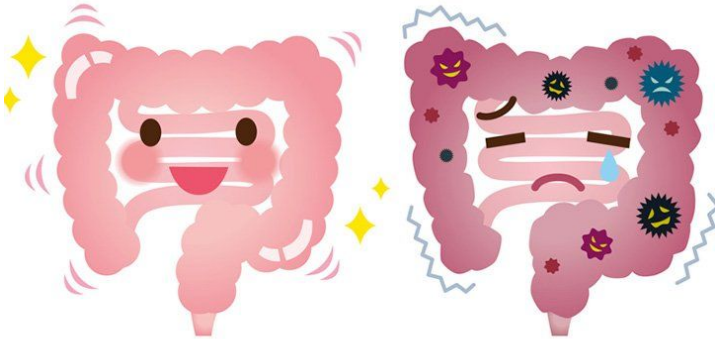
ALIMENTAZIONE E SALUTE DELLA DONNA.
CIBO E SOSTENIBILITA' AMBIENTALE
17.02.2024 - sala «G. Cordova», Pescara

MICROBIOTA E ALIMENTAZIONE:

LA SALUTE PASSA ATTRAVERSO IL NOSTRO INTESTINO

Dott. Maria Teresa ILLICETO



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The **HUMAN MICROBIOME PROJECT** (2007)

GENOMA UMANO (23000)
MICROBIOMA INTESTINALE (oltre 3 milioni)

CO-EVOLUZIONE in SIMBIOSI

IPOTESI di un "**SUPER ORGANISMO**" costituito da organismo umano e microrganismi

INTESTINO UMANO
ECOSISTEMA COMPLESSO

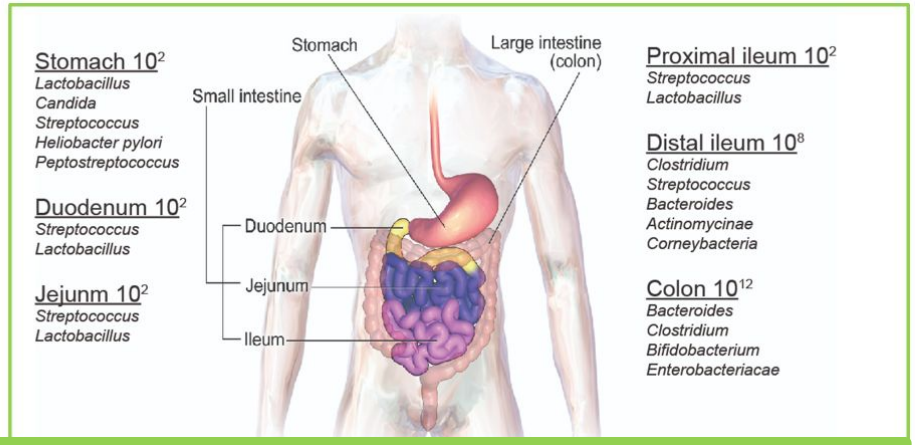
BATTERI RESIDENTI RUOLO CRUCIALE NELLO STATO DI SALUTE

INTERAZIONI TRA BATTERI (COOPERAZIONE – COMPETIZIONE)

1- favorire la colonizzazione e la crescita di specie batteriche

2- stabilizzare la comunità intestinale

DIFFENZE di ABBONDANZA e SPECIE MICROBICHE nell'apparato G-I

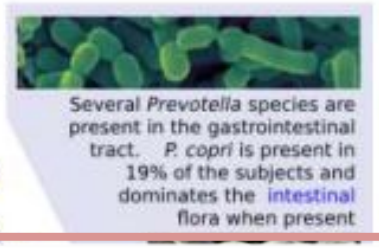


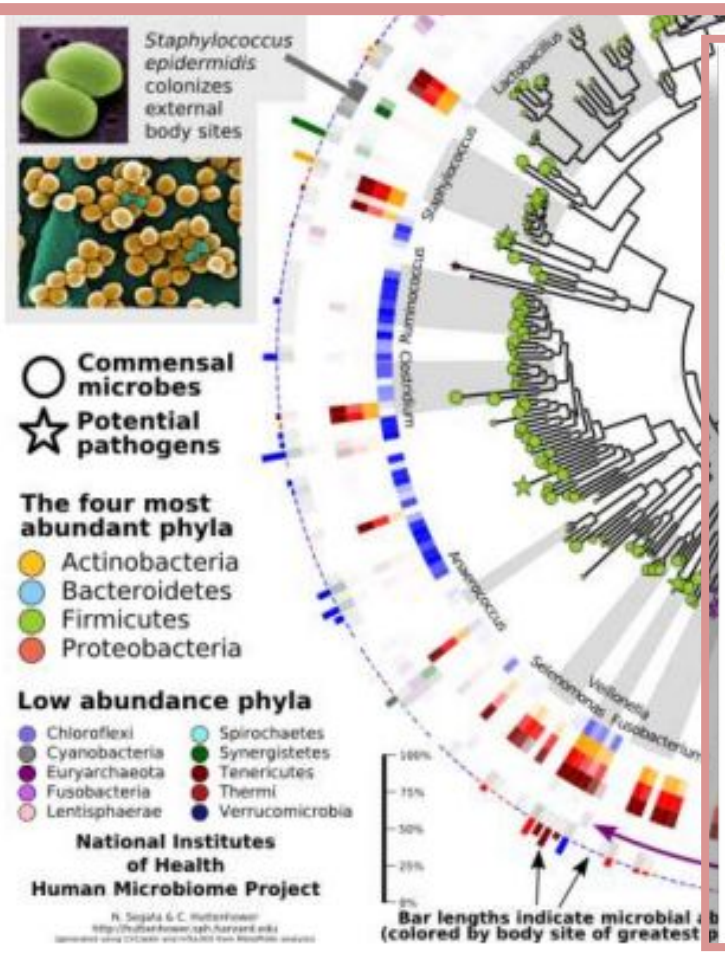
ECOSISTEMA MICROBICO CORRETTAMENTE BILANCIATO

