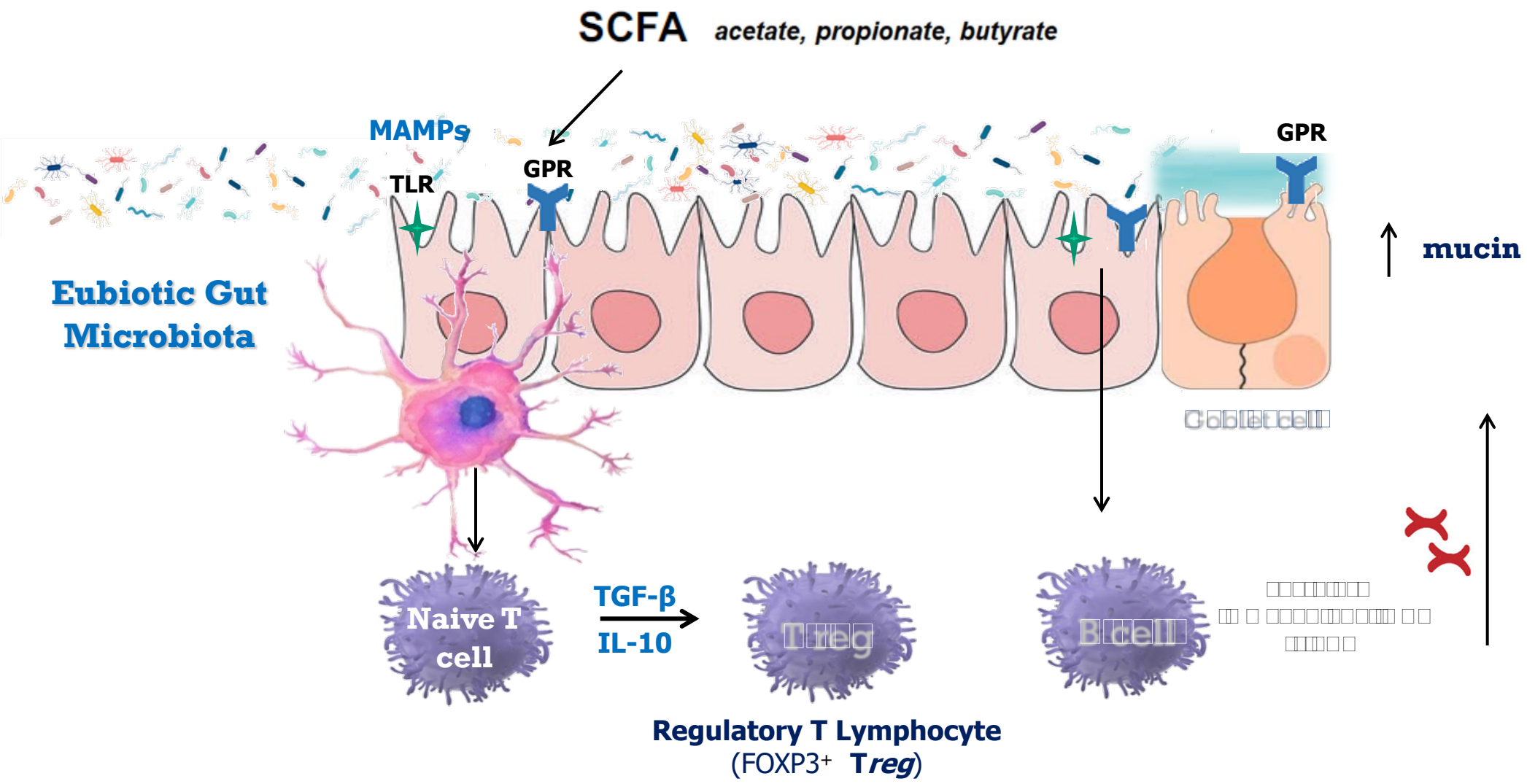


Acetic acid **Propionic acid** **Butyric acid**

Gut functions

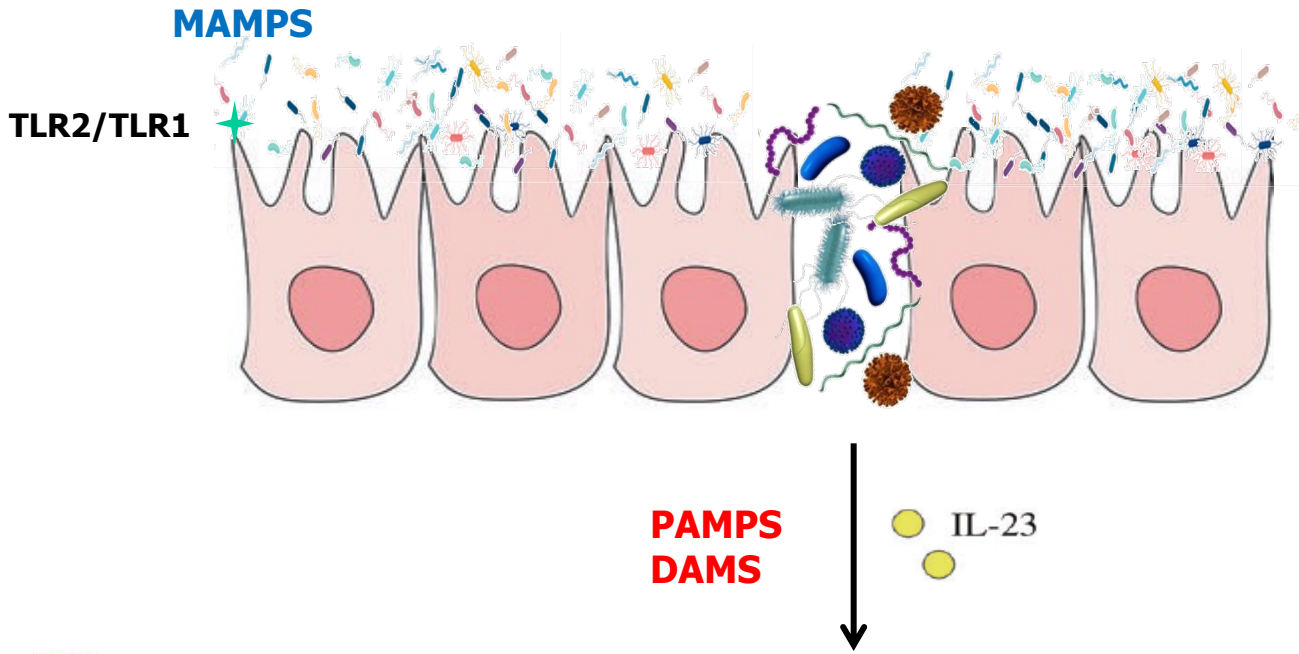
- **Protect gut from inflammation**
- **Maintain integrity of gut barrier**
- **Facilitate epithelial cells in nutrient absorption**
- **Prevent entering harmful entities and infectious agents**

M. Akhtar, (2022)



Regulatory T Lymphocyte
(FOXP3+ T*reg*)

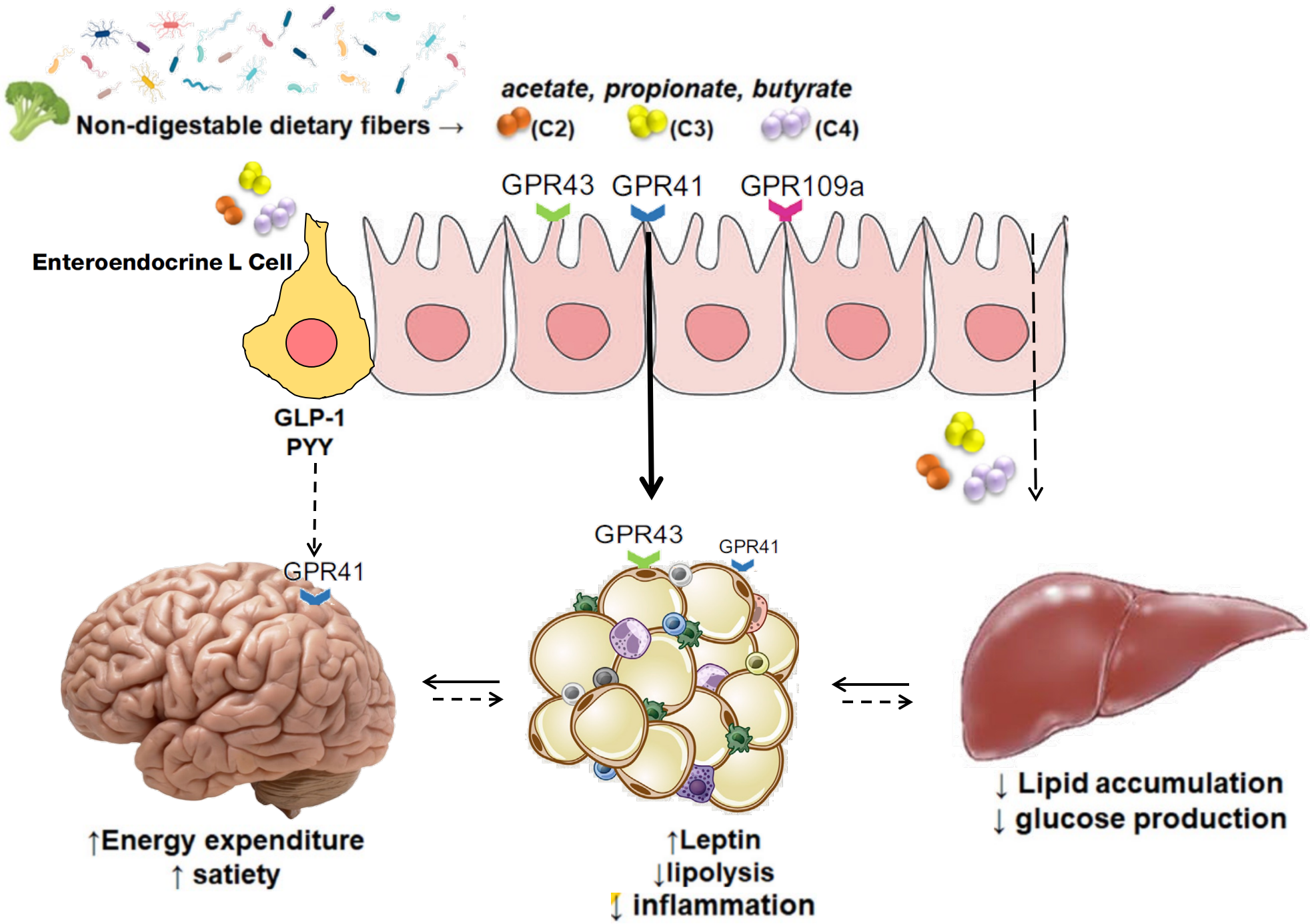
Disbiosi intestinale



Perdita di integrità

Linfociti T regolatori

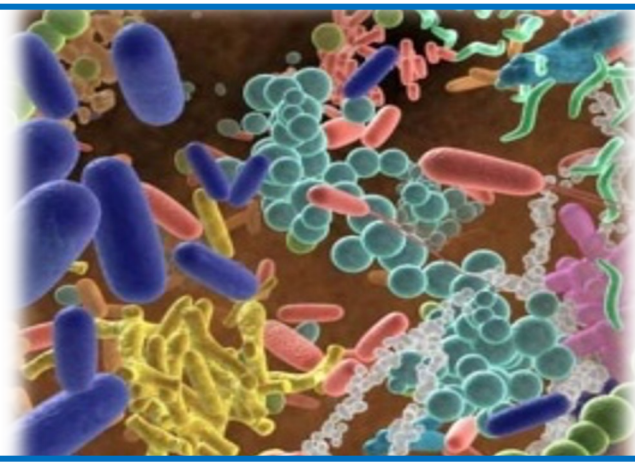
- **MAMPS: Microbe-Associated Molecular Patterns**
- **PAMPS: Pathogen-Associated Molecular Patterns**
- **Damage-Associated Molecular Patterns**


