LE TRE VIE DELLA SALUTE

Cibo movimento e gestione delle emozioni nei pazienti con patologie croniche
Aosta 1 Dicembre 2017

IL MICROBIOTA INTESTINALE: NUOVA FRONTIERA NELLA CURE DI MOLTE PATOLOGIE

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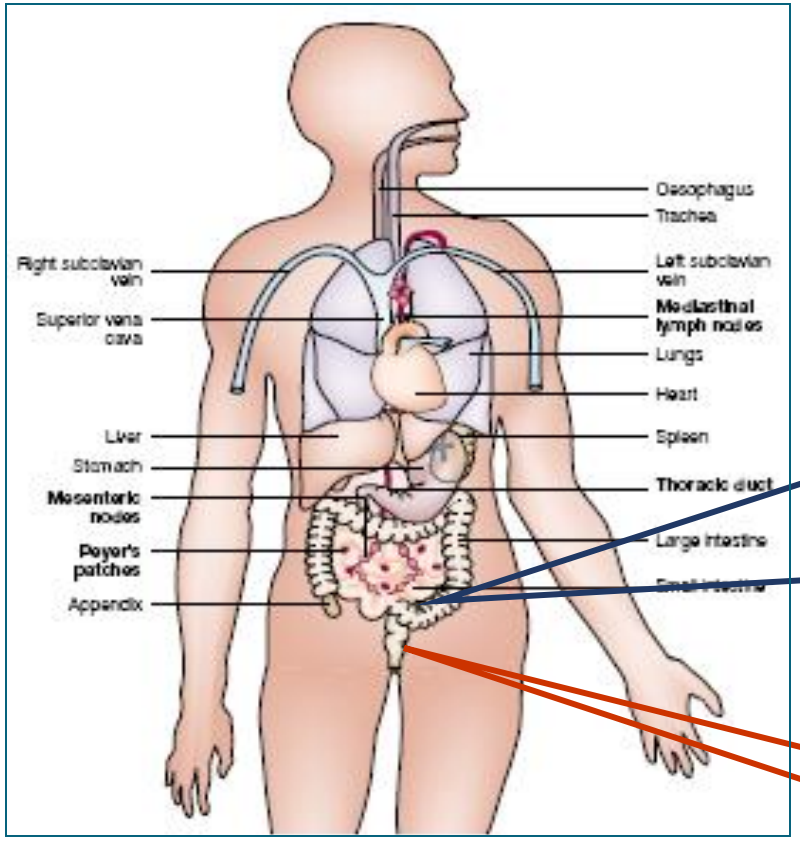
Agenda

1. MICROBIOTA
2. OBESITA’ E CANCRO
3. MICROBIOTA E CANCRO

“THE HUMAN/MICROBIOTA SUPERORGANISM”