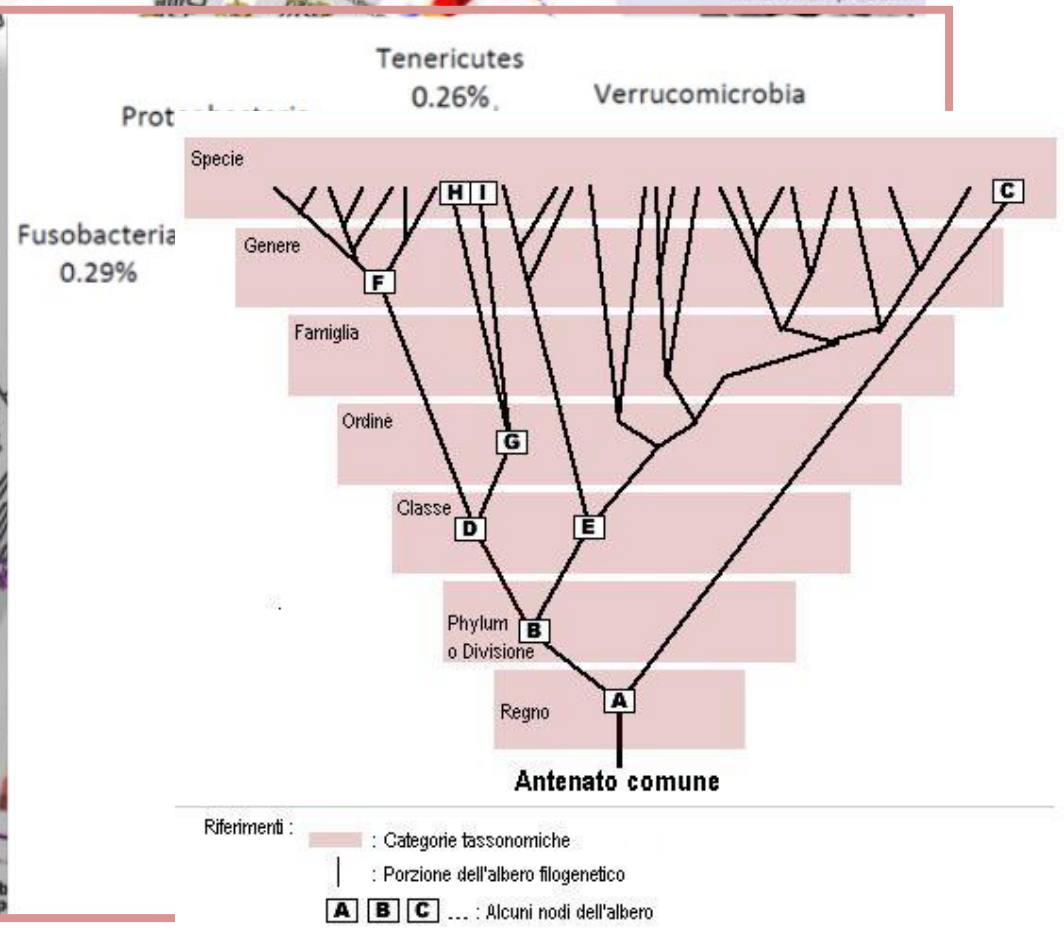
EUBIOSI

FAR FUNZIONARE AL MEGLIO IL NOSTRO ORGANISMO

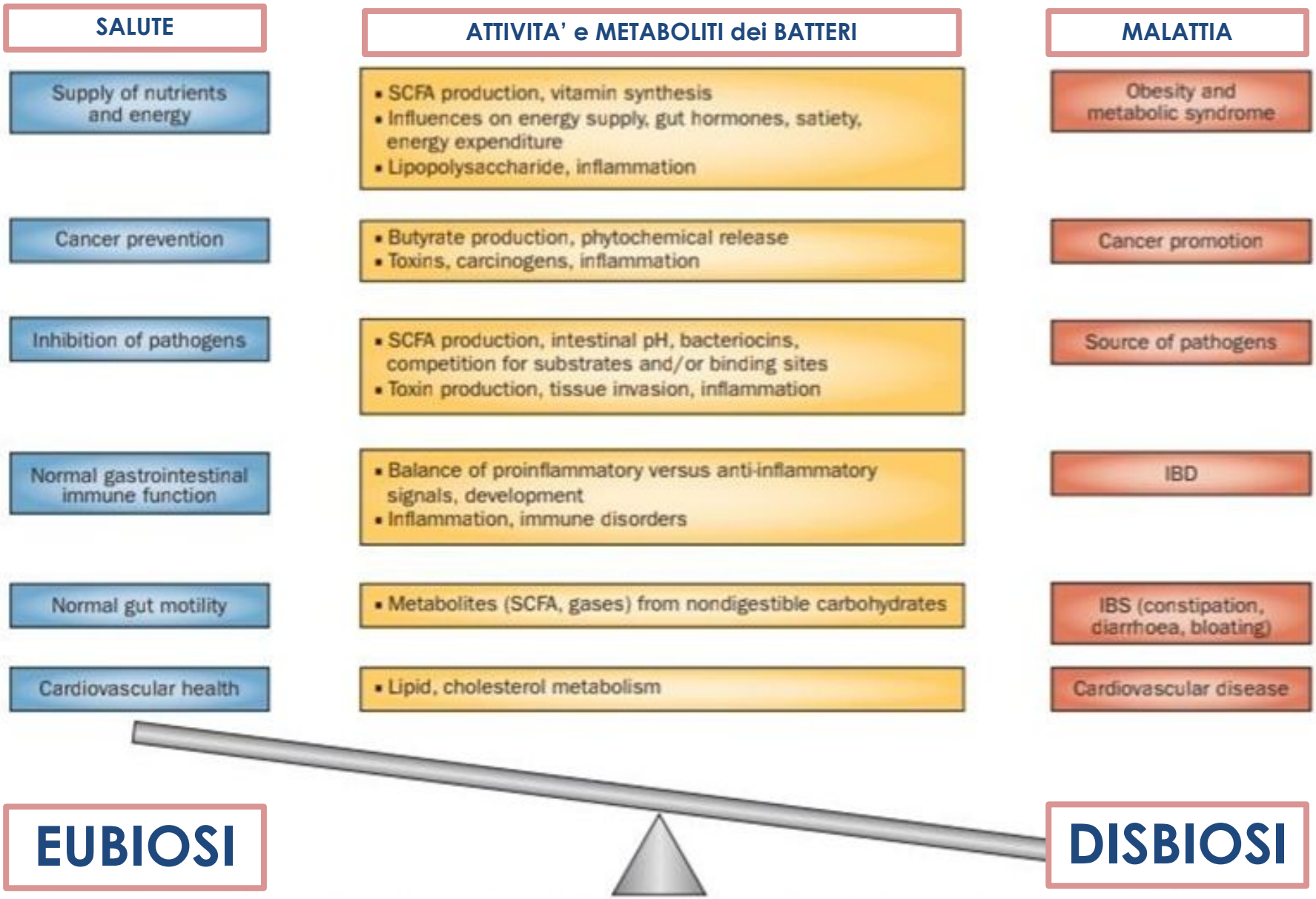
- **Firmicutes** (Gram-positivi); almeno 250 generi tra cui Mycoplasma, Bacillus, Clostridium, Dorea, Faecalibacterium, Ruminococcus, Eubacterium, Staphylococcus, Streptococcus, **Lactobacillus**, Lactococcus, Enterococcus, Sporobacter e Roseburia.
- **Actinobacteria** (Gram-positivi); **Bifidobacterium**, Collinsella, Eggerthella e Propionibacterium.
- **Bacteroidetes** (Gram-negativi); oltre 20 generi tra cui Bacteroides, Prevotella e Corynebacterium.
- **Proteobacteria** (Gram-negativi); Escherichia, Klebsiella, Shigella, Salmonella, Citrobacter, Helicobacter e Serratia.





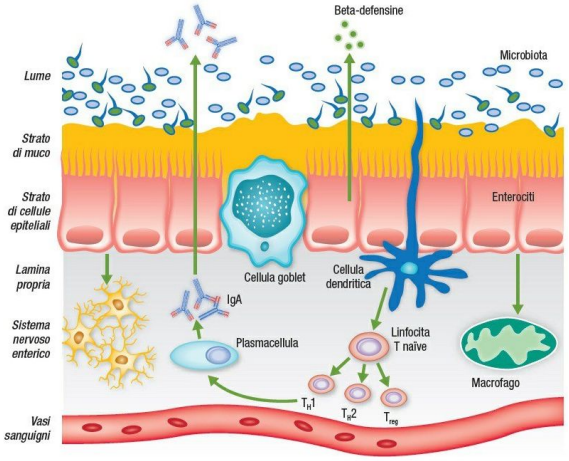


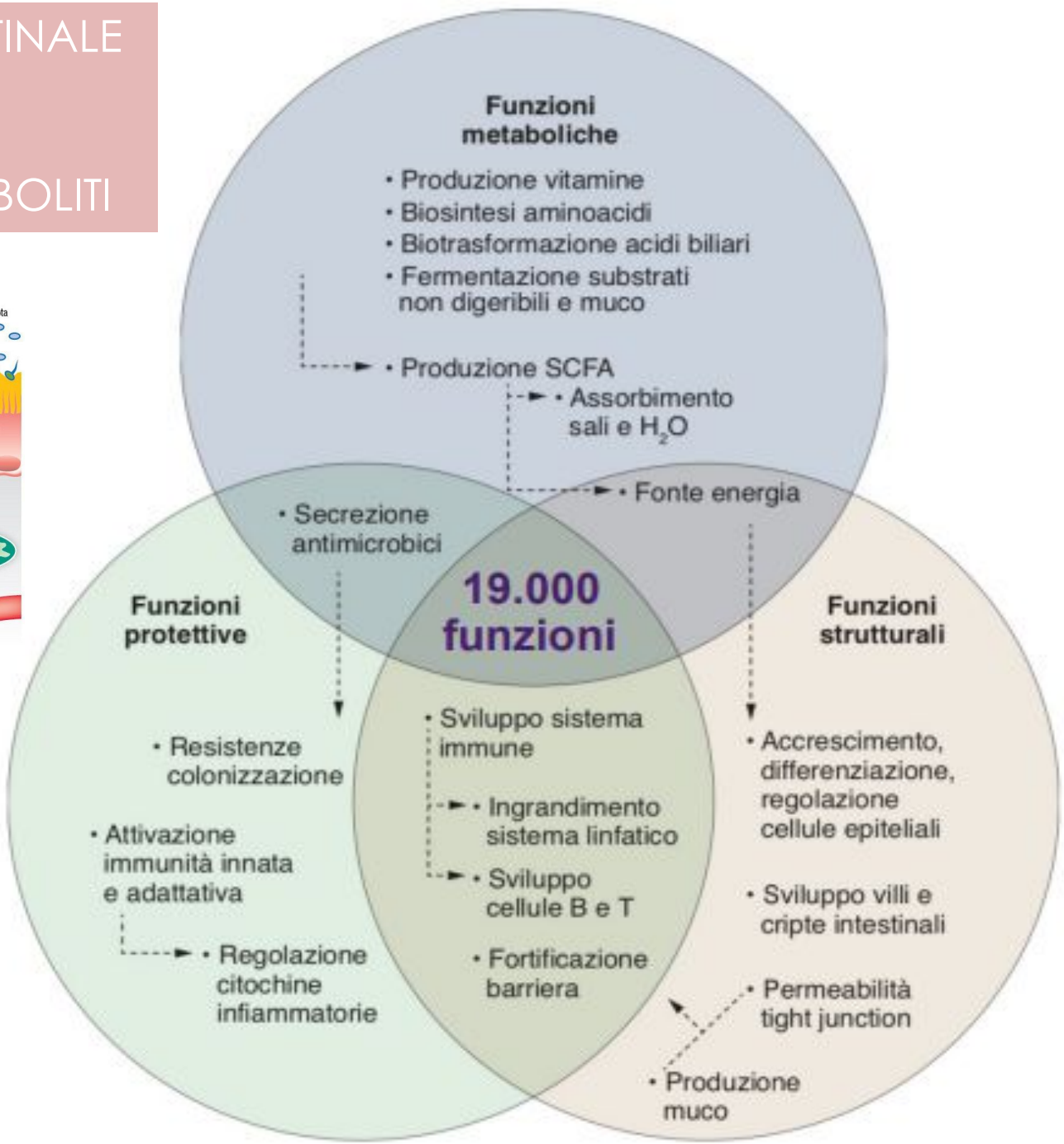
RUOLO del MICROBIOTA INTESTINALE sullo STATO DI SALUTE



MICROBIOMA INTESTINALE
oltre 3 milioni

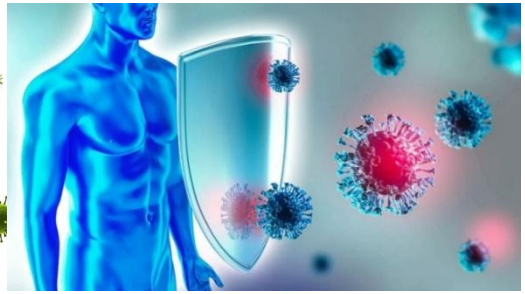
CENTINAIA DI METABOLITI

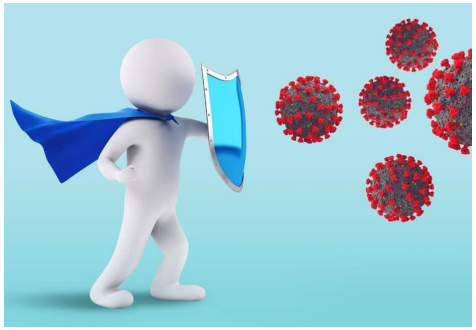


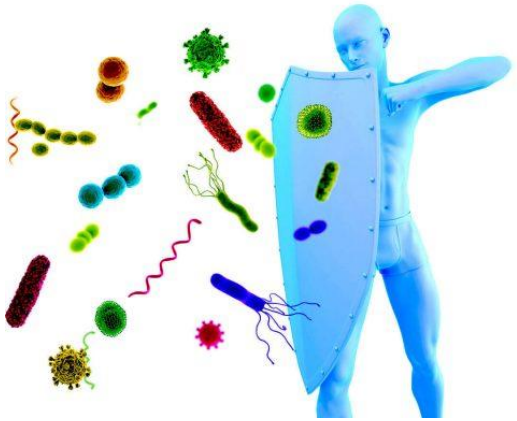


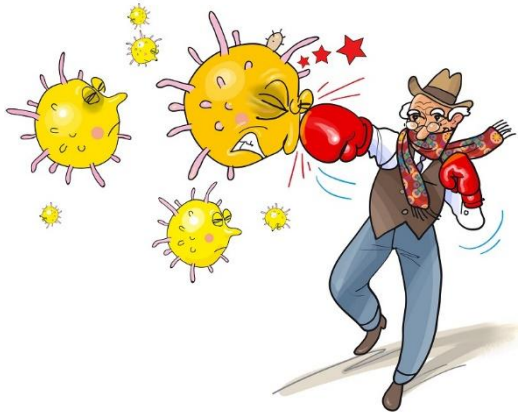
QUALITA' - DIVERSITA' BATTERICA

BASSA DIVERSITA' = CLUSTER INFIAMMATORIO CRONICO









ECOSISTEMA INTESTINALE RICCO DI SPECIE
PIÙ ROBUSTO

LA DIVERSITÀ SEMBRA ESSERE
UN BUON INDICATORE di "INTESTINO SANO"