Non-digestable dietary fibers →
acetate, propionate, butyrate
(C2)
(C3)
(C4)
GPR43
GPR41
GPR109a
Enteroendocrine L Cell
GLP-1
PYY
GPR41
GPR43
GPR41
↑Energy expenditure
↑ satiety
↑Leptin
↓lipolysis
↓ inflammation
↓ Lipid accumulation
↓ glucose production

Journal of Probiotics & Health
ISSN: 2329-8901
Review Article

The Importance of Being Eubiotic 2017,

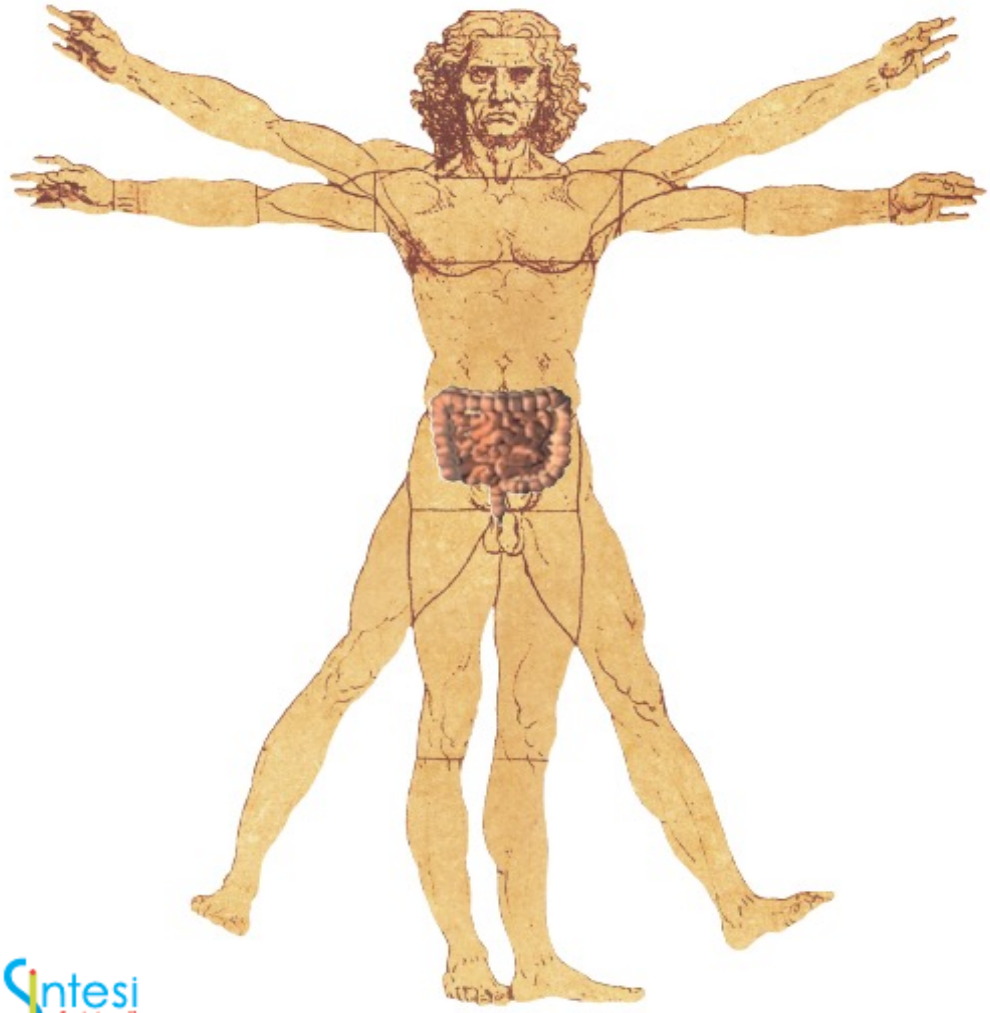
Vito Leonardo Miniello[1], Lucia Diaferio[1], Carlotta Lassandro[2] and Elvira Verduci[2*]



Gut microbiota biomodulators, when the stork comes by the scalpel

Vito Leonardo Miniello *, Angela Colasanto, Fernanda Cristofori, Lucia Diaferio, Laura Ficele, Valentina Santoiemma, Ruggiero Francavilla

L'organo fragile



Sintesi InfoMedica

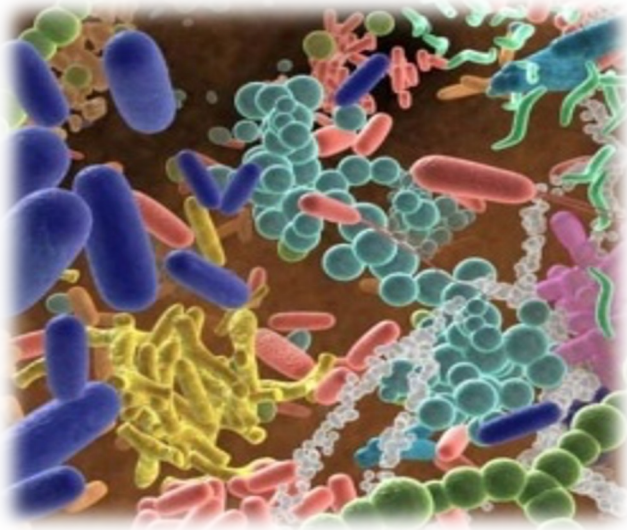
Vito Leonardo Miniello

Modalità del **parto**

Modalità **allattamento**

Antibiotici Ferro PPI

Apgar score **LGA**



Eubiosi

Microbiota bilanciato e diversificato

Disbiosi

Alterata composizione (non diversificata, 'povera')

Disregolazione immunitaria e metabolica

"Prega per noi adesso
e nell'ora della nostra nascita"
Thomas Stearns Eliot

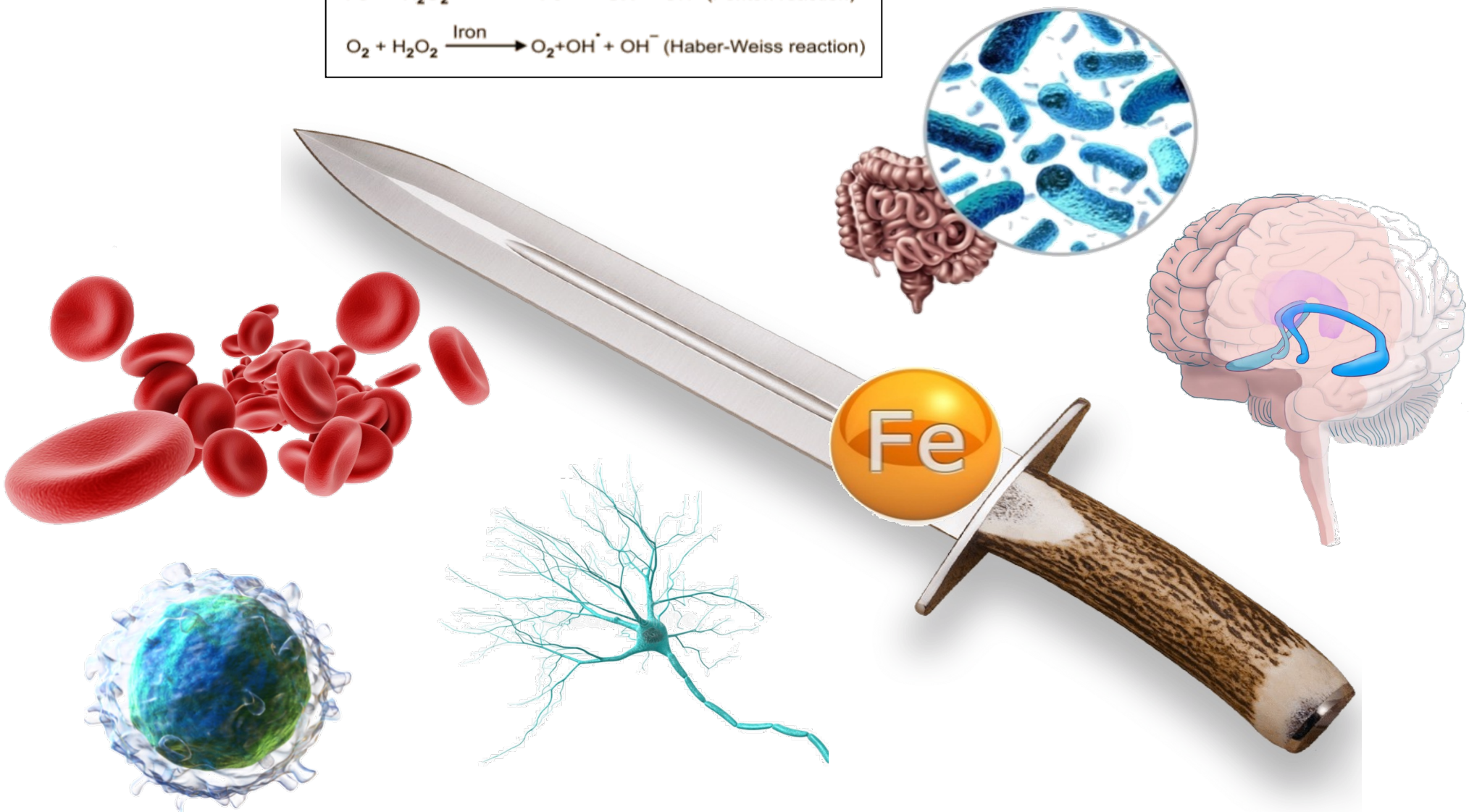
EVIDENCE
BASED
MEDICINE

Complementary Feeding and Iron Status: *"The Unbearable Lightness of Being"* Infants

V.L. Miniello et al. *Nutrients* **2021**

$Fe^{++} + H_2O_2 \longrightarrow Fe^{+++} + OH^{\cdot} + OH^{-}$ (Fenton reaction)

$O_2 + H_2O_2 \xrightarrow{\text{Iron}} O_2{+}OH^{\cdot} + OH^{-}$ (Haber-Weiss reaction)



Administration of ferrous sulfate drops has significant effects on the gut microbiota of iron-sufficient infants: a randomised controlled study

Kotryna Simonyté Sjödin,[1] Magnus Domellöf,[1] Carina Lagerqvist,[1] Olle Hernell,[1] Bo Lönnerdal,[2] Ewa A Szymlek-Gay,[3] Andreas Sjödin,[4] Christina E West,[1] Torbjörn Lind[1]

Gut 2018

1.2 mg Fe/day

Low-iron formula

6.6 mg Fe/day

High-iron formula

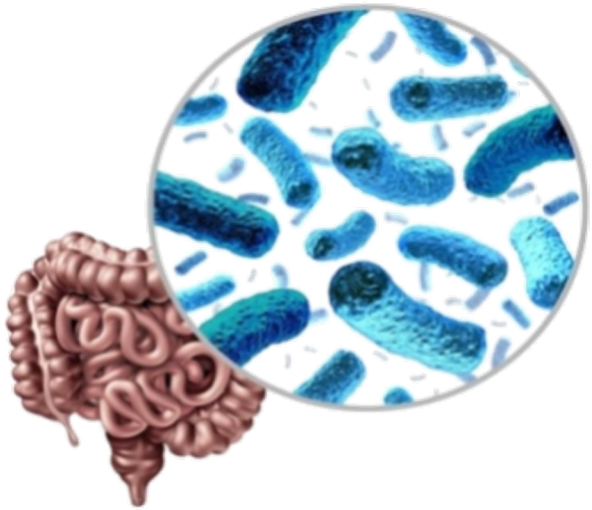
no-added-iron formula

6.6 mg Fe/day

To summarise, in healthy, non-anaemic Swedish infants, consumption of high-iron formula is associated with significantly lower abundance of bifidobacteria compared with low-iron formula, and

High-iron formula

$p<0.001$



administration of iron as drops, even in a dose comparable with the daily iron requirement and for a short time, leads to decreased relative abundance of lactobacilli and potentially increases susceptibility to bacterial infection.