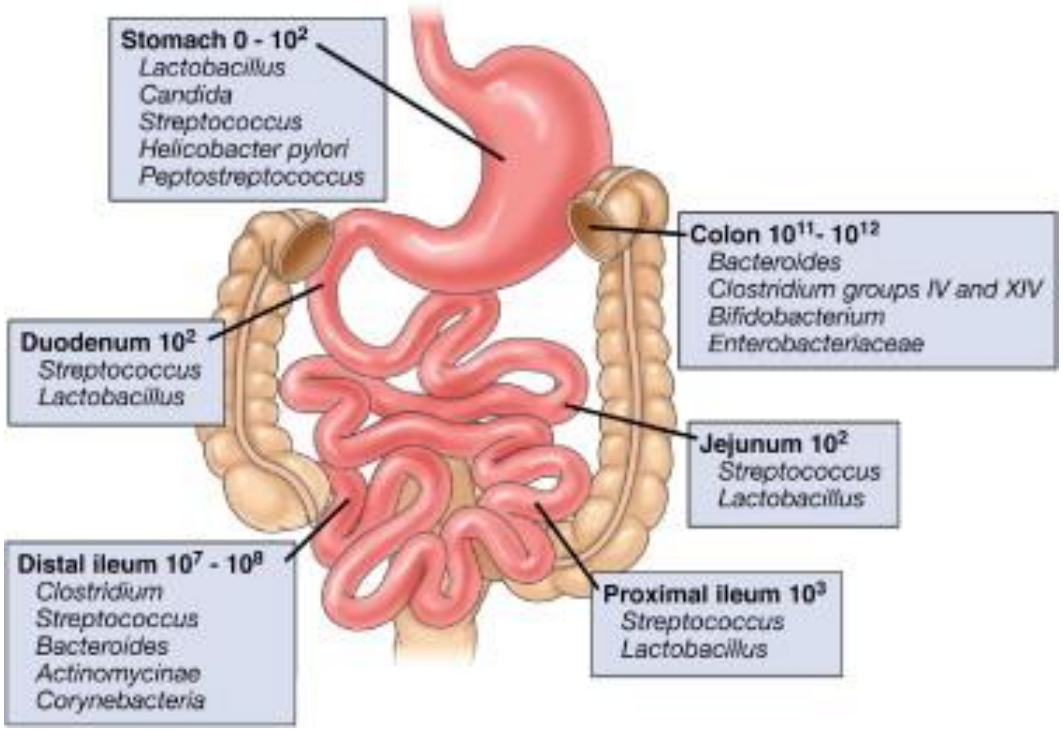
FLORA BATTERICA INTESTINALE



- più di 800 specie
- 100.000 miliardi di batteri
- Oltre 2Kg di massa biologica
- 70% del peso delle feci

80% delle cellule del sistema immunitario

IL MICROBIOMA INTESTINALE



Composizione della concentrazione delle specie microbiche diverse presenti nelle vari parti del tratto gastrointestinale.

Il microbioma intestinale è un insieme di microrganismi che occupano la lunghezza e la larghezza di tutto il tratto gastrointestinale.
La composizione della comunità microbica è ospite specifica, ed è suscettibile delle modificazioni esogene ed endogene esterne e dallo stile di vita dell'ospite.

IL MICROBIOTA:
Fisiologia (I)

KEYPOINTS

DEFINIZIONE

Insieme delle forme microbiche che colonizza il nostro corpo (*Microbiota*) e dei geni che lo costituiscono (*Microbioma*);

Batteri + Virus, Funghi e Archei;

≈3.8x10^{13}cell batteriche/individuo vs 3x10^{13} cellule umane, la **maggior parte** risiede nel nostro **intestino** (Colon);

TASSONOMIA

≈160 specie/individuo e >1000 specie riconosciute;

4 grandi ***phyla*** ma ↑ **variabilità** *interindividuale* **tassonomica** di generi e specie;

90% rappresentato dalle famiglie ***Firmicutes*** e ***Bacteroidetes***, il cui *ratio* ↑ correla con Obesità, Diabete e Sindrome Metabolica;

GENOMA

>3˙000˙000 di **geni** codificati **≈ 100-150 volte** il **genoma umano**.

IL MICROBIOTA:
Fisiologia (II)

FUNZIONI PRINCIPALI

➢ **METABOLICHE**

- Fermentazione dei residui alimentari non altrimenti digeribili (polisaccaridi++) e del muco intestinale→ **SCFA** → ***Energy Balance*** e metabolismo glicidico-lipidico;
- Sintesi di alcune **Vitamine** (gruppo B, H e K);
- Assorbimento di **minerali e ioni**;
- Metabolismo xenobiotici, **ormoni** e farmaci;

➢ **TROFICHE**

- Proliferazione e differenziamento degli **enterociti**;
- Sviluppo e omeostasi del **Sistema Immunitario**;