Role of the gut microbiota in nutrition and health

Ana M Valdes and colleagues discuss strategies for modulating the gut microbiota through diet and probiotics

Microbiome refers to the collective genomes of the micro-organisms in a particular environment, and microbiota is the community of micro-organisms themselves (box 1). Approximately 100 trillion micro-organisms (most of them bacteria, but also viruses, fungi, and protozoa) exist in the human gastrointestinal tract[1 2]—the microbiome is now best thought of as a virtual organ of the body. The human genome consists of about 23 000 genes, whereas the microbiome encodes over three million genes producing thousands of metabolites, which replace many of the functions of the host,[1 3] consequently influencing the host's fitness, phenotype, and health.[2]

Box 1: Glossary

- *Microbiome*—the collective genomes of the micro-organisms in a particular environment
- *Microbiota*—the community of micro-organisms themselves
- *Microbiota diversity*—a measure of how many different species and, dependent on the diversity indices, how evenly distributed they are in the community. Lower diversity is considered a marker of dysbiosis (microbial imbalance) in the gut and has been found in autoimmune diseases and obesity and cardiometabolic conditions, as well as in elderly people
- *Operational taxonomic unit*—a definition used to classify groups of closely related organisms. DNA sequences can be clustered according to their similarity to one another, and operational taxonomic units are defined based on the similarity threshold (usually 97% similarity) set by the researcher
- *Colonocytes*—epithelial cells of the colon
- *Germ-free animals*—animals that have no micro-organisms living in or on them
- *Short chain fatty acids*—fatty acids with two to six carbon atoms that are produced by bacterial fermentation of dietary fibres

Studying the gut microbiota

Twin studies have shown that, although there is a heritable component to gut microbiota, environmental factors related to diet, drugs, and anthropometric measures are larger determinants of microbiota composition.[4 5]

Gut microbes are key to many aspects of human health including immune,[6] metabolic[5] and neurobehavioural traits (fig 1).[7 8] Different levels of evidence support the role of gut microbiota in human health, from animal models[9 10] and human studies.[4 11-13]

Animal models can help identify gut microbes and mechanisms, though the degree to which findings translate to humans is unknown. In humans, observational studies can show cross-sectional associations between microbes and health traits but are limited by the inability to measure causal relations. The strongest level of evidence is obtained from interventional clinical studies—in particular, randomised controlled trials.

The composition of gut microbiota is commonly quantified using DNA based methods, such as next generation sequencing of 16S ribosomal RNA genes or whole genome shotgun sequencing,

KEY MESSAGES

- Gut microbiota influences many areas of human health from innate immunity to appetite and energy metabolism
- Targeting the gut microbiome, with probiotics or dietary fibre, benefits human health and could potentially reduce obesity
- Drugs, food ingredients, antibiotics, and pesticides could all have adverse effects on the gut microbiota
- Microbiota should be considered a key aspect in nutrition; the medical community should adapt their education and public health messages
- Fibre consumption is associated with beneficial effects in several contexts

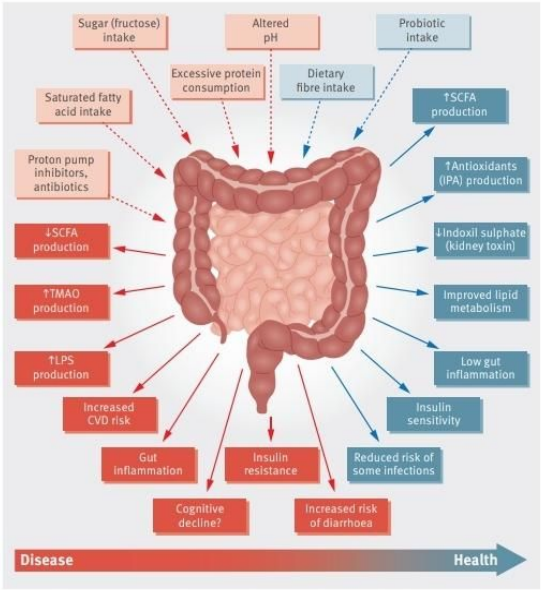


Fig 1 | Schematic representation of the role of the gut microbiota in health and disease giving some examples of inputs and outputs. CVD=cardiovascular disease; IPA=indolepropionic acid; LPS=lipopolysaccharide; SCFA=short chain fatty acids; TMAO=trimethylamine N-oxide

QUALITA' del M.
FUNZIONE del M.

CORRELATI CON I LORO
MAGGIORI
«DETEREMINANTI»

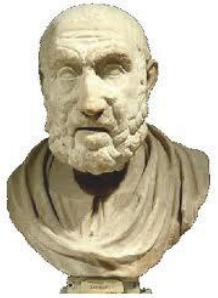
DIETA E FARMACI

BMJ 361: Suppl1 Jun 2018

NUTRIZIONE

Il complesso dei PROCESSI BIOLOGICI che consentono o condizionano la conservazione, l'accrescimento, lo sviluppo dell'organismo vivente e la reintegrazione delle perdite materiali ed energetiche che accompagnano le diverse attività funzionali.

"LASCIA CHE IL CIBO SIA LA TUA MEDICINA, E LA MEDICINA SIA IL TUO CIBO" Ippocrate 400 a.C.



"SIAMO QUELLO CHE MANGIAMO "
Ludwig Feuerbach 1800

Dietary element	Effect on gut microbiome	Effect on health outcomes mediated by gut microbiome	Human observational studies
Low FODMAP diet	Low FODMAP diet increased Actinobacteria; high FODMAP diet decreased abundance of bacteria involved in gas consumption[58]	Reduced symptoms of irritable bowel syndrome[56]	
Cheese	Increased *Bifidobacteria*,[97 98] which are known for their positive health benefits to their host through their metabolic activities.[99] Decrease in *Bacteroides* and *Clostridia*, some strains of which are associated with intestinal infections[58]	Potential protection against pathogens.[100] Increased production of SCFA and reduced production of TMAO[99]	
Fibre and prebiotics	Increased microbiota diversity and SCFA production[22 101 102]	Reduced type 2 diabetes[22] and cardiovascular disease[103]	
Artificial sweeteners	Overgrowth of Proteobacteria and *Escherichia coli*.[104] *Bacteroides*, *Clostridia*, and total aerobic bacteria were significantly lower, and faecal pH was significantly higher[47]	Induced glucose intolerance[105]	
Polyphenols (eg, from tea, coffee, berries, and vegetables such as artichokes, olives, and asparagus)	Increased intestinal barrier protectors (*Bifidobacteria* and *Lactobacillus*), butyrate producing bacteria (*Faecalibacterium prausnitzii* and *Roseburia*) and *Bacteroides vulgatus* and *Akkermansia muciniphila*.[107] Decreased lipopolysaccharide producers (*E coli* and *Enterobacter cloacae*)[106]	Gut micro-organisms alter polyphenol bioavailability resulting in reduction of metabolic syndrome markers and cardiovascular risk markers[108]	
Vegan	Very modest differences in composition and diversity in humans and strong differences in metabolomic profile compared with omnivore diet in humans[50]	Some studies show benefit of vegetarian over omnivore diet,[109] others fail to find a difference[110]	

FODMAP=fermentable oligosaccharides, disaccharides, monosaccharides and polyols; SCFA=small chain fatty acids; TMAO= trimethylamine N-oxide

EVIDENZE CLINICHE INSUFFICIENTI

PER CONCLUSIONI E RACCOMANDAZIONI

REGIME DIETETICO PREFERIBILE

FIBRA E MICROBIOTA INTESTINALE

L'ORGANISMO UMANO NON POSSIEDE GLI ENZIMI
PER SCOMPORRE LA **FIBRA** CHE ASSUMIAMO CON L'ALIMENTAZIONE.

MICROBIOTA DIGERISCE LE FIBRE

⇩

SCFA
BUTIRRATO, ACETATO, PROPRIONATO

effetti metabolici

riduzione del pH intestinale
prevenendo la crescita di microrganismi potenzialmente patogeni

effetti immunomodulatori (riduzione delle citochine pro-infiammatorie)

NUTRIMENTO PER IL MICROBIOTA INTESTINALE = SOSTANZA PREBIOTICA

Table 1 Factors, types of dysbiosis caused in the gut, consequences and alternative therapeutic approaches

Extrinsic Factors	Observations in the gut	Alteration in the gut	Alternative remedies
Dietary			
High-fat/high-sugar		Permeability in the intestinal mucosal and reduced expression of tight junction proteins zo-1 and occluding. Compromising selective absorption and triggers the onset of metabolic endotoxemia (Martinez-Medina et al. 2014)	PUFA and conjugated linoleic acid (CLA), phytochemicals, Mediterranean diet
A high-protein diet		Deleterious and toxic for the intestine (Martinez et al. 2010)	PUFA and conjugated linoleic acid (CLA), phytochemicals, Mediterranean diet
Excess dietary intake of protein and acids		Development of an obesity-associated microbiota, ulcerative colitis (Martinez-Medina et al. 2014), lead to DNA damage (Martinez-Medina et al. 2014; Irrazábal et al. 2014)	PUFA and conjugated linoleic acid (CLA) due to anti-inflammatory characteristic
Excess nutrient intake		Obesity related to inflammatory metabolic disorders culminating from dysbiosis (Frank et al. 2007)	Probiotic (*Lactobacillus paracasei*) [a]circulating levels of ANGPTL4 and reduces body fat
Vitamin D deficiency		Play a role in the pathogenesis of IBD and [a]risk of colitis (Ananthakrishnan 2015)	Vitamin D supplementation had an anti-inflammation due to the inhibition of pro inflammatory genes such as TNF genes
Red meat (thiol-containing amino a		[b]Mucus formation, inhibits methylation of DNA and [a] the generation of reactive oxygen species (Ananthakrishnan 2015)	Stress such as exercise under sun or heat exposure) is recommended
Saturated fatty acids and low in poly saturated fatty acids (vegetable oil model		Inflammatory reaction mediated by Th1 cells and colitis, high bad low-density lipoprotein (LDL) cholesterol level (Ananthakrishnan 2015; Liu et al. 2020)	Feeding on mono-saturated fats and polyunsaturated fatty acids (vegetable oil)
Sucralose (aspartame and saccharin) model		Pro-inflammatory genes and unpredictable faecal metabolites (Zhang et al. 2012)	FMT, PUFA and conjugated linoleic acid (CLA), mediterranean diet
Gluten		[a] Risk of coeliac diseases or even proven gluten intolerance, constipation and diarrhea (Schroeder et al. 2018)	Gluten-free diet and hydration
Fasting and hibernation		Capable of degrading mucin, suppress the immune system thus [a] *Firmicutes* (more polysaccharides) the tolerance of the host to its microbes (Secor and Carey 2016)	PUFA and conjugated linoleic acid (CLA), phytochemicals, Mediterranean diet and hydrating