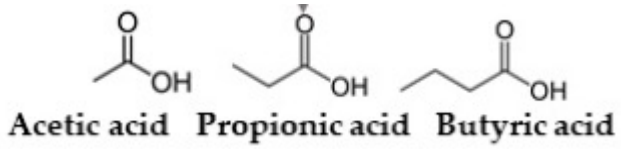
$p<0.007$

Gut 2018

Gut Microbiome Alterations following Postnatal Iron Supplementation Depend on Iron Form and Persist into Adulthood

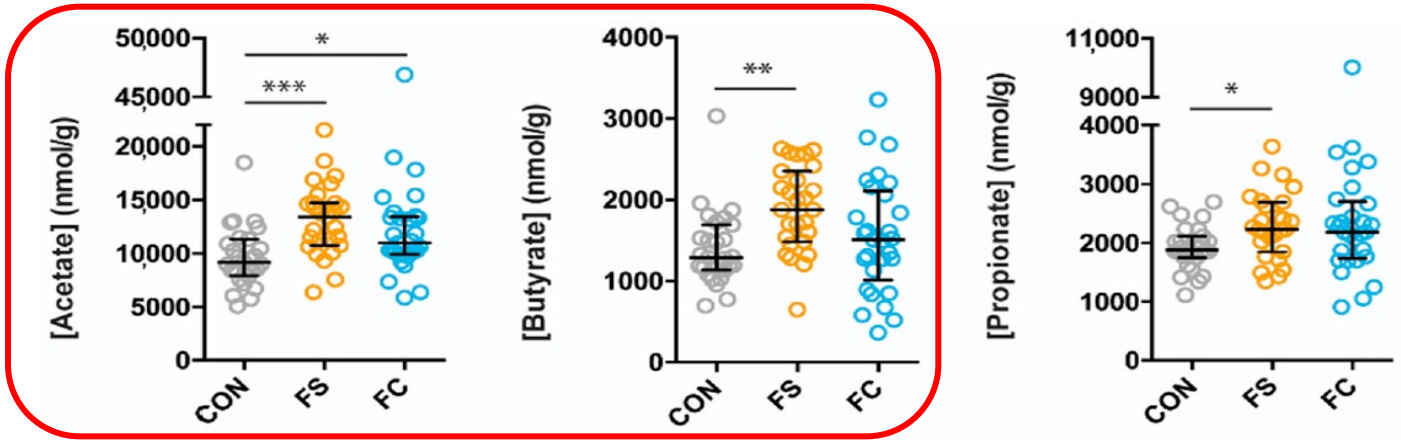
Recent evidence suggests that iron alters development of the gut microbiota in infants [8,19]. The developing microbiota confers an array of health benefits for the infant, such as improved intestinal barrier function and nutrient absorption, as well as infection resistance [21–25]. The development of the microbiota is influenced by the infant's diet [26,27]. Iron salts, such as ferrous sulfate (FS), are commonly used in supplements and infant formula, despite relatively low bioavailability—only 10% of FS iron is absorbed by infants [28]. Unabsorbed iron in the gut may exert effects on the microbiota [10,19,29–31]. Postnatal iron administration has been shown to suppress typical populations comprising the commensal bacteria and promote pathogen-associated bacteria, which may consequently potentiate adverse development outcomes [10,29–32].

Acidi grassi a catena corta
(SCFA)



control (CON)
ferrous sulfate (FS)
ferrous bis-glycinate chelate (FC)

Cecal metabolite differences due to iron form



differences in metabolite concentrations were largely due to FS treatment

McMillen, S. *Nutrients* **2022**

Società Italiana di Pediatria Preventiva e Sociale
SIPPS

fimp
Federazione Italiana Medici Pediatri

Società Italiana di Nutrizione Pediatrica
SINUPE

THE AMERICAN ACADEMY OF PEDIATRICS

ESPGHAN

Canadian Paediatric Society

SIDOHaD
Società Italiana Developmental Origins of Health and Disease

2010
2019

2014
2017

2019

2021

Term infants, 0 to 6 months

CPS [20]	AAP [8,21]	ESPGHAN [19,22]	Italian Intersociety Document
Canadian Paediatric Society	The American Academy of Pediatrics		Società Italiana di Pediatria Preventiva e Sociale SIPPS
2019	2019	2017	2021
Exclusive breastfeeding is sufficient to meet iron requirements until 6 months of age	Exclusive breastfeeding is sufficient to meet iron requirements until 4 months of age	Exclusive breastfeeding is sufficient to meet iron requirements until 6 months of age	Iron stores acquired prenatally along with a small amount of iron from breast milk are adequate to meet needs for full-term infants
Formula-fed infants: Iron-fortified formula	Exclusively or >50% breastfed infants: 1 mg/kg/day iron supplement from 4 to 6 months Formula-fed infants: formula containing 4 mg/L to 12 mg/L of iron	Formula-fed infants: formula containing 4 mg/L to 8 mg/L iron	Exclusive breastfeeding is sufficient to meet iron requirements until 6 months of age Exclusively or >50% breastfed infants are not at risk for inadequate intakes Formula-fed infants: formula containing 4 mg/L to 8 mg/L iron

V.L. Miniello et al. *Nutrients* **2021**

Term infants, 0 to 6 months

CPS [20]	AAP [8,21]	ESPGHAN [19,22]	Italian Intersociety Document
Canadian Paediatric Society			
2019	2019	2017	2021
Exclusive breastfeeding is sufficient to meet iron requirements until 6 months of age Formula-fed infants: Iron-fortified formula	Exclusive breastfeeding is sufficient to meet iron requirements until 4 months of age Exclusively or >50% breastfed infants: 1 mg/kg/day iron supplement from 4 to 6 months Formula-fed infants: formula containing 4 mg/L to 12 mg/L of iron	Exclusive breastfeeding is sufficient to meet iron requirements until 4 to 6 months of age Formula-fed infants: formula containing 4 mg/L to 8 mg/L iron	Iron stores acquired prenatally along with a small amount of iron from breast milk are adequate to meet iron needs for most healthy full-term infants Exclusive breastfeeding is sufficient to meet iron requirements until 6 months of age Exclusively or >50% breastfed infants are not at risk for inadequate intakes Formula-fed infants: formula containing 4 mg/L to 8 mg/L iron

V.L. Miniello et al. *Nutrients* **2021**

Term infants, 0 to 6 months

CPS [20]	AAP [8,21]	ESPGHAN [19,22]	Italian Intersociety Document
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V.L. Miniello et al. *Nutrients* **2021**

Term infants, 7 to 12 months

CPS [20]	AAP [8,21]	ESPGHAN [19,22]	Italian Intersociety Document
Canadian Paediatric Society			Società Italiana di Pediatria Preventiva e Sociale SIPPS
2019	2019	2017	2021
Continued breastfeeding with the introduction of iron-rich complementary foods at about 6 months Delay cow's milk until 9 to 12 months of age (then limit to 750 mL/day)	The recommended dietary allowance (RDA) for iron, according to the Institute of Medicine (IOM), is 11 mg/day	0.9 to 1.3 mg/kg/day Delay cow's milk until 12 months of age (then limit to 500 mL/day)	Continued breastfeeding with the introduction of iron-rich complementary foods at 6 months Although bioavailability of iron from breast milk is high, the overall intake is low. Delay cow's milk until 12 months of age and possibly until 24 months (then limit to 200-300 mL/day). Routine iron supplementation is not recommended as a preventative measure against iron deficiency for healthy term infants.

V.L. Miniello et al. *Nutrients* **2021**

Reducing Iron Content in Infant Formula from 8 to 2 mg/L Does Not Increase the Risk of Iron Deficiency at 4 or 6 Months of Age: A Randomized Controlled Trial

Nutrients **2021**

Reducing infant formula iron concentration from 8 to 2 mg/L marginally reduced iron stores but did not increase the risk of ID or IDA at 4 or 6 months of age. Additionally, adding lactoferrin had no effect on iron status and no benefits or adverse effects were observed on growth or gastrointestinal symptoms. Consequently, the study supports the conclusion that 2 mg/L is an adequate and safe level of iron fortification in a well-nourished population with low risk of ID, and that it results in an iron status more similar to breastfed infants. Future evaluations of morbidity and neurodevelopment will be performed to further compare benefits and harm of the different levels of iron fortification and lactoferrin supplementation.

Björmsjö, M.; Hernell, O.; Lönnerdal, B.; Berglund, S.K.