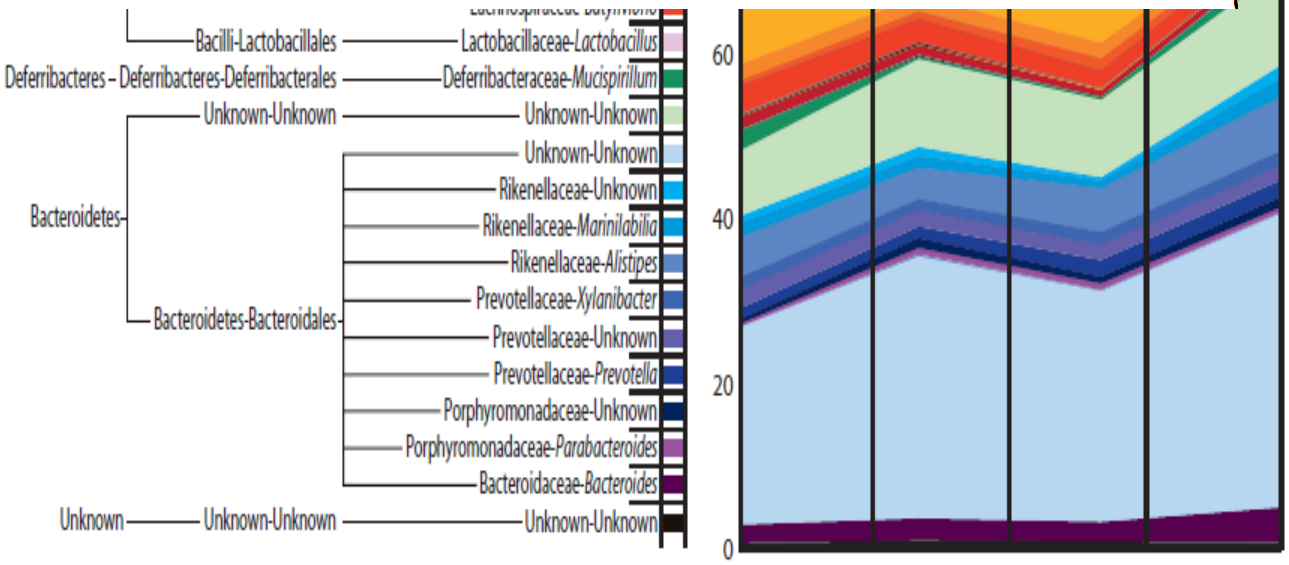
➢ **BARRIERA**

- **Interfaccia** tra il sistema immunitario locale e l'ambiente esterno;
- **Protezione** da microorganismi patogeni concorrenti e dalle loro tossine attraverso la produzione di ***batteriocidine****;*
- **Permeabilità intestinale**→↓passaggio di **LPS** e altre tossine pro-infiammatorie.

Il microbiota intestinale

Table 1. The gut microbiota is dominated by five bacterial phyla

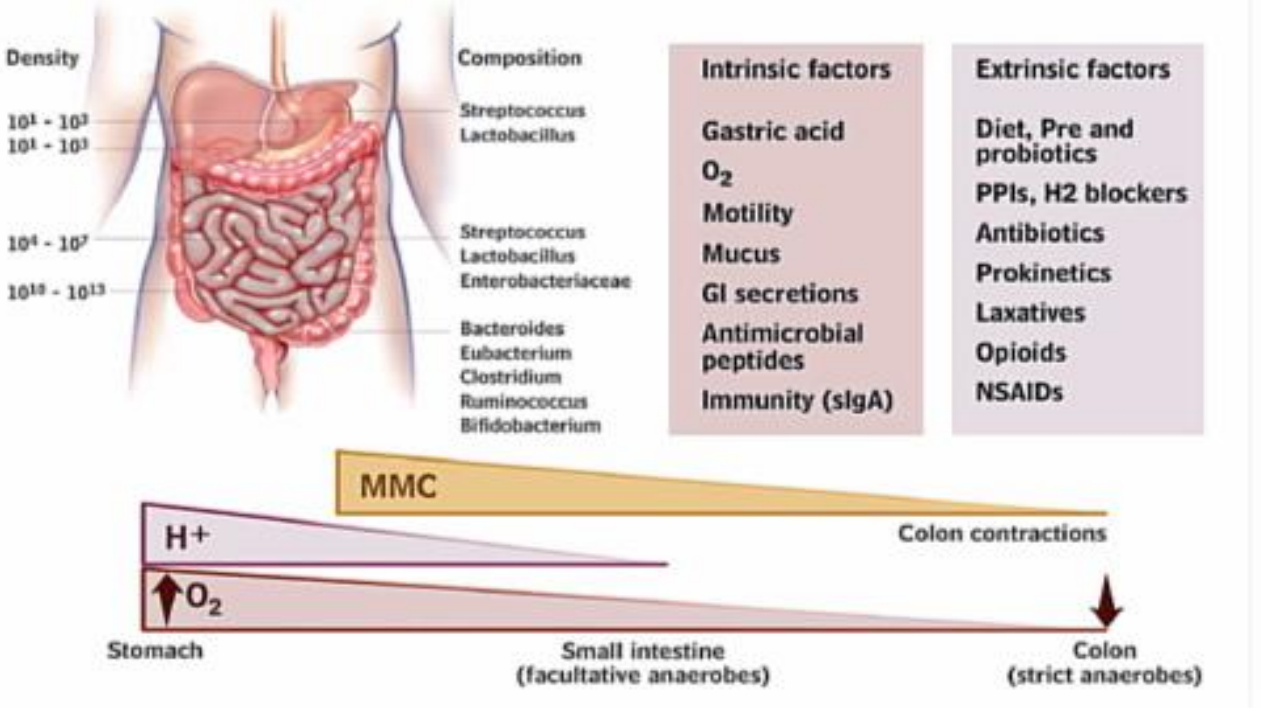
Phylu	Firmicutes (50-60% of the microbiota) including more than 180 species of Lactobacillus, Clostridiales and Streptococcaceae.
	Bacteroidetes (25-40% of the microbiota) with Bacteroides Fragilis and Porphyromonadaceae both reported upregulated in CRC
	Actinobacteria (2-5%) including the Bifidobacteriae
	Proteobacteria (2-5%) E. coli), salmonella, yersinia, shigella, vibrio, haemophilus,
Firmicu	Fusobacteria (2-5%) Fusobacterium Nucleatum, faecalibacterium prausnitzii