Bajinka et al AMB Expr 2020

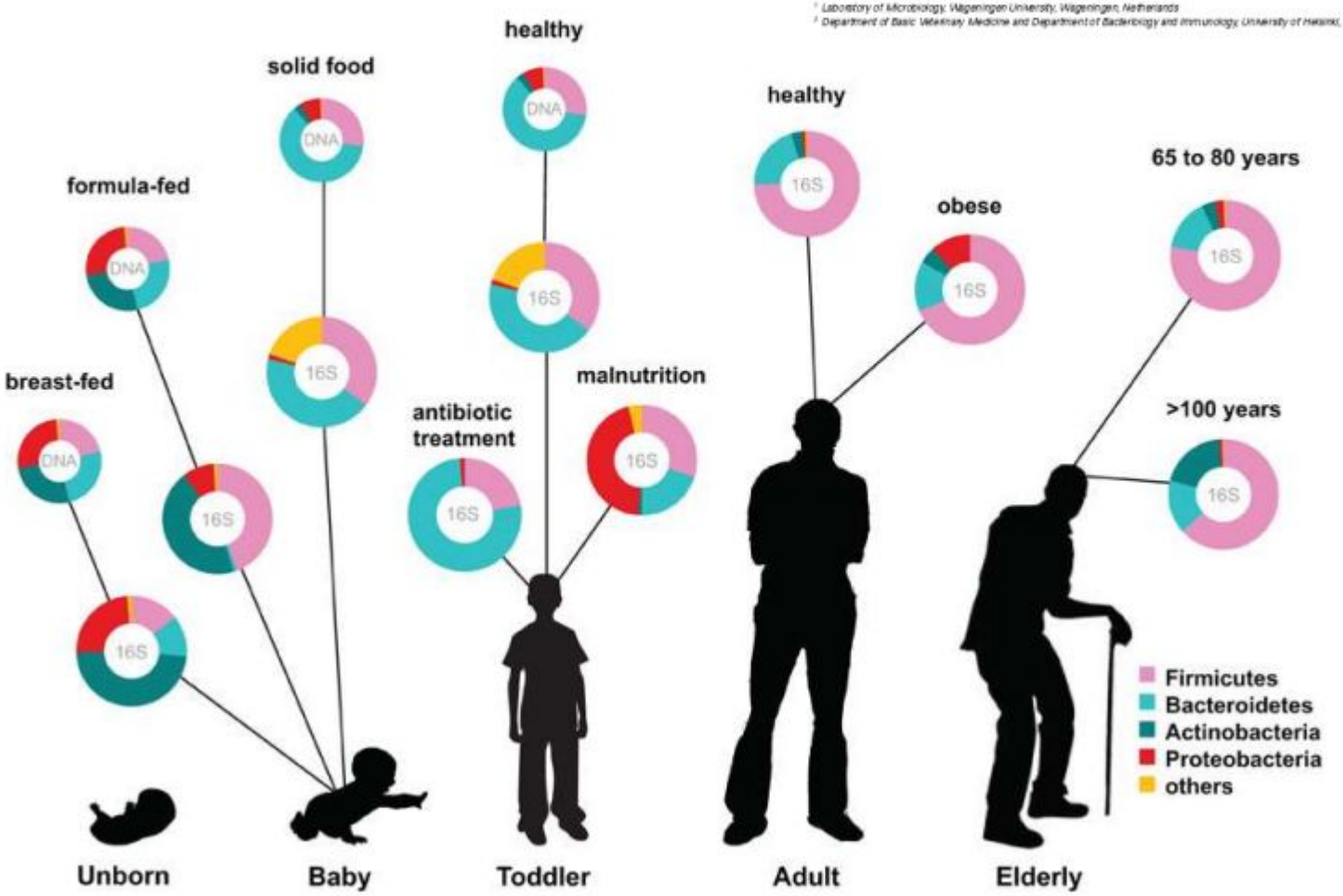
Microbiota nel tempo

frontiers in
CELLULAR AND INFECTION MICROBIOLOGY
REVIEW ARTICLE
published: 09 August 2012

The function of our microbiota: who is out there and what do they do?

*Noora Ottman[1], Hauke Smidt[1], Willem M. de Vos[1,2] and Clara Belzer[1]**

[1] Laboratory of Microbiology, Wageningen University, Wageningen, Netherlands
[2] Department of Basic Veterinary Medicine and Department of Bacteriology and Immunology, University of Helsinki, Helsinki, Finland

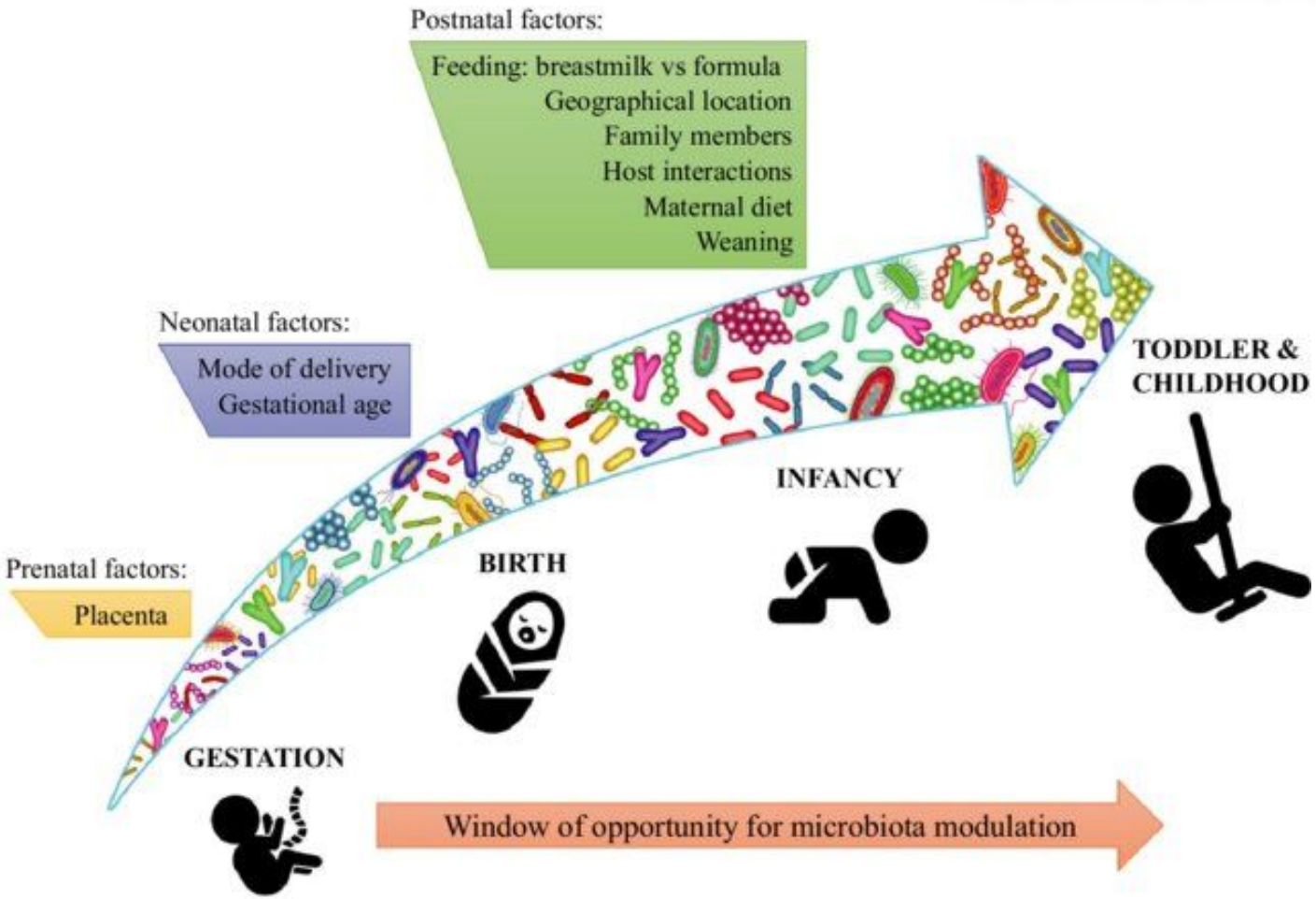


LA COMPOSIZIONE DEL MICOBIOTA RIMANE SOSTANZIALMENTE STABILE

«PERTURBAZIONI» POSSONO SHIFTARE IL MICROBIOTA INDIVIDUALE AD UN «NUOVO STATO»