Term infants, 7 to 12 months

CPS [20]	AAP [8,21]	ESPGHAN [19,22]	Italian Intersociety Document
Canadian Paediatric Society			Società Italiana di Pediatria Preventiva e Sociale SIPPS
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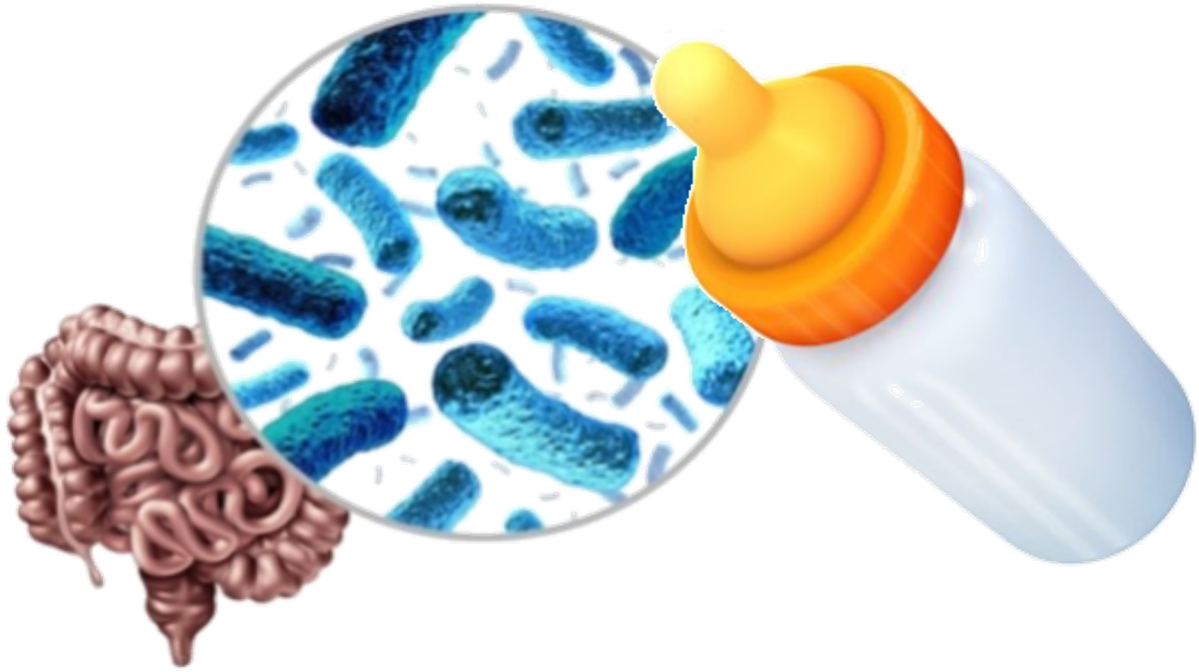
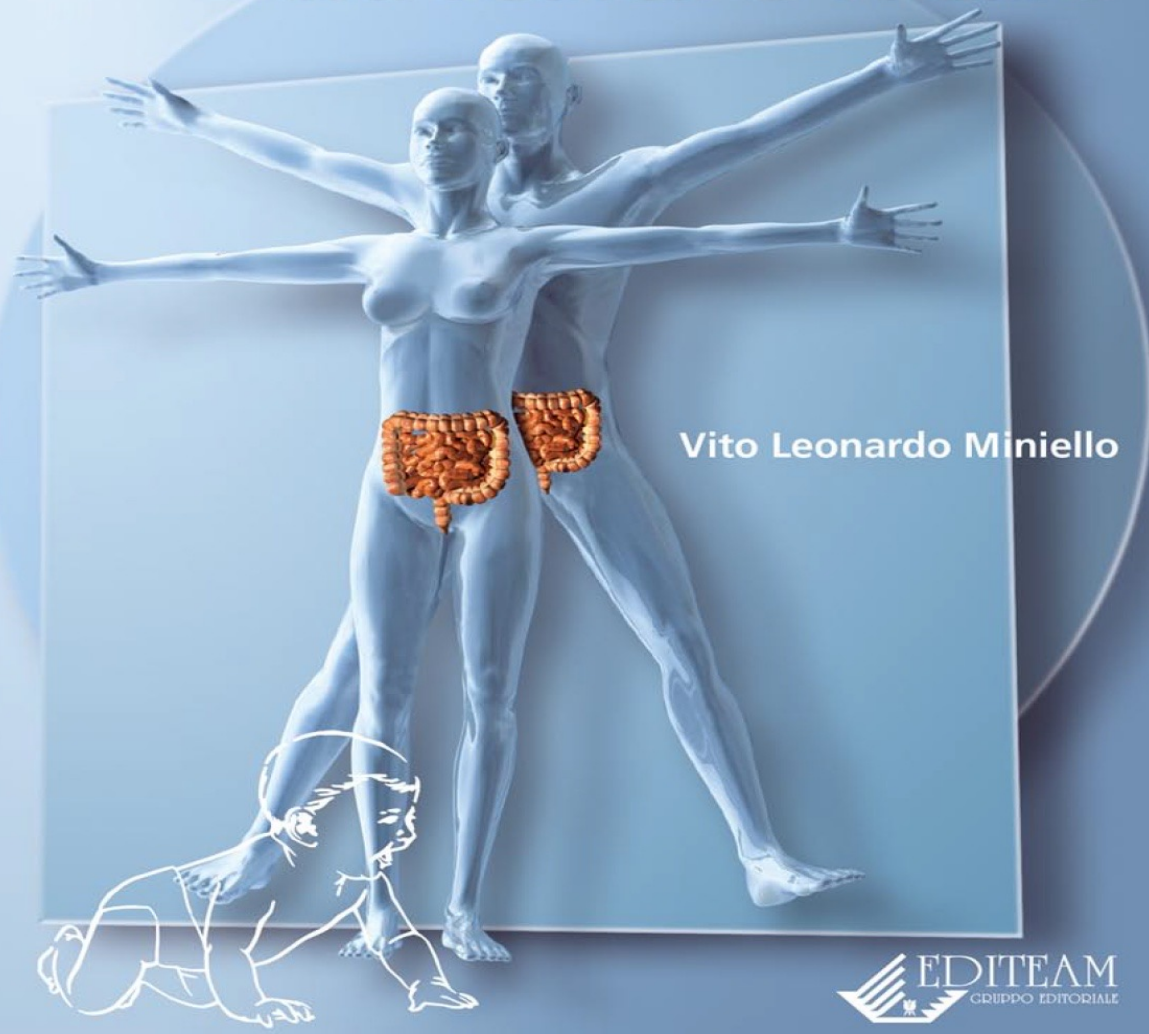
V.L. Miniello et al. *Nutrients* **2021**

Term Infant Formulas Influencing Gut Microbiota



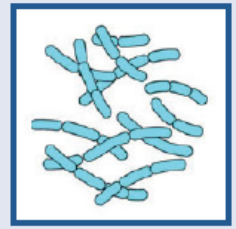
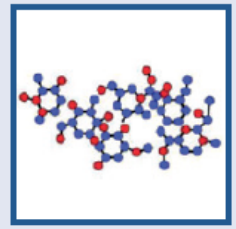
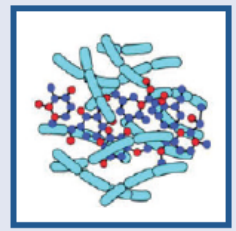
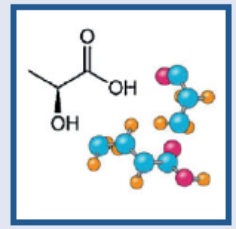
BIOMODULATORI DEL MICROBIOTA INTESTINALE: tra realtà e futuro



Vito Leonardo Miniello

EDITEAM
GRUPPO EDITORIALE

Biomodulatori del microbiota intestinale

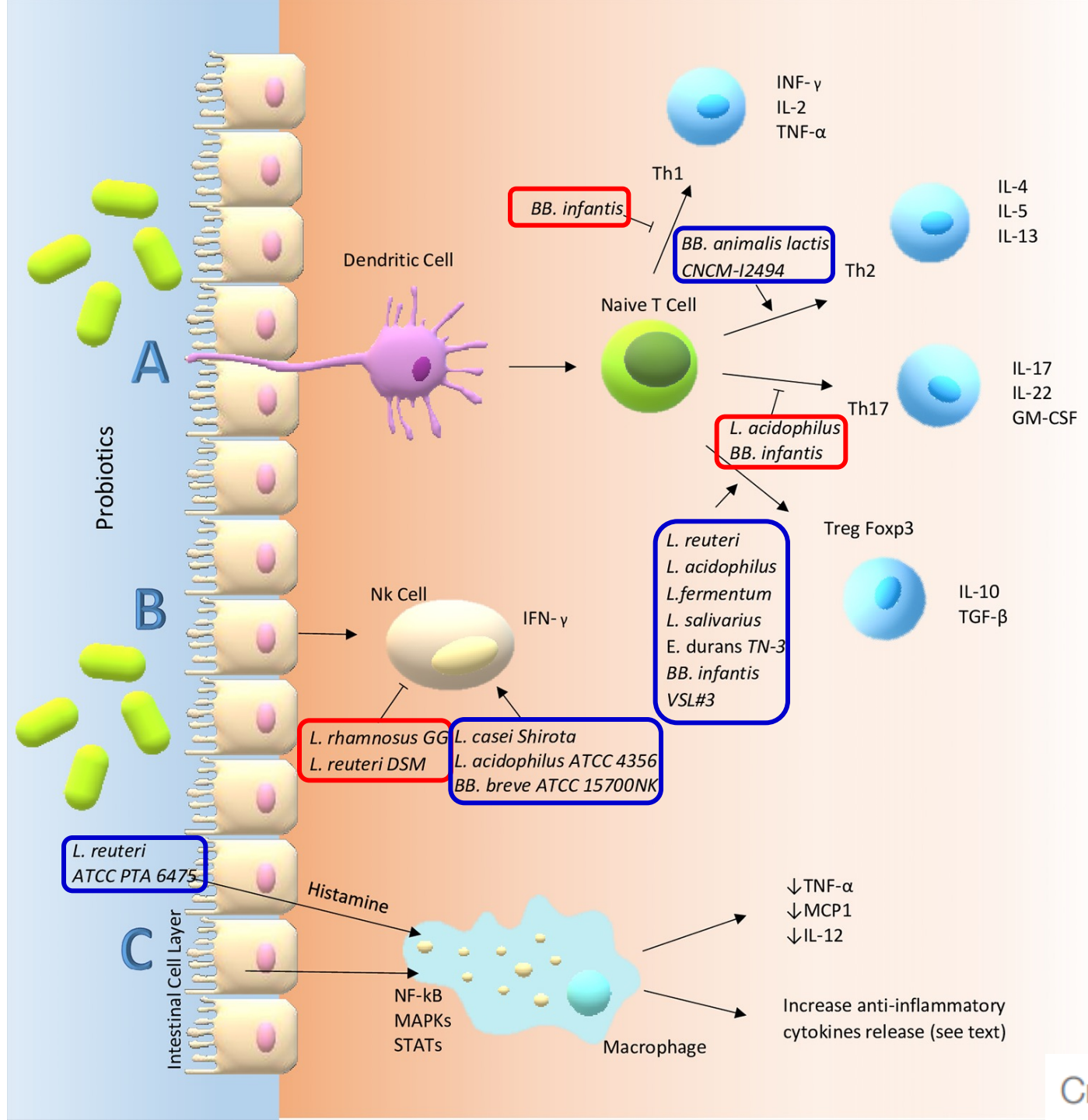
PROBIOTICI	Microrganismi vivi che, assunti in quantità adeguata, conferiscono all'organismo ospite effetti benefici sulla salute	
PREBIOTICI	Substrati selettivamente utilizzati dai microrganismi indigeni in grado di indurre effetti benefici sulla salute	
SIMBIOTICI	Associazione di prebiotici e probiotici	
POSTBIOTICI	Preparazione di microrganismi non vivi e/o di loro componenti che conferisce un beneficio per la salute dell'organismo ospite	

Seppo Salminen NATURE REVIEWS | GASTROENTEROLOGY & HEPATOLOGY 2021

Anti-Inflammatory and Immunomodulatory Effects of Probiotics in Gut Inflammation: A Door to the Body