I Firmicutes e i Bacteroidetes sono i 2 principali phyla presenti nell'intestino dei mammiferi

FATTORI CHE INFLUENZANO IL MICROBIOTA INTESTINALE

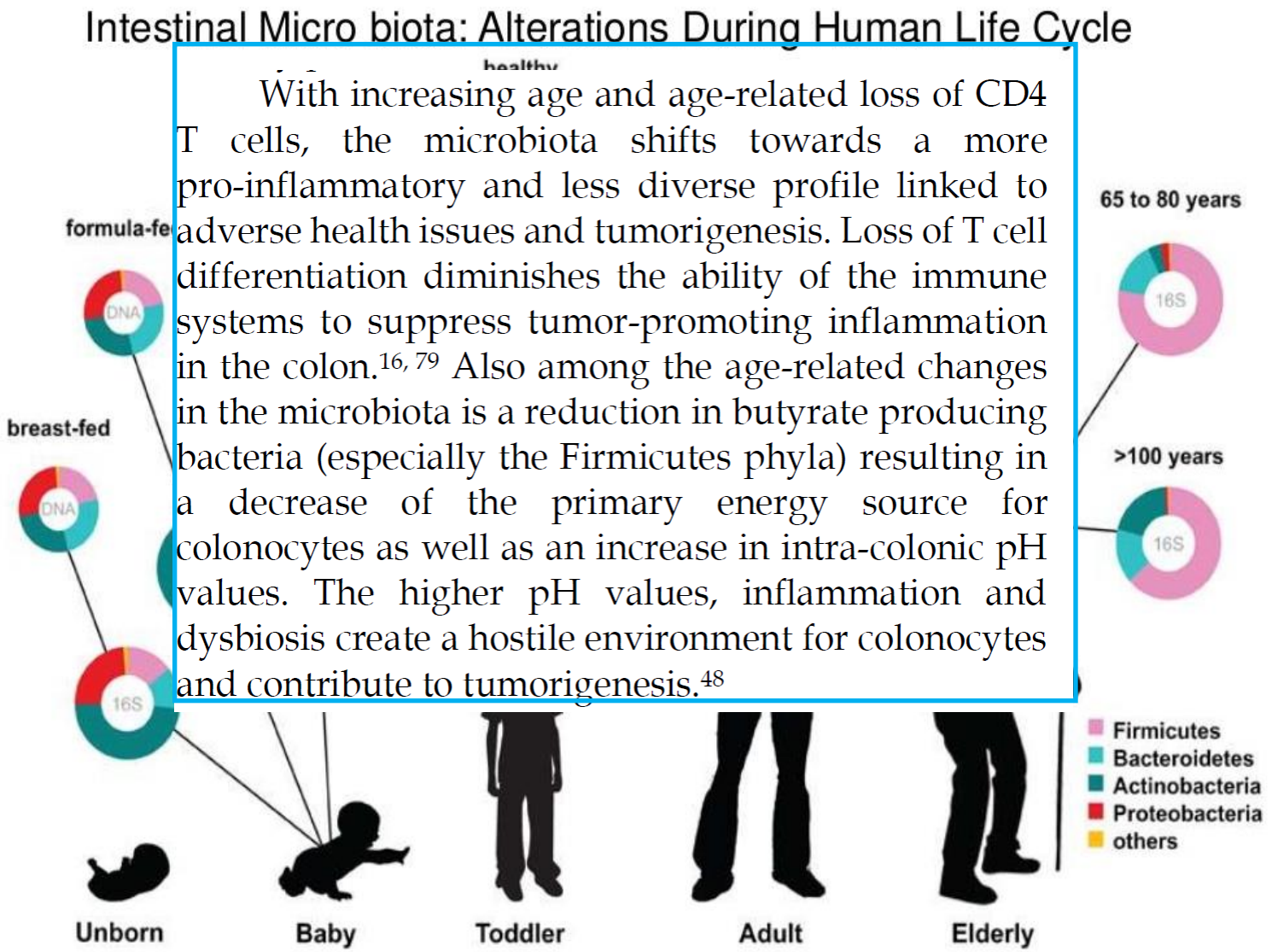
Microbiota intestinale
Fattori che ne influenzano la distribuzione e la composizione