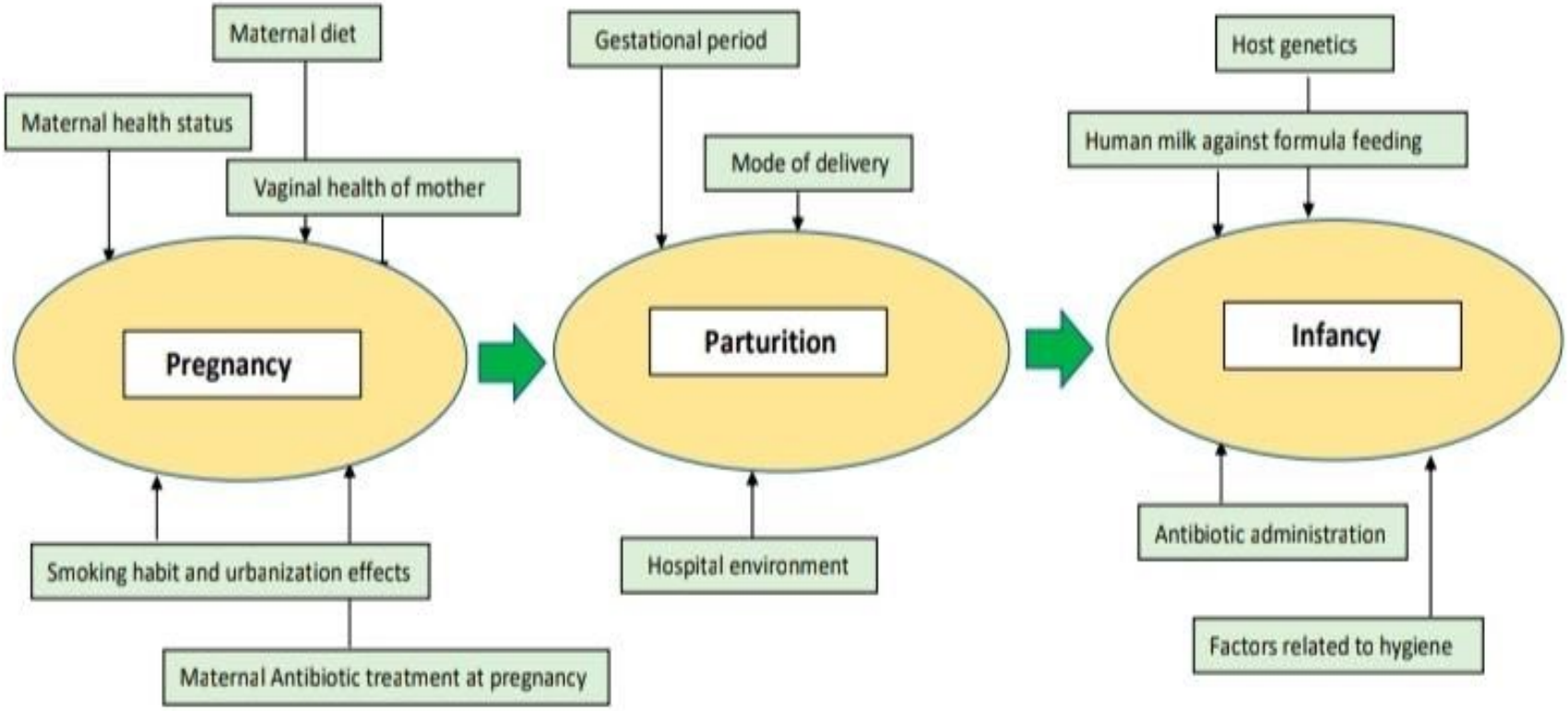
EVOLUZIONE DEL MICROBIOTA INTESTINALE NEL CORSO DELLA VITA

FATTORI PRENATALI, NEONATALI E POSTNATALI
che possono contribuire alla
COSTITUZIONE, MATURAZIONE E STABILIZZAZIONE

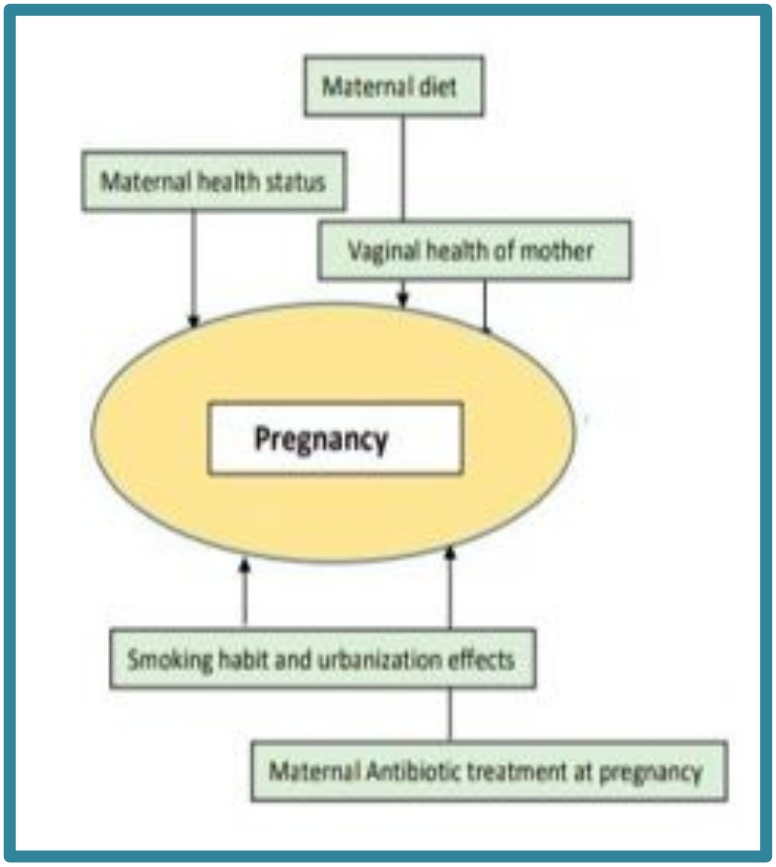


Ventura M et al "Health benefits conferred by the human gut microbiota during infancy"
Microbial Biotechn 2019 Mar; 12(2):243-248

FATTORI RILEVANTI CHE DETERMINANO LA RICCHEZZA E L'ABBONDANZA DEL MICROBIOTA NELLE PRIME FASI DELLA VITA



J. Clin. Med. **2021**, *10*, 459.



-STATO DI SALUTE DELLA MADRE (EUBIOSI)

-DIETA DELLA MADRE

-EUBIOSI VAGINALE

Lattobacilli produttori batteriocine

-FUMO, STILE DI VITA, STATO SOCIO-ECONOMICO, USO FARMACI

stress, ore di lavoro, …

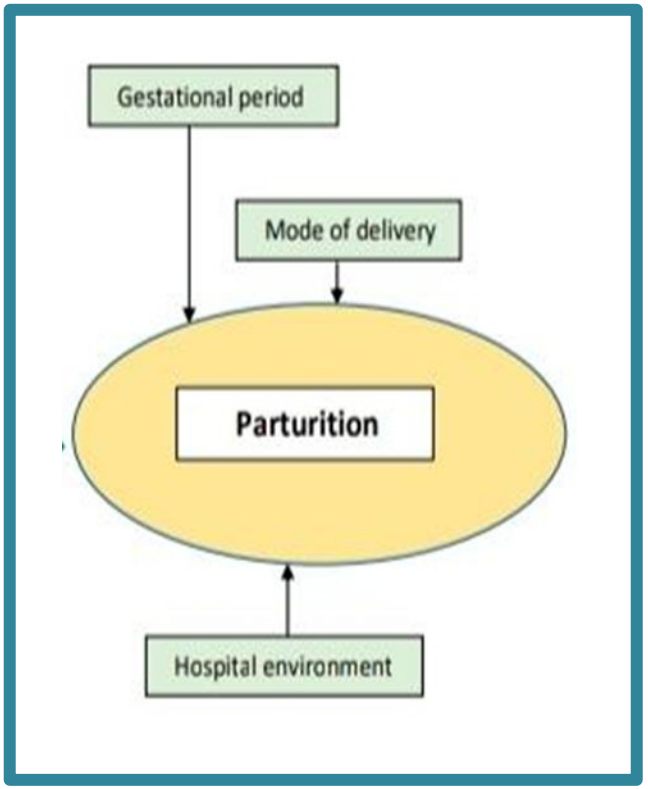
-ANTIBIOTICI IN GRAVIDANZA

↓ diversità microbiota

< Bifidobatteri

> Clostridium ed Enterococcus faecium

> Streptococchi



-ETA' GESTAZIONALE

PRETERMINE: < Bifidobatteri, < biodiversità
DISBIOSI peggiore se terapia antibiotica

-TIPO DI PARTO =

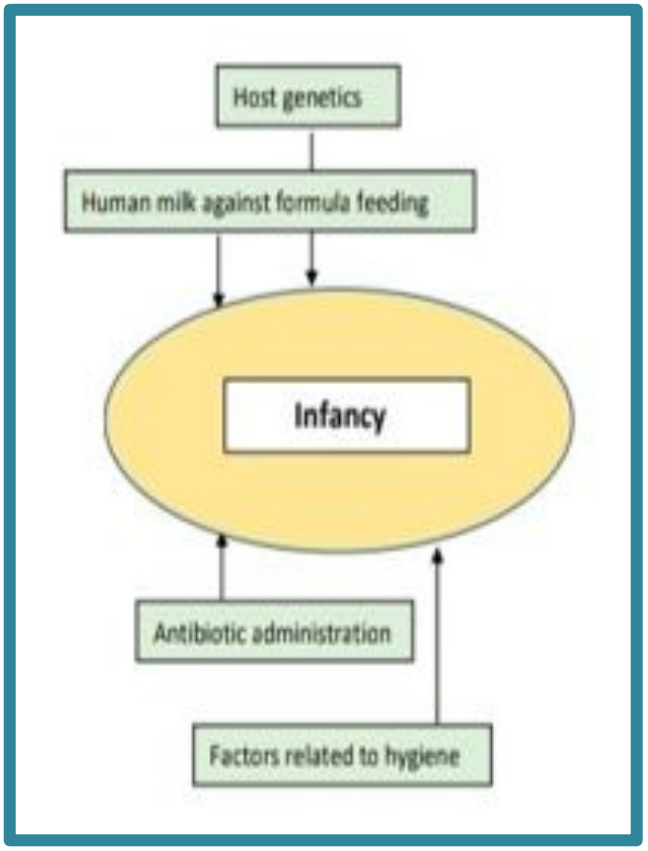
maggior determinante per il microbiota del neonato
dura per mesi e oltre

PARTO VAGINALE
CONTATTO MICROBIOTA VAGINALE E FECALE DELLA MADRE
Bifidobacterium, Lactobacillus, Prevotella, Bacteroides, Parabacteroides, Escherichia

PARTO CESAREO
CONTATTO MICROBIOTA CUTE MADRE – BATTERI AMBIENTE SALA OPERATORIA
Staphylococcus, Propionibacterium e Corynebacterium; pochi Bifidobacterium

-AMBIENTE OSPEDALIERO(NIDO/TIN)

FAMIGLIA, STAFF OSPEDALIERO, LOCALITA' GEOGRAFICA, QUALITA' ARIA



-GENETICA

-ALLATTAMENTO

MATERNO (HMO, FATTORI ANTIMICROBICI, IgA secretorie)