Fernanda Cristofori [1], Vanessa Nadia Dargenio [1], Costantino Dargenio [1], Vito Leonardo Miniello [1], Michele Barone [2] and Ruggiero Francavilla [1]*

frontiers in Immunology 2021



Cristofori et al. *2021*

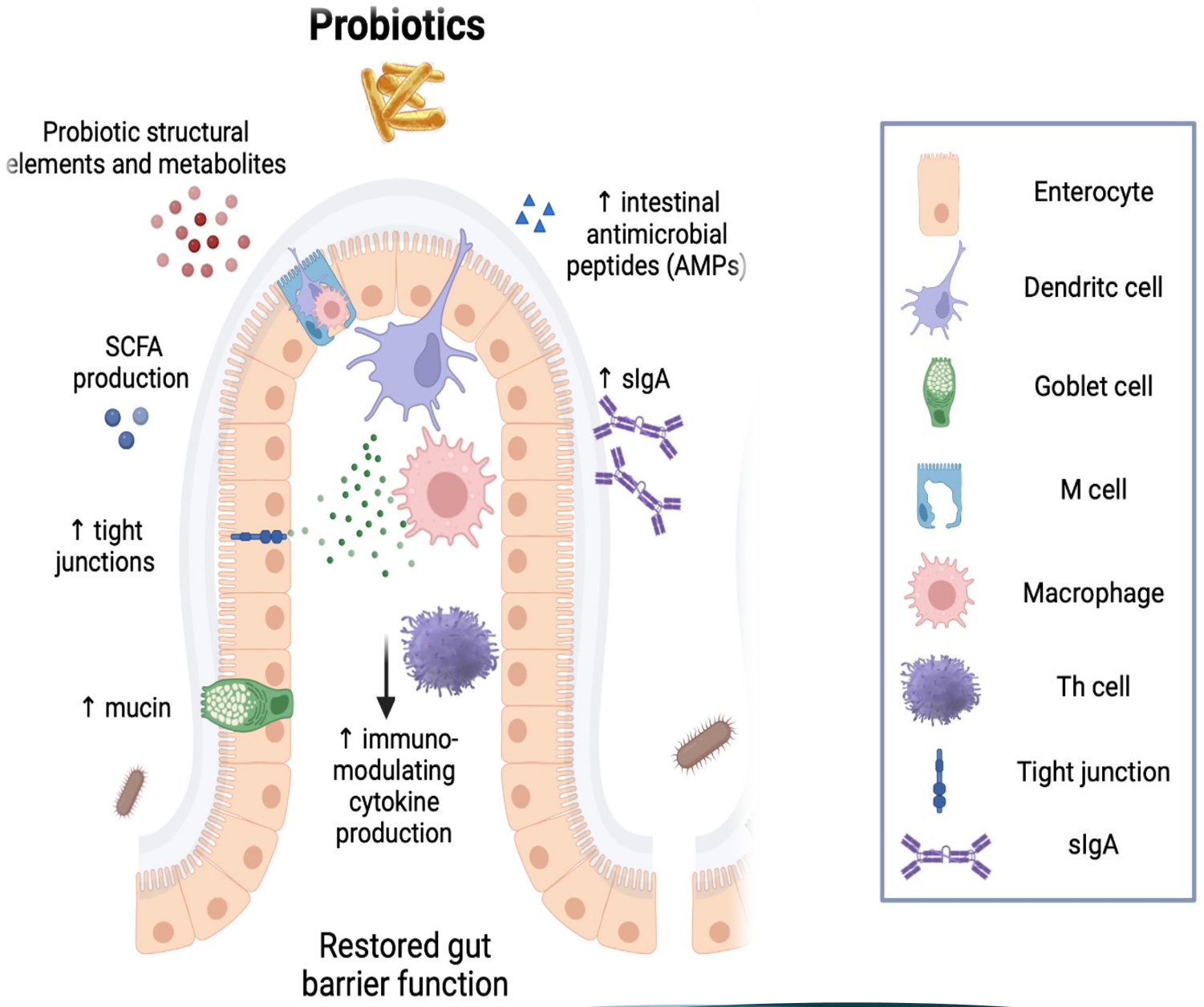
nutrients

Review

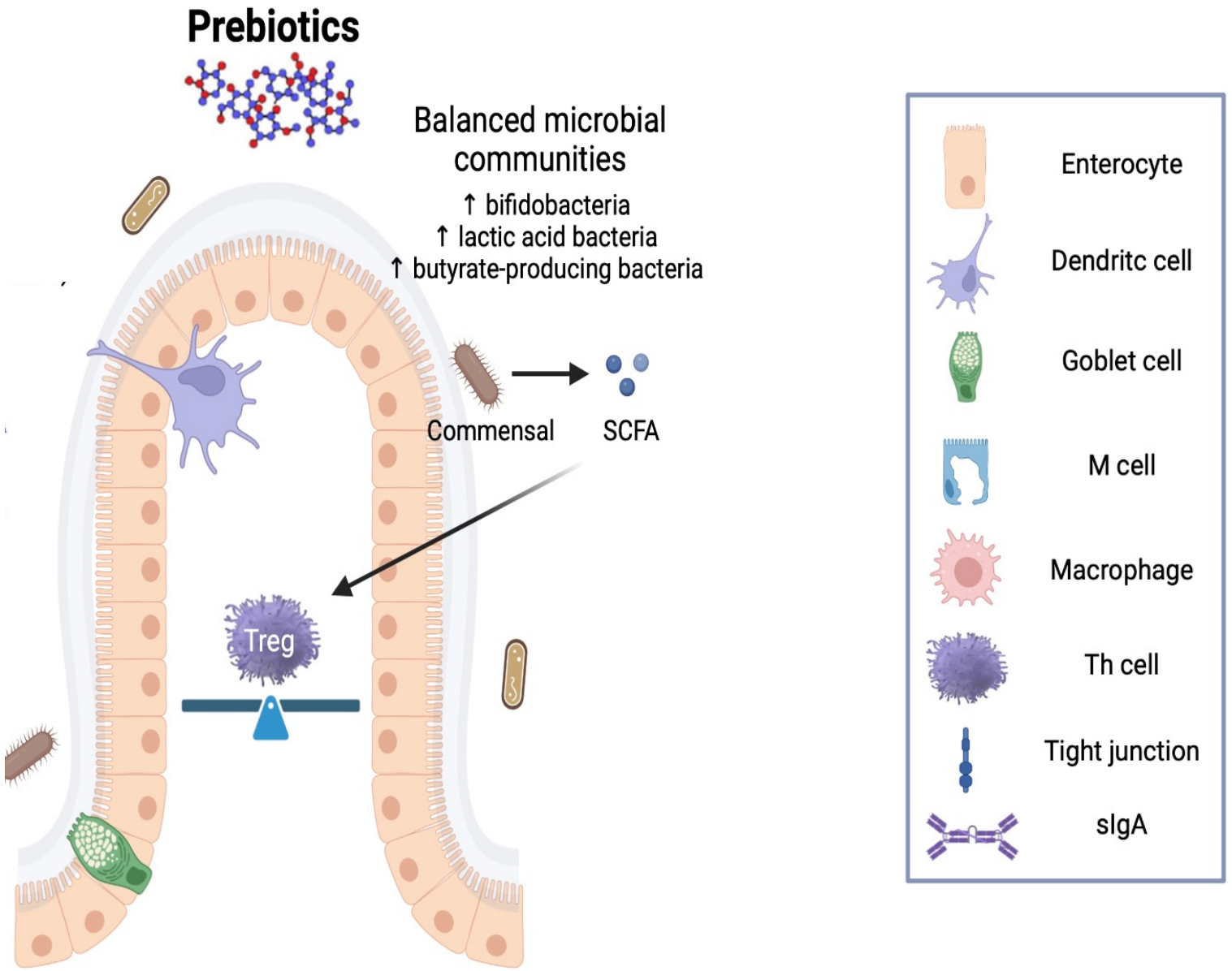
Gut Immunobiosis and Biomodulators

Vito Leonardo Miniello [1], Andrea Miniello [2], Laura Ficele [1], Aleksandra Skublewska-D'Elia [1], Vanessa Nadia Dargenio [3], Fernanda Cristofori [3,*] and Ruggiero Francavilla [3]

Nutrients **2023**



V.L. Miniello et al. *Nutrients* **2023**



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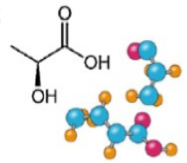
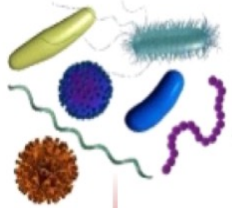
Postbiotics



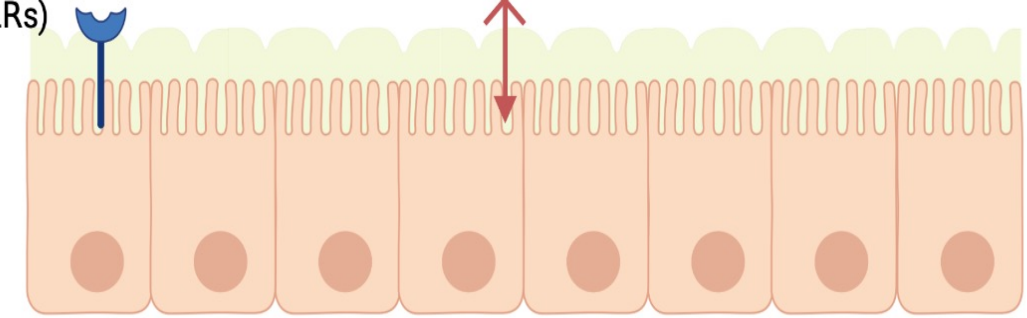
Inhibition of pathogen penetration into epithelial cells

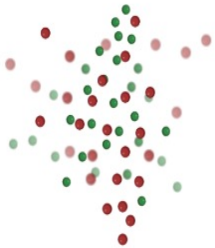


Production of antimicrobial compounds

Beneficial Effect on Intestinal Barrier Function

↑ expression in Toll like receptors (TLRs)





↑ **anti-**inflammatory cytokine production

↓ **pro-**inflammatory cytokine production

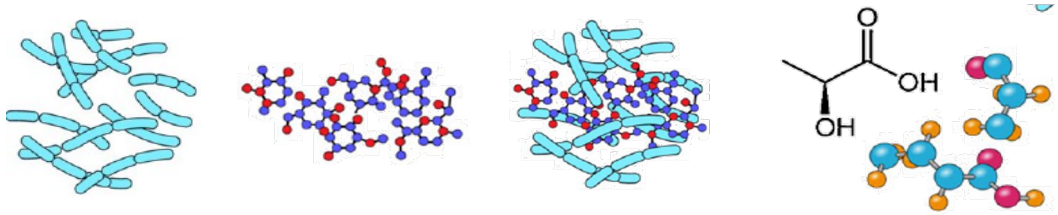
Immune modulation

Regulation of Th1- and Th2-mediated immune response

V.L. Miniello et al. *Nutrients* **2023**

correlato funzionale ?