(Simren M, GUT 2013)

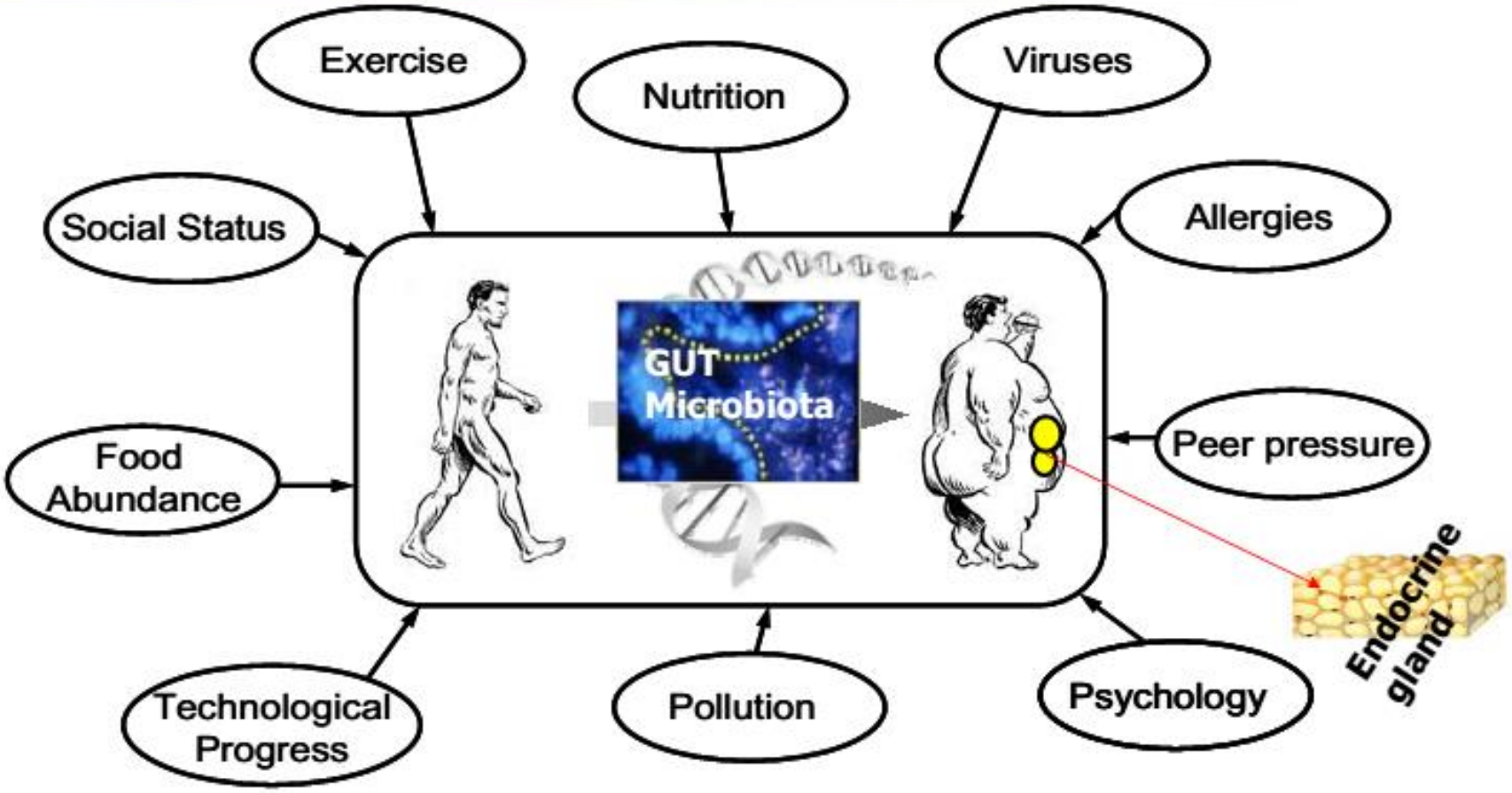
Nello stile di vita occidentale il microbiota e la relazione tra il microbiota e l'ospite sta drammaticamente cambiando come una conseguenza dello stile di vita, dell'ambiente e specialmente della dieta, come i cibi confezionati, l'aumento dell'assunzione dei carboidrati, la mancanza di esercizio fisico e l'obesità