FORMULA

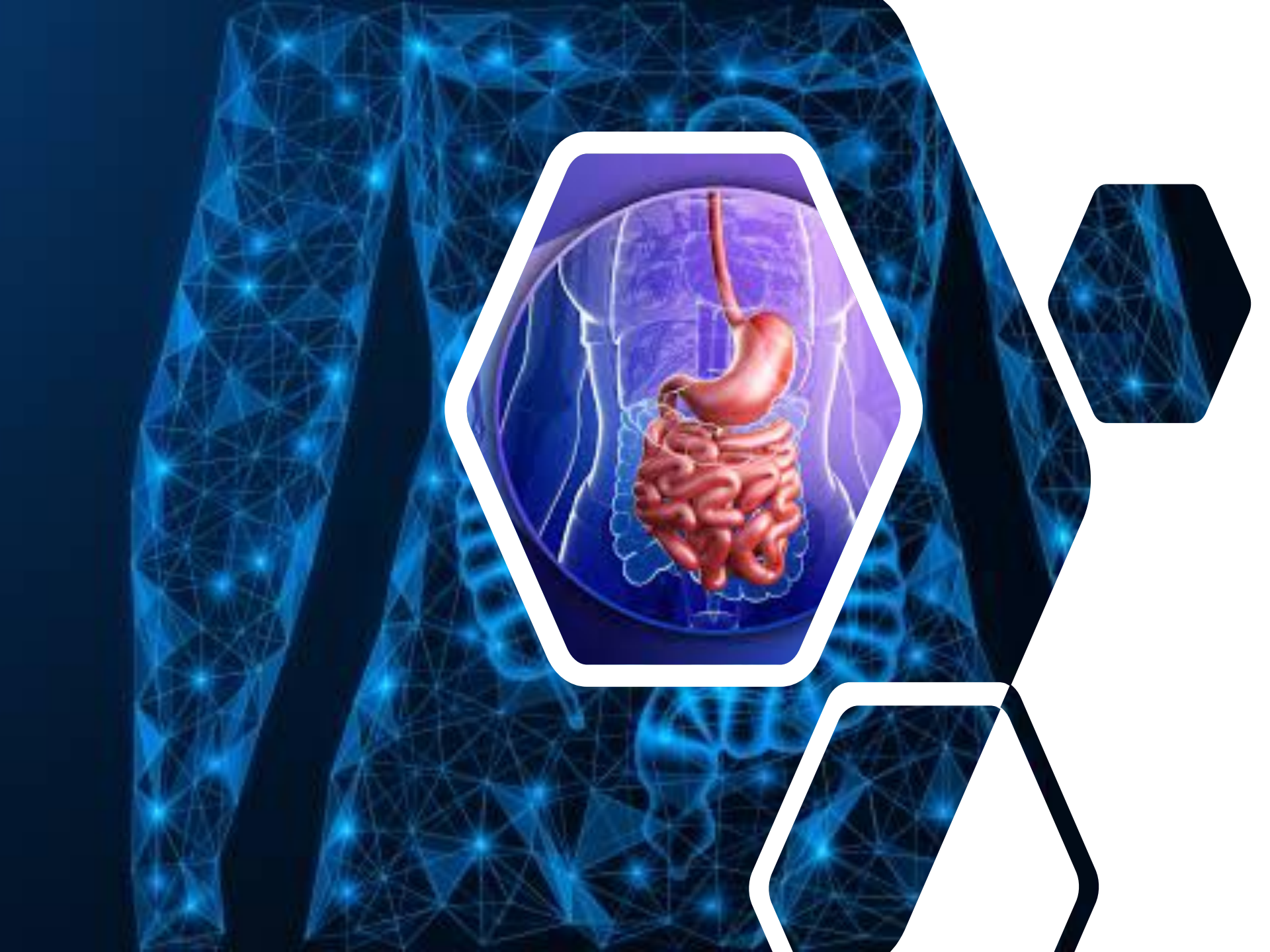
World Health Organization

-FATTORI CORRELATI all'IGIENE

ECCESSIVA IGIENE -> SIST. IMMUNE SOTTOSVILUPPATO
CON POCA MEMORIA
E POCA «PREPARAZIONE» x contrastare
INFEZIONI negli incontri futuri

-ANTIBIOTICI

CAMBIAMENTI CONSIDEREVOLI
TRATTAMENTO PRECOCE -> MODIFICA M. A LUNGO
CICLI RIPETUTI -> > DISBIOSI
< PRODUZIONE IgG
> SUSCETTIBILITA' INFEZIONI



Gebrayel et al.
Journal of Translational Medicine (2022) 20:111
https://doi.org/10.1186/s12967-022-03296-9