Gut microbiota biomodulators



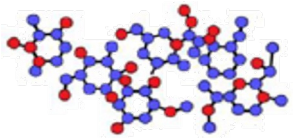
EVIDENCE BASED MEDICINE

Term Infant Formulas Influencing Gut Microbiota

MIFs Enriched with Probiotics—Key Points
• The intestinal microbiota (IM) contributes to the early and healthy development of gut functions
• Commensal microbes are essential for maturation of the immune system
• IFs supplementation with probiotics has the purpose to modulate the activity of the intestinal microbiota of infants by modifying its balance
• Probiotics enriched IFs have modest benefit in preventing acute gastrointestinal tract infections in healthy infants
• Probiotics reduce the incidence of antibiotic-associated diarrhea
• The effectiveness of probiotic supplemented IFs to reduce colic frequency, crying and irritability is debated
• Major issues related to the use of probiotics: timing, duration of treatment

Fabiano, V. *Nutrients* **2021**

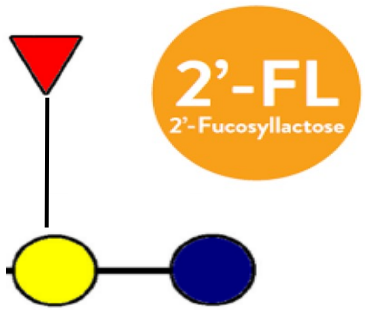
Term Infant Formulas Influencing Gut Microbiota

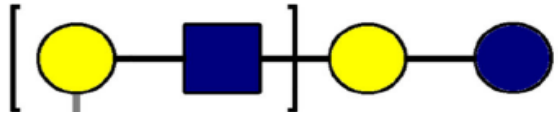


MIFs Enriched with Prebiotics—Key Points
• Prebiotics stimulate the establishment and maintenance of a healthy gut environment
• Commensal microbes are essential for maturation of the immune system
• Prebiotics act through selective fermentation in the GI tract, which stimulates the growth of bifidobacteria and *Lactobacilli*
• Different types of prebiotics substrates act differently on the growth of intestinal bacteria
• Prebiotics enriched IFs are associated with lower intestinal pH, with a SCFAs pattern more similar to breastfed infants
• Prebiotics enriched IFs are not associated with increased frequency of stool
• Prebiotic supplemented formulas may be considered in infants with hard stool

Fabiano, V. *Nutrients* **2021**

Term Infant Formulas Influencing Gut Microbiota

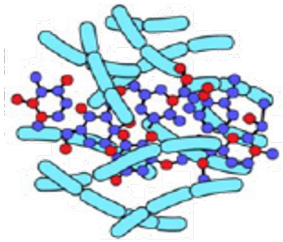




MIFs Enriched with HMOs—Key Points
• HMOs are non-digestible carbohydrates present in high concentrations in human milk
• HMOs play a key role in promoting intestinal microbiome composition and diversity
• HMOs prevent pathogen adhesion and could act as antiviral components
• HMOs-enriched IFs result from the addition of industrially produced HMOs of two types 2o FL and LNnT
• HMOs-enriched IFs are associated with normal infants' growth
• Incidence of GI symptoms, including flatulence, spitting up, and vomiting did not differ between HMOs-supplemented and unsupplemented IFs
• IF enriched with 2 HMOs, 2o FL and LNnT, are considered as safe and approved for use as food
• There is limited evidence regarding the potential preventive effects of supplemented IFs with one or both the above-mentioned HMOs

Fabiano, V. *Nutrients* **2021**

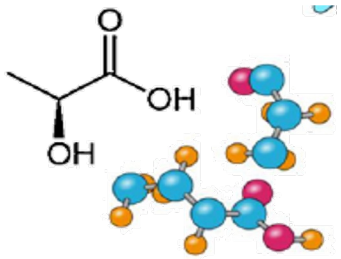
Term Infant Formulas Influencing Gut Microbiota



MIFs Enriched with Synbiotics—Key Points
• The substrates do not need to be prebiotics but should be metabolized only by the co-administered microorganism with a synergistic beneficial effect on the host
• Each component must fulfill the requirements for prebiotic or probiotic
• Synbiotics might offer an added effect on the intestinal microbiota homeostasis
• Infants' growth parameters did not differ between synbotics-supplemented and unsupplemented IFs
• Synbiotics enriched IFs seem to be associated with reduced incidence of GI infections
• Frequency of flatulence, fussing, vomiting, crying and spitting up is not reduced in infants fed with synbiotics-enriched IFs
• No specific therapeutic indications may be provided for synbiotics-enriched IFs

Fabiano, V. *Nutrients* **2021**

Term Infant Formulas Influencing Gut Microbiota

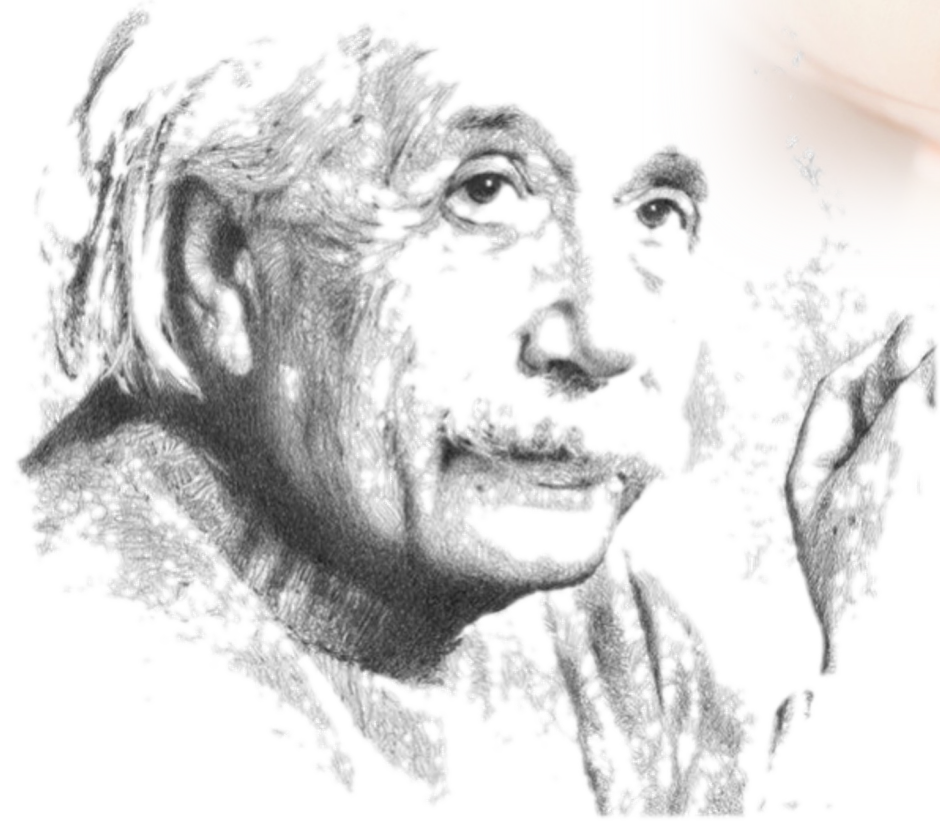


MIFs Enriched with Postbiotics—Key Points
• Postbiotics are metabolites and fragments of microorganisms resulting from fermentation with live bacteria
• Postbiotics may exert a beneficial effect in the host by pleiotropic properties
• Postbiotics influence gut epithelium and microbiota, immune system, systemic metabolism, and the nervous system. Synbiotics might offer added beneficial effects on intestinal microbiota homeostasis
• Infants' growth parameters did not differ between postbiotics-supplemented and unsupplemented IFs
• Postbiotics-enriched IFs are associated with softer stool
• Contrasting results on the efficacy of postbiotics in reducing diarrhea episodes: there is limited evidence to recommend using postbiotics for prevention or treatment of acute gastroenteritis

Fabiano, V. *Nutrients* **2021**

To date, there is no perfect formula that combines all the "ingredients" to exactly mimic and reproduce all the benefits of breastmilk, which itself varies interindividually (from one mother to another) and over time according to the ages of newborns and infants. The choice of infant formula is a decision made by parents from a very wide range on the market, possibly after informed advice from their doctor, pediatrician, or pharmacist, based on rather strong evidence of efficacy in line with the scientific literature.