Il microbiota si modifica con l'età



With increasing age and age-related loss of CD4 T cells, the microbiota shifts towards a more pro-inflammatory and less diverse profile linked to adverse health issues and tumorigenesis. Loss of T cell differentiation diminishes the ability of the immune systems to suppress tumor-promoting inflammation in the colon.[16, 79] Also among the age-related changes in the microbiota is a reduction in butyrate producing bacteria (especially the Firmicutes phyla) resulting in a decrease of the primary energy source for colonocytes as well as an increase in intra-colonic pH values. The higher pH values, inflammation and dysbiosis create a hostile environment for colonocytes and contribute to tumorigenesis.[48]

Complex interactions underlying polygenic obesity



Mutch D & Clement K, Plos genet 2006

WHAT YOU NEED TO KNOW ABOUT OBESITY AND CANCER

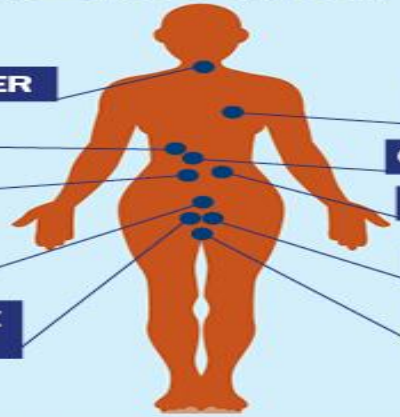
American Institute for Cancer Research

After not smoking,

BEING AT A HEALTHY WEIGHT

is THE MOST IMPORTANT THING you can do to prevent cancer.

Overweight and obesity INCREASE RISK FOR



- ESOPHAGEAL CANCER
- LIVER CANCER
- KIDNEY CANCER
- COLORECTAL CANCER
- ADVANCED PROSTATE CANCER
- POST-MENOPAUSAL BREAST CANCER
- GALLBLADDER CANCER
- PANCREATIC CANCER
- OVARIAN CANCER
- ENDOMETRIAL CANCER

AICR ESTIMATES THAT **EXCESS BODY FAT** IS A CAUSE OF APPROXIMATELY

128,200

U.S. CANCER CASES EVERY YEAR.

AND YET...

7 in 10 Americans are currently overweight or obese.

AND ...

Only about half of all Americans are even aware of the obesity-cancer link.

PROTECT YOURSELF!

Move More

Eat Smart

For tips on getting to, and staying at, a healthy weight, visit www.aicr.org

1. Cancer Statistics, 2016. CA Cancer J Clin 2016;66:7-30, 2. AICR/WCRF Policy Report and Continuous Update Project reports.
3. US Center for Disease Control and Prevention: Obesity and Overweight, 4. 2015 AICR Cancer Risk Awareness Survey

The evidence is the latest from the *Continuous Update Project* (CUP), which systematically updates and reviews the research conducted worldwide into cancer risk related to diet, physical activity and body weight. All the evidence gathered is then assessed by a panel of independent scientists who make recommendations for cancer prevention.

CUP Continuous Update Project