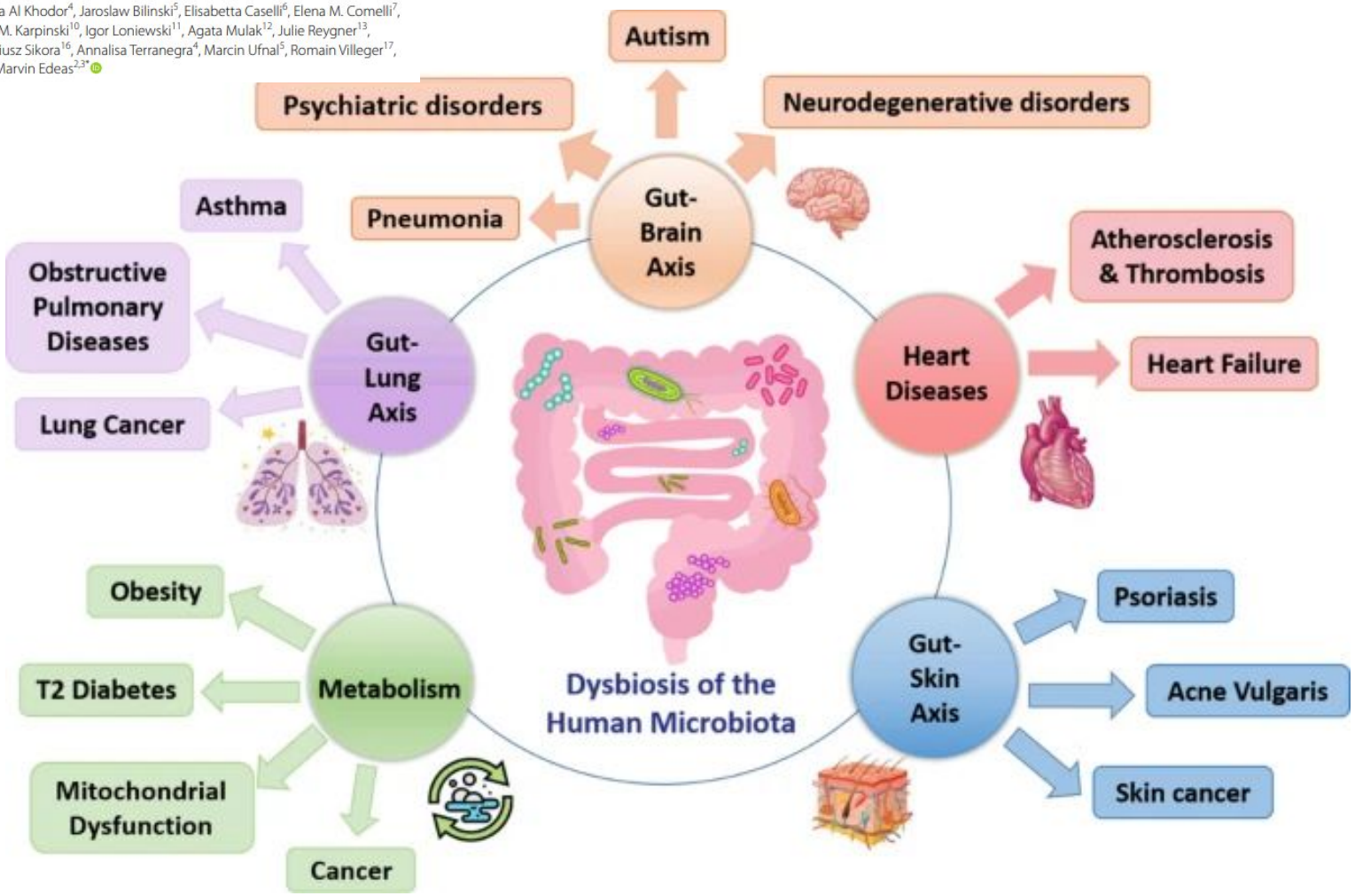
Journal of Translational Medicine

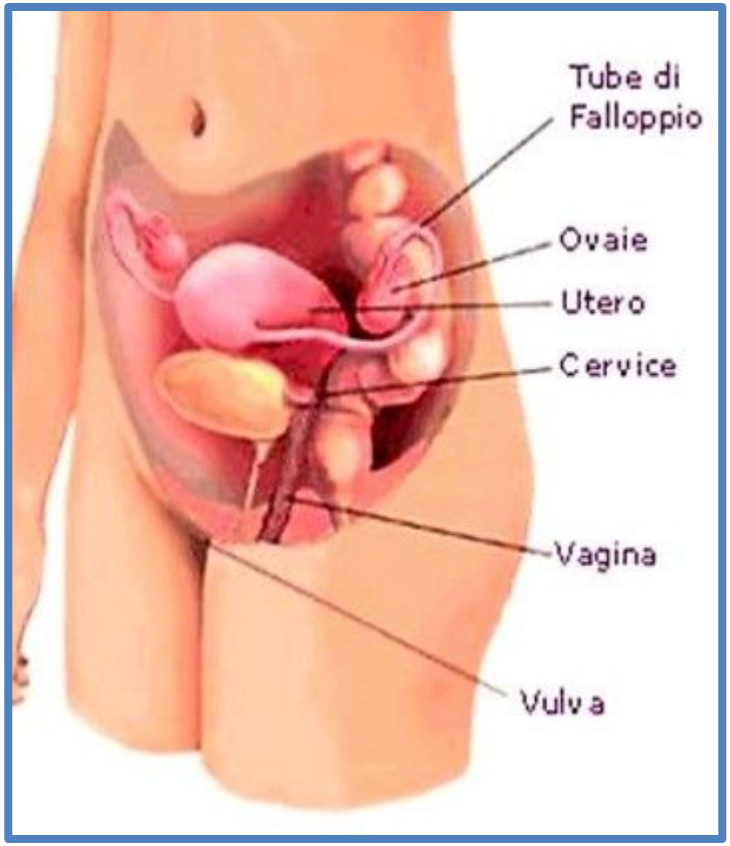
REVIEW Open Access

Microbiota medicine: towards clinical revolution

2022

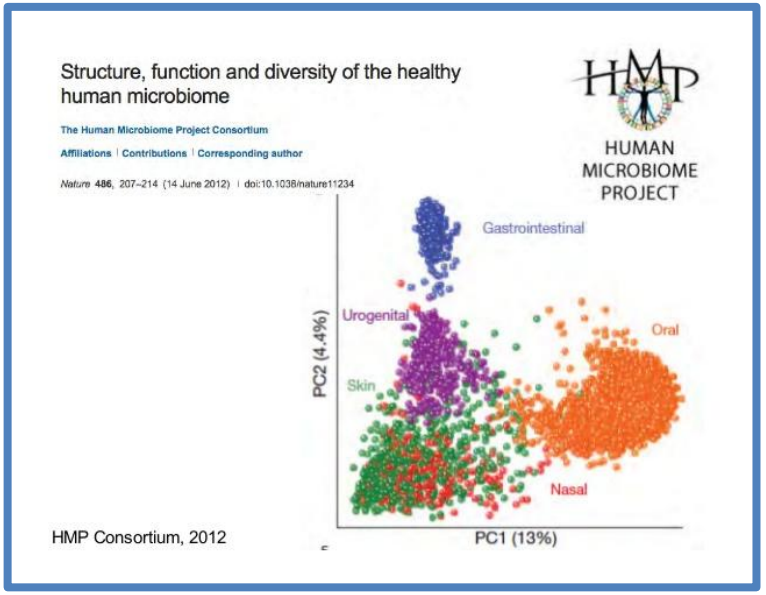
Prisca Gebrayel[1], Carole Nicco[2,3], Souhaila Al Khodor[4], Jaroslaw Bilinski[5], Elisabetta Caselli[6], Elena M. Comelli[7], Markus Egert[8], Cristina Giaroni[9], Tomasz M. Karpinski[10], Igor Loniewski[11], Agata Mulak[12], Julie Reygner[13], Paulina Samczuk[14], Matteo Serino[15], Mariusz Sikora[16], Annalisa Terranegra[4], Marcin Ufnal[5], Romain Villeger[17], Chantal Pichon[18], Peter Konturek[19] and Marvin Edeas[2,3]*





CONTIGUITA'

MICROBIOMA= ORGANO INVISIBILE



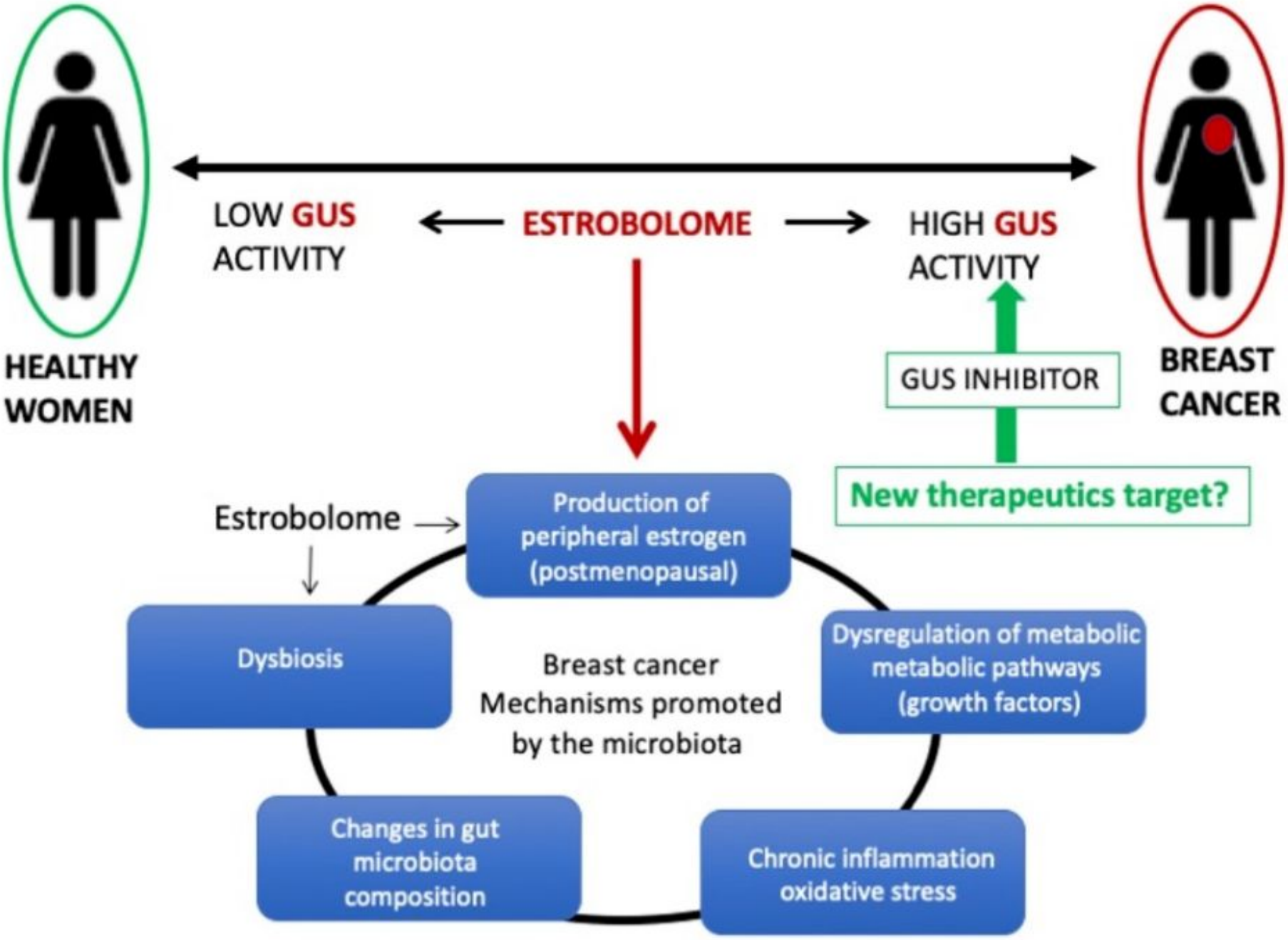
ESTROBOLOMA

INSIEME DI BATTERI IN GRADO DI MODULARE IL RICIRCOLO ENTEROEPATICO DI ESTROGENI

INFLUENZARE I LIVELLI CIRCOLANTI DI QUESTI ORMONI E LA LORO ESCREZIONE

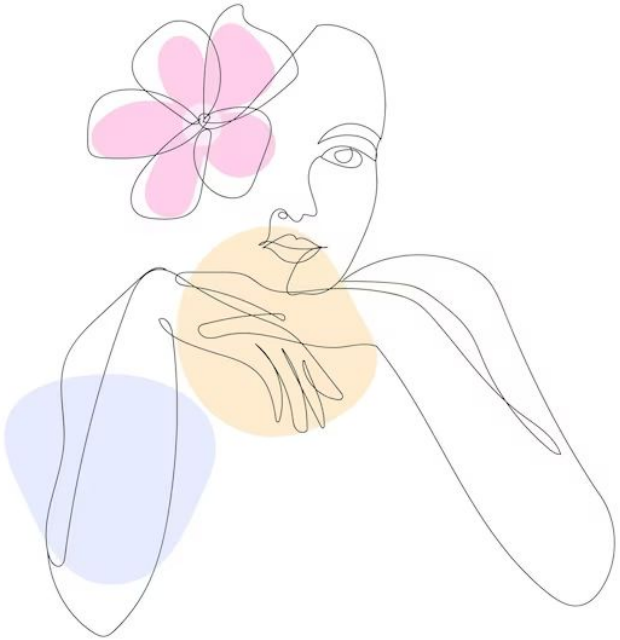
PRODUTTORI DI BETA-GLUCURONIDASI

enzima che deconiuga gli estrogeni e li trasforma nella loro forma attiva, capace di legarsi ai recettori degli estrogeni e influenzare i processi estrogeno-dipendenti


HEALTHY WOMEN
LOW GUS ACTIVITY
ESTROBOLOME
HIGH GUS ACTIVITY
BREAST CANCER
GUS INHIBITOR
New therapeutics target?
Estrobolome
Production of peripheral estrogen (postmenopausal)
Dysbiosis
Dysregulation of metabolic metabolic pathways (growth factors)
Breast cancer Mechanisms promoted by the microbiota
Changes in gut microbiota composition
Chronic inflammation oxidative stress

ORMONI SESSUALI
Modulano risposta innata ed acquisita
attraverso recettori di membrana e intracellulari delle cellule del sist. immune