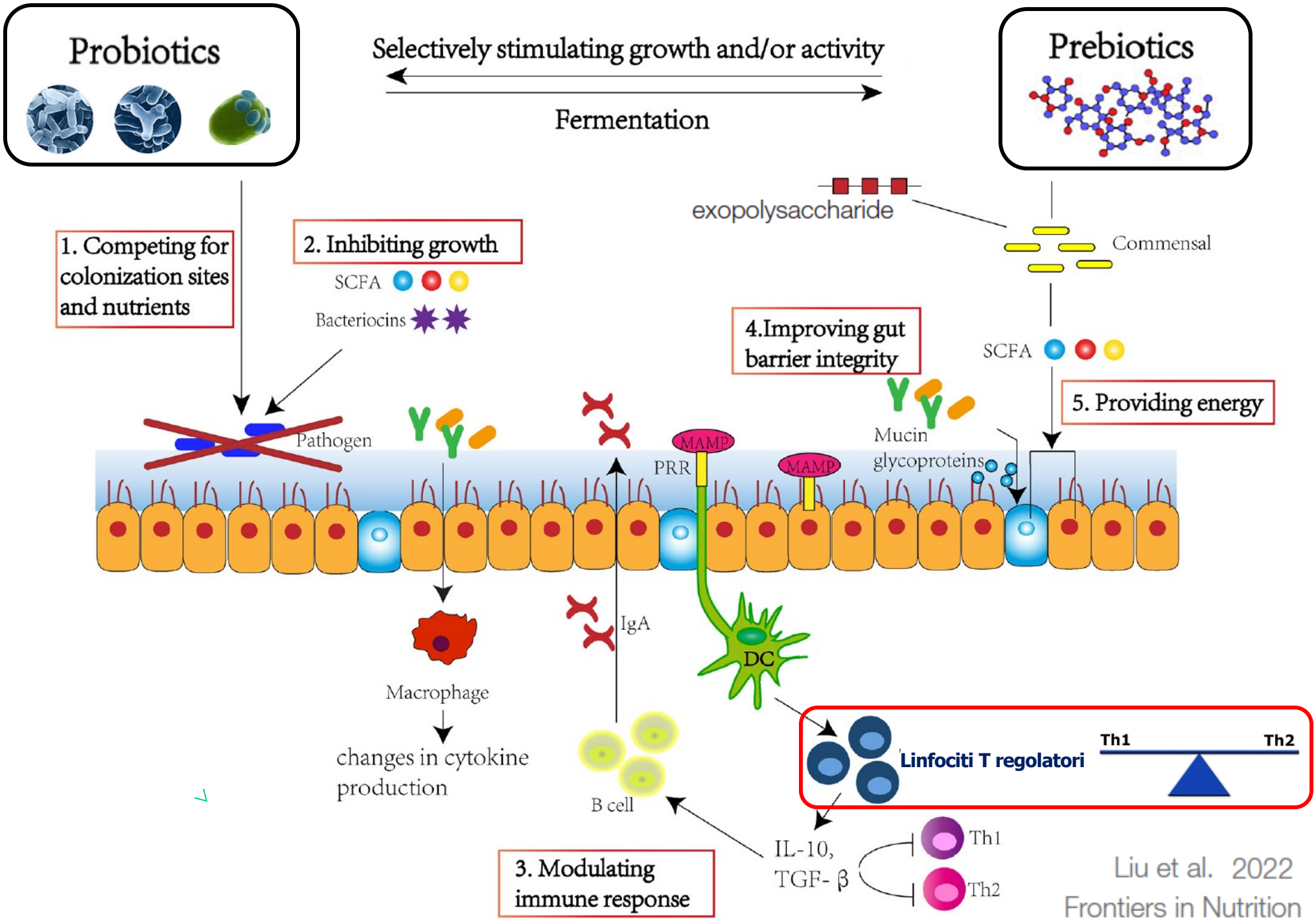
Lemoine, A. *Nutrients* **2023**,



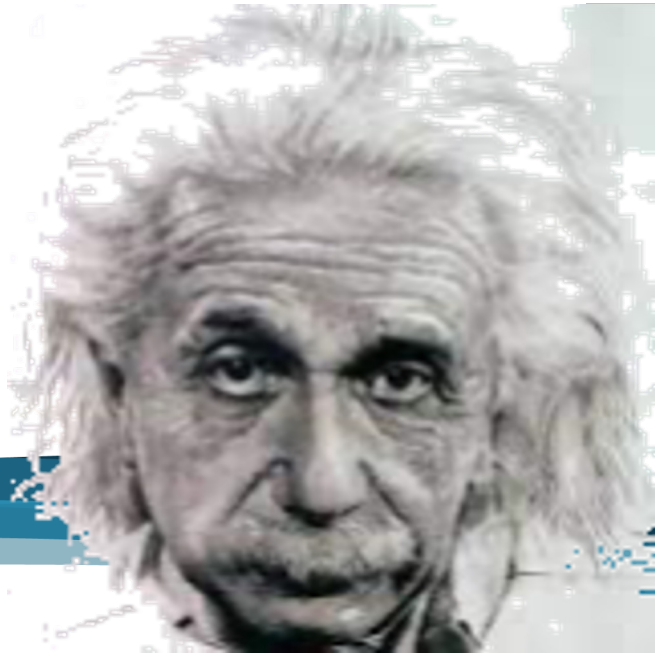
“Ogni cosa che puoi immaginare,

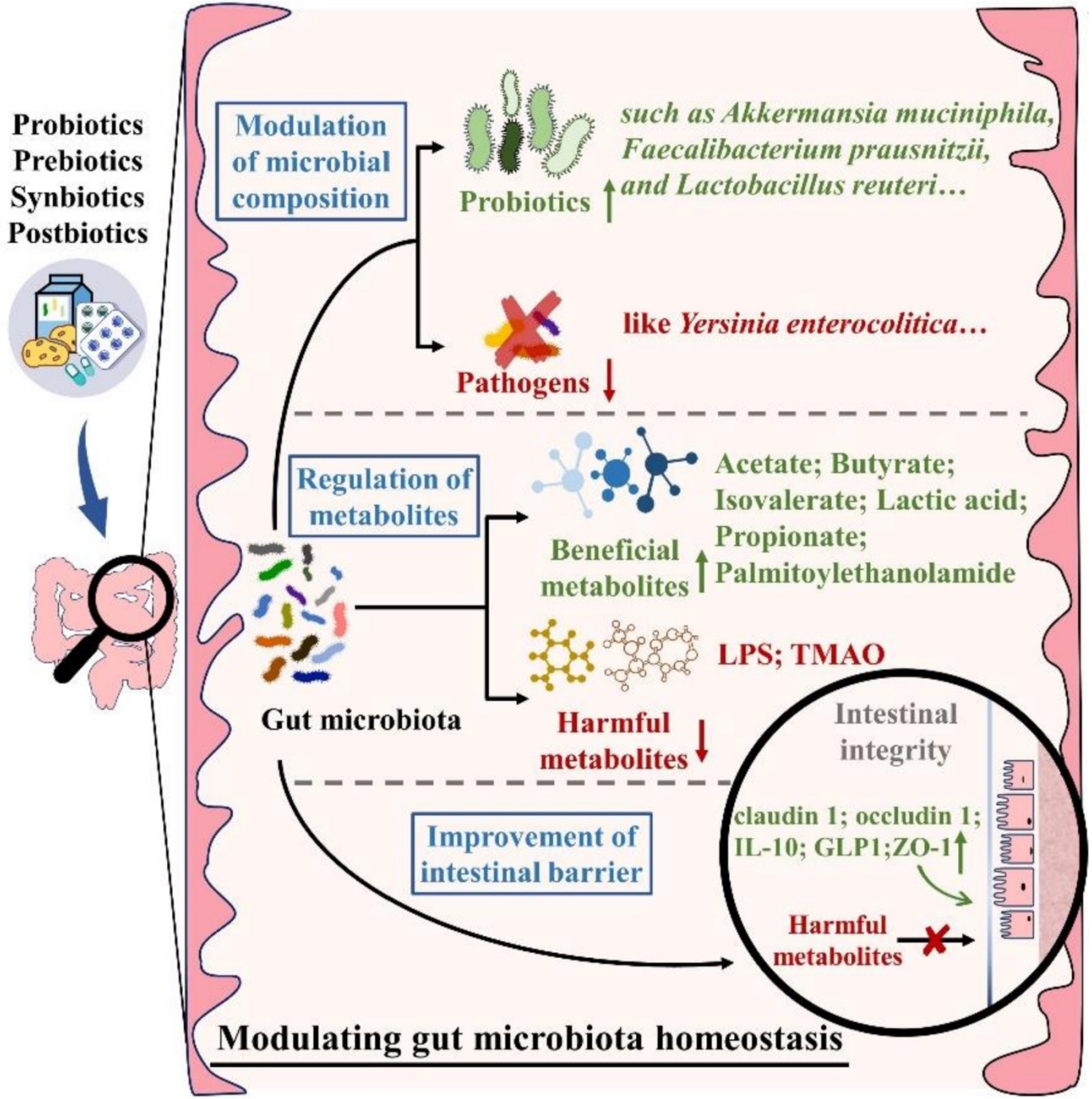
la natura l’ha già creata.”

Albert Einstein


Probiotics
Selectively stimulating growth and/or activity
Fermentation
Prebiotics
exopolysaccharide
Commensal
1. Competing for colonization sites and nutrients
2. Inhibiting growth
SCFA
Bacteriocins
4.Improving gut barrier integrity
SCFA
5. Providing energy
Pathogen
MAMP
PRR
MAMP
Mucin glycoproteins
IgA
DC
Macrophage
changes in cytokine production
B cell
Linfociti T regolatori
Th1
Th2
IL-10, TGF- β
Th1
Th2
3. Modulating immune response
Liu et al. 2022
Frontiers in Nutrition

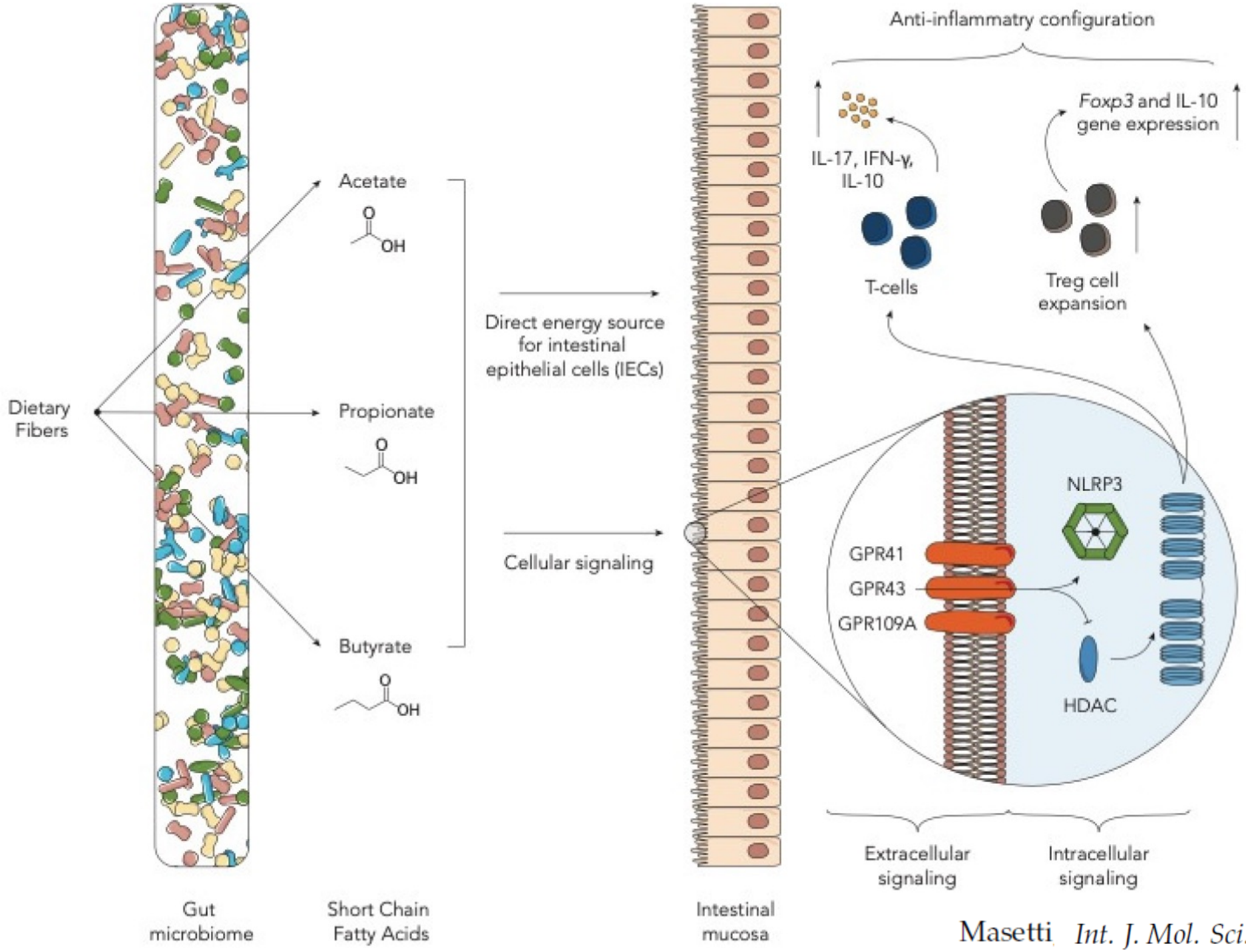
L'uomo incontra Dio
dietro ogni porta
che la scienza riesce ad aprire.
(Albert Einstein)