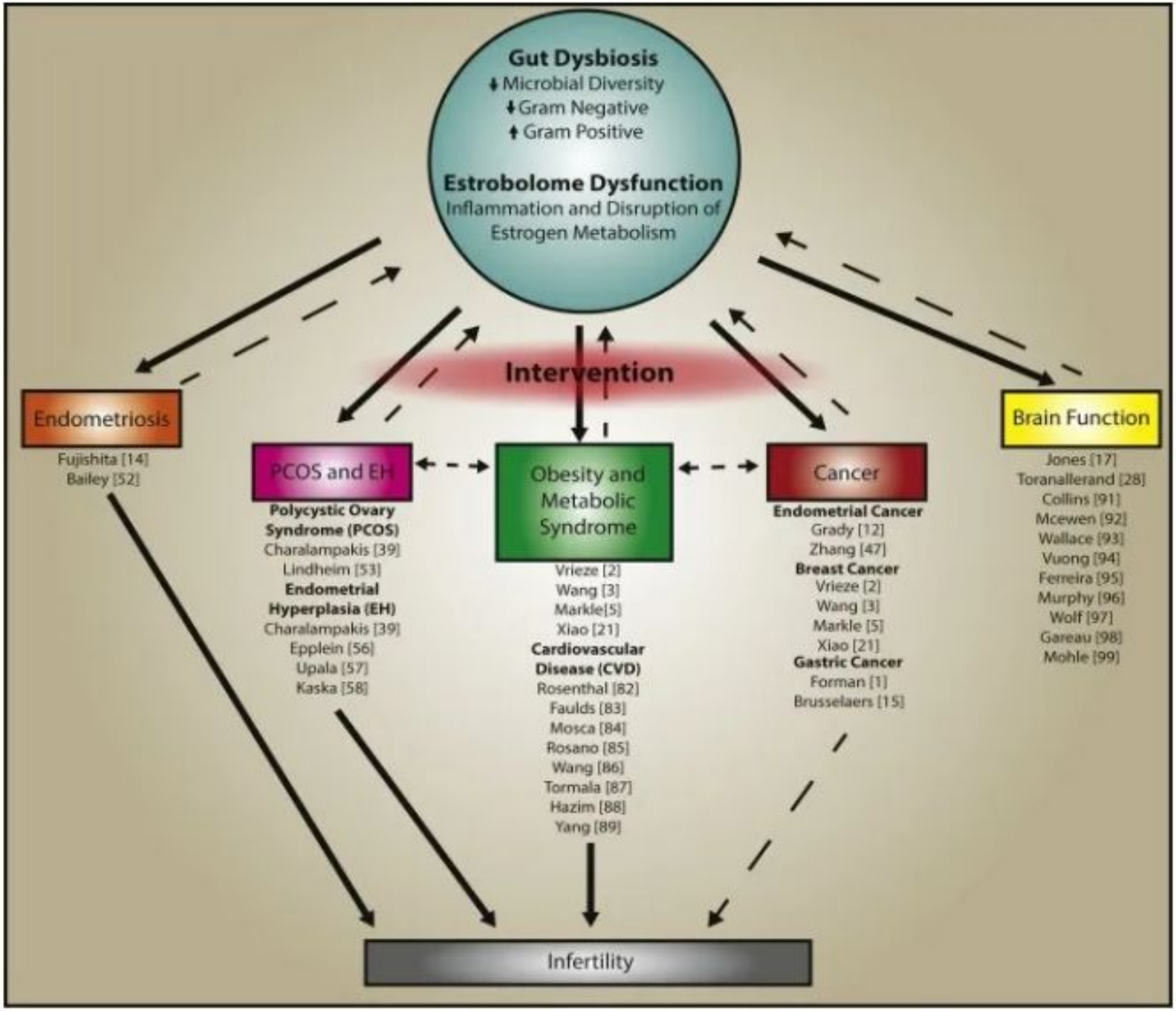
Interferiscono quindi con la trascrizione di specifici geni



RISPOSTA IMMUNITARIA MAGGIORE
- > produzione citochine in risposta alle infezioni
- FAGOCITOSI più efficace
- numero maggiore linfociti T
- livelli maggiori di ANTICORPI circolanti

MAGGIORE RESISTENZA ALLE INFEZIONI

MAGGIORE SUSCETTIBILITÀ A MALATTIE AUTOIMMUNI


Gut Dysbiosis
Microbial Diversity
Gram Negative
Gram Positive
Estrobolome Dysfunction
Inflammation and Disruption of Estrogen Metabolism
Intervention
Endometriosis
Fujishita [14]
Bailey [52]
PCOS and EH
Polycystic Ovary Syndrome (PCOS)
Charalampakis [39]
Lindheim [53]
Endometrial Hyperplasia (EH)
Charalampakis [39]
Epplein [56]
Upala [57]
Kaska [58]
Obesity and Metabolic Syndrome
Vrieze [2]
Wang [3]
Markle[5]
Xiao [21]
Cardiovascular Disease (CVD)
Rosenthal [82]
Faulds [83]
Mosca [84]
Rosano [85]
Wang [86]
Tormala [87]
Hazim [88]
Yang [89]
Cancer
Endometrial Cancer
Grady [12]
Zhang [47]
Breast Cancer
Vrieze [2]
Wang [3]
Markle [5]
Xiao [21]
Gastric Cancer
Forman [1]
Brusselaers [15]
Brain Function
Jones [17]
Toranallerand [28]
Collins [91]
Mcewen [92]
Wallace [93]
Vuong [94]
Ferreira [95]
Murphy [96]
Wolf [97]
Gareau [98]
Mohle [99]
Infertility

INTERFERENZE ESTROBOLOMA

STILE DI VITA - USO DI ANTIBIOTICI - USO DI CO

DIETA: FITOESTROGENI

Sostanze presenti nelle piante assomigliano agli estrogeni che noi produciamo

Interagiscono con gli stessi recettori degli estrogeni umani attivando i processi fisiologici a loro legati

Hanno una potenza molto minore e per tale motivo sono chiamati anche ESTROGENI DEBOLI

3 classi:
- isoflavoni (soia e derivati, trifoglio, cereali integrali)
- lignani (semi di lino e di sesamo, luppolo, frutta e verdura, cereali)
- cumestani (fagioli, germogli, chiodi di garofano, semi di girasole, trifoglio rosso, germogli di soia)

FITOESTROGENI

Dipendono dal momento e modalità della raccolta, dal tipo di terreno

Concentrati nella buccia (meglio consumare cibi integrali anziché lavorati)

Inattivi; l'attivazione è favorita dal microbiota, se funzionale, vitale ed in equilibrio

Effetto protettivo sul sistema cardiovascolare

Effetto protettivo sull'osso

↓ i sintomi vasomotori della menopausa

Potenziale effetto protettivo su alcuni tipi di tumore (seno, prostata). Tale effetto è stato studiato nei paesi asiatici dove il consumo di soia è più elevato rispetto al nostro

Effetto più protettivo (sui tumori) se assunti nell'adolescenza, più neutro se in età adulta

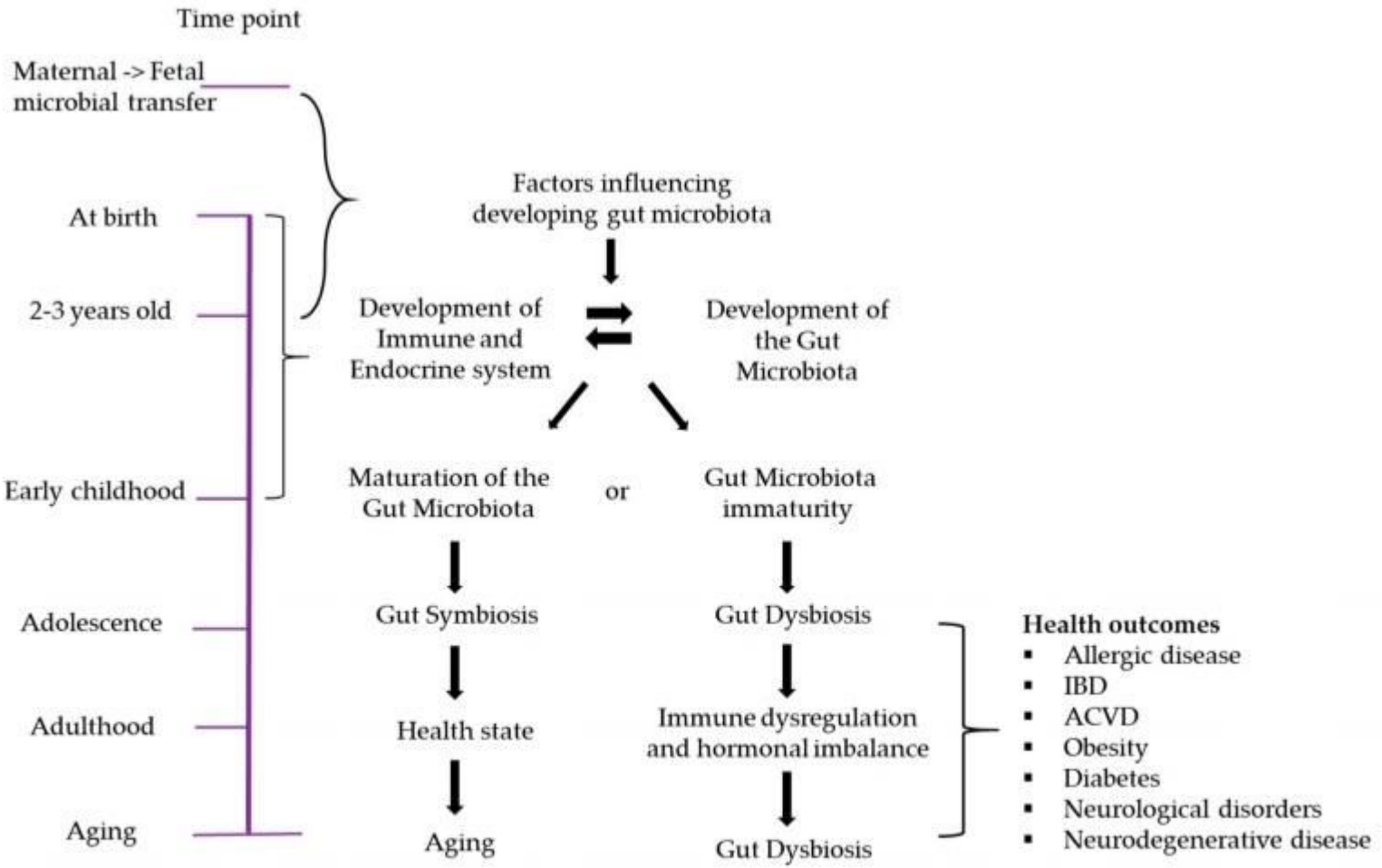
Alcune molecole si comportano da «endocrine disruptors»

A seconda del contesto possono ↑ o ↓ l'effetto degli estrogeni endogeni

Mancano conclusioni definitive sul rapporto fitoestrogeni e cancro ormono-sensibile

DOHaD hypothesis - Development of Origins of Health and Disease (DOHaD)-

La teoria dello «sviluppo delle origini della salute e della malattia»



Sarkar A et Al «The association between early-life gut microbiota and long-term health and diseases» J Clin Med 2021

PROSPETTIVE FUTURE

DISBIOSI PRECOCE – ALTERATO METABOLOMA

accumulo di cambiamenti patofisiologici cronici a sviluppo lento

MALATTIE CRONICHE IN ETA' SUCCESSIVE

STRATEGIA FUTURA

Tradurre questo corpo emergente di prove in interventi che interrompono e alterano il microbioma intestinale precoce IN SENSO EUBIOTICO

SOLUZIONE TERAPEUTICA

OTTIMIZZAZIONE DIAGNOSI E TERAPIA

«COMPETENZE GEMELLE»

TRATTAMENTO SPECIFICO ETA' – QUADRO CLINICO – SOSPETTO DATI DI LABORATORIO

MALATTIE INFIAMMATORIE INTESTINALI, MALATTIE METABOLICHE, RICORRENZE INFETTIVE, ATOPIA[14]

«E' meglio costruire un adulto sano dal grembo della madre e dall'età pediatrica che riparare e curare un adulto malato»

Prof. Vassilios Fanos