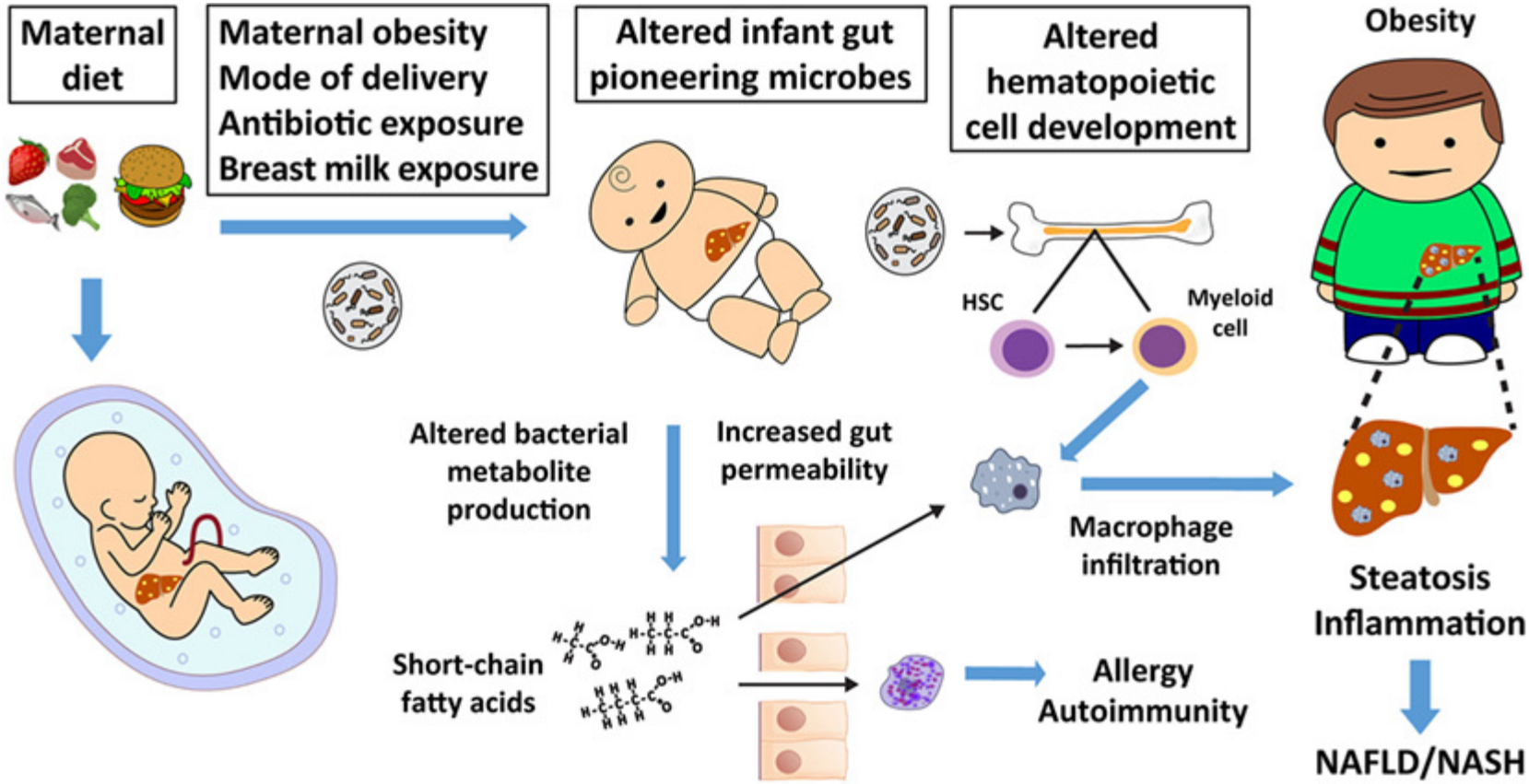


Hang-Yu Li

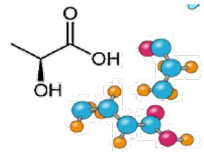
Nutrients 2021



Masetti *Int. J. Mol. Sci.* **2021**

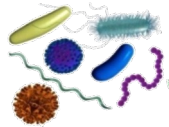

Maternal diet
Maternal obesity
Mode of delivery
Antibiotic exposure
Breast milk exposure
Altered infant gut pioneering microbes
Altered hematopoietic cell development
Obesity
HSC
Myeloid cell
Altered bacterial metabolite production
Increased gut permeability
Macrophage infiltration
Steatosis
Inflammation
Short-chain fatty acids
Allergy
Autoimmunity
NAFLD/NASH

POSTBIOTICS



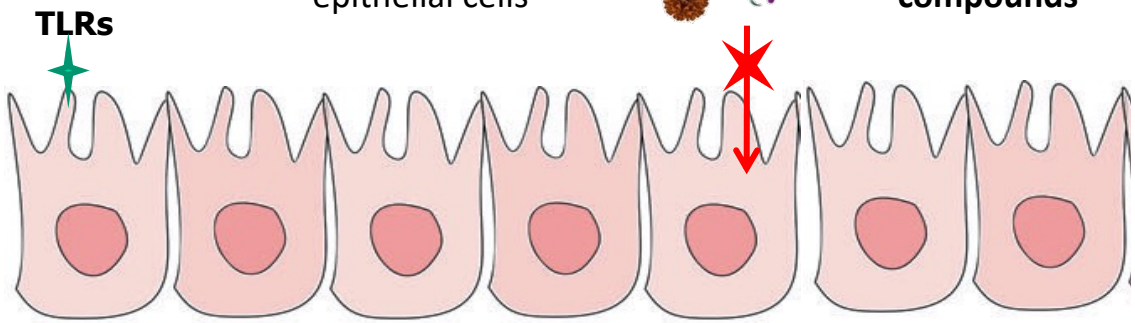
↑ **expression** in Toll like receptors (TLRs)

Inhibition of pathogen penetration into epithelial cells



Production of **antimicrobial compounds**

↑ **Intestinal Barrier Function**



↓ **pro-inflammatory** cytokine production

↑ **anti-inflammatory** cytokine production

Regulation of Th1- and Th2- mediated immune responses

Immune modulation

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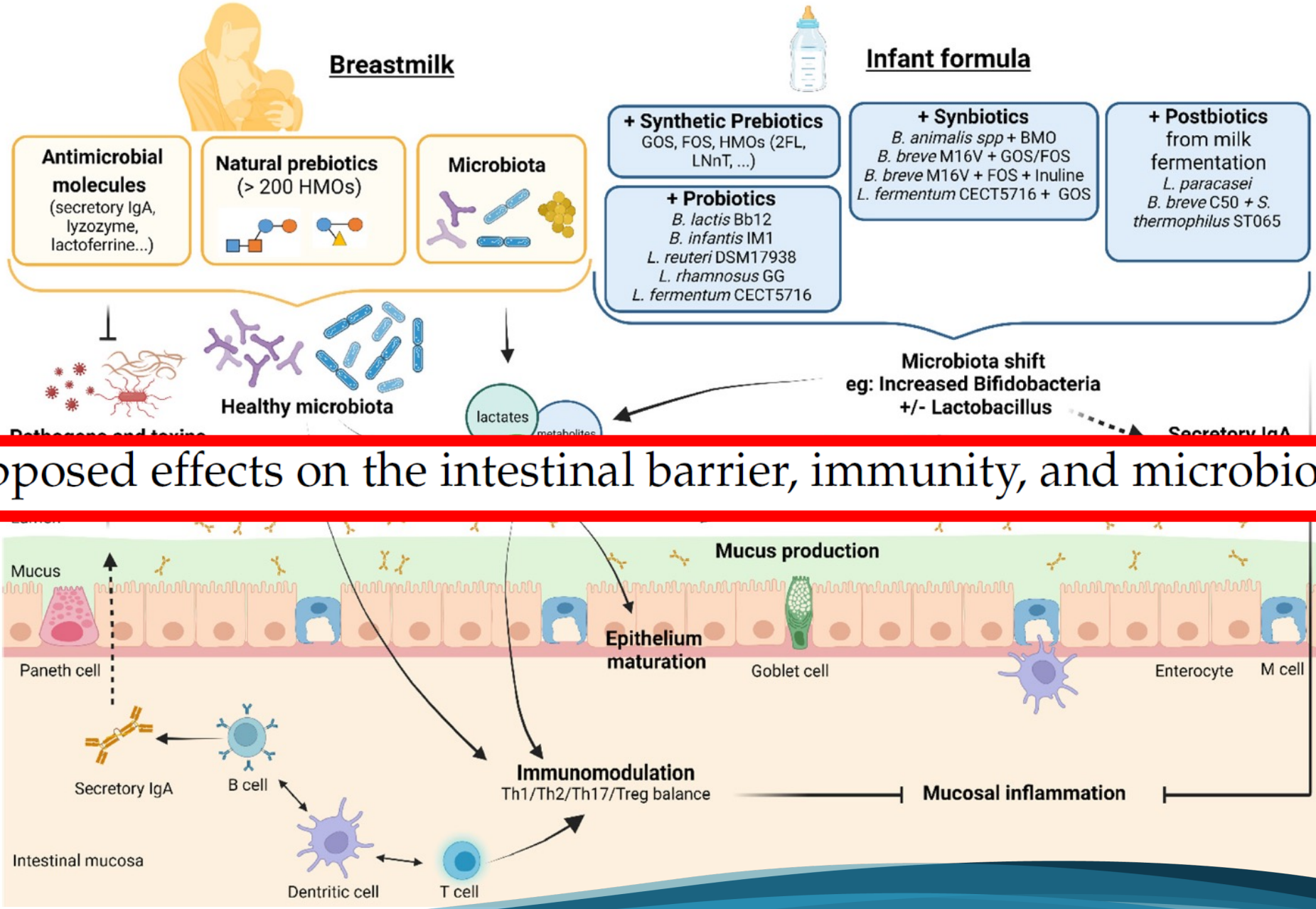
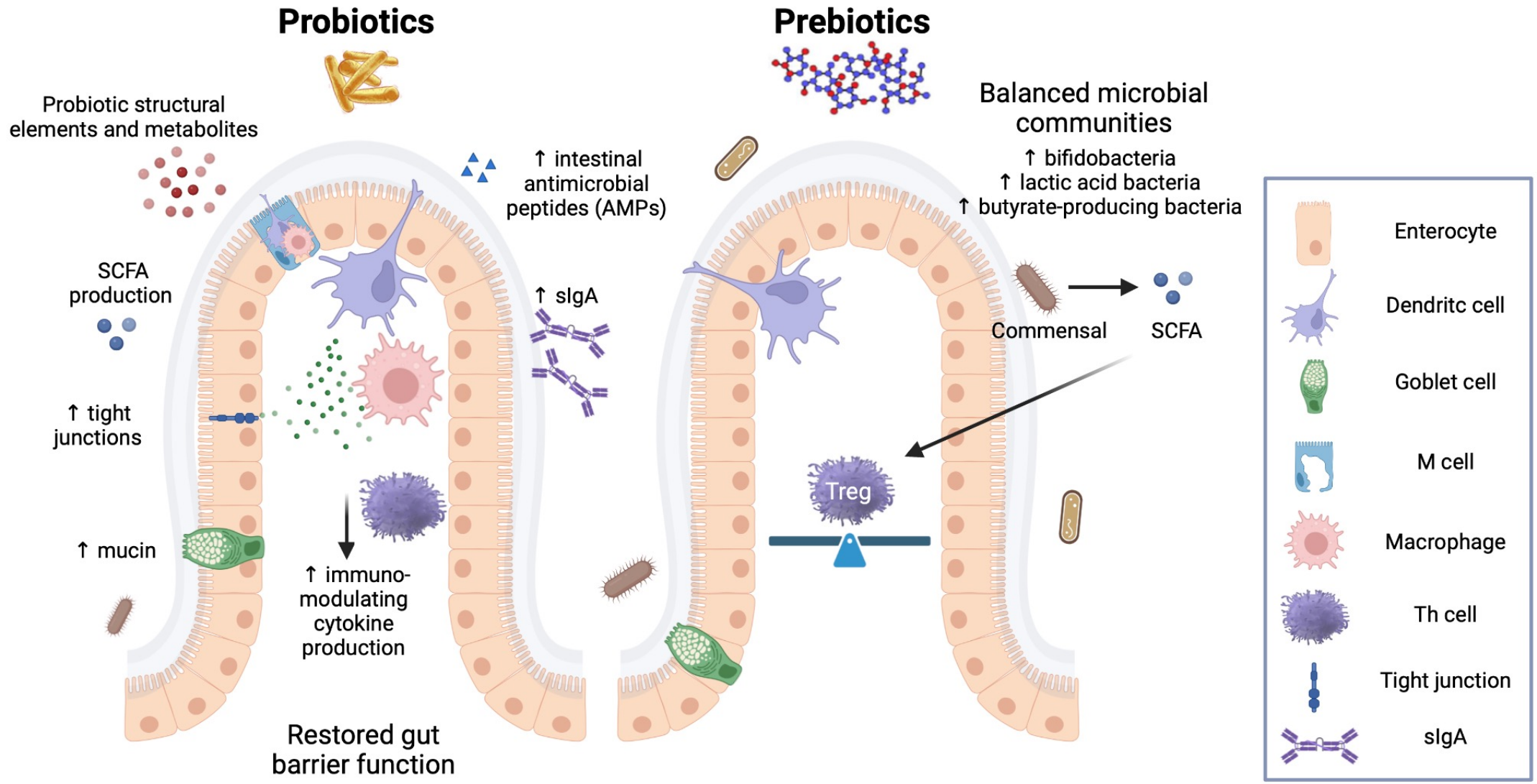


Lemoine, A. *Nutrients* 2023



V.L. Miniello et al. *Nutrients* **2023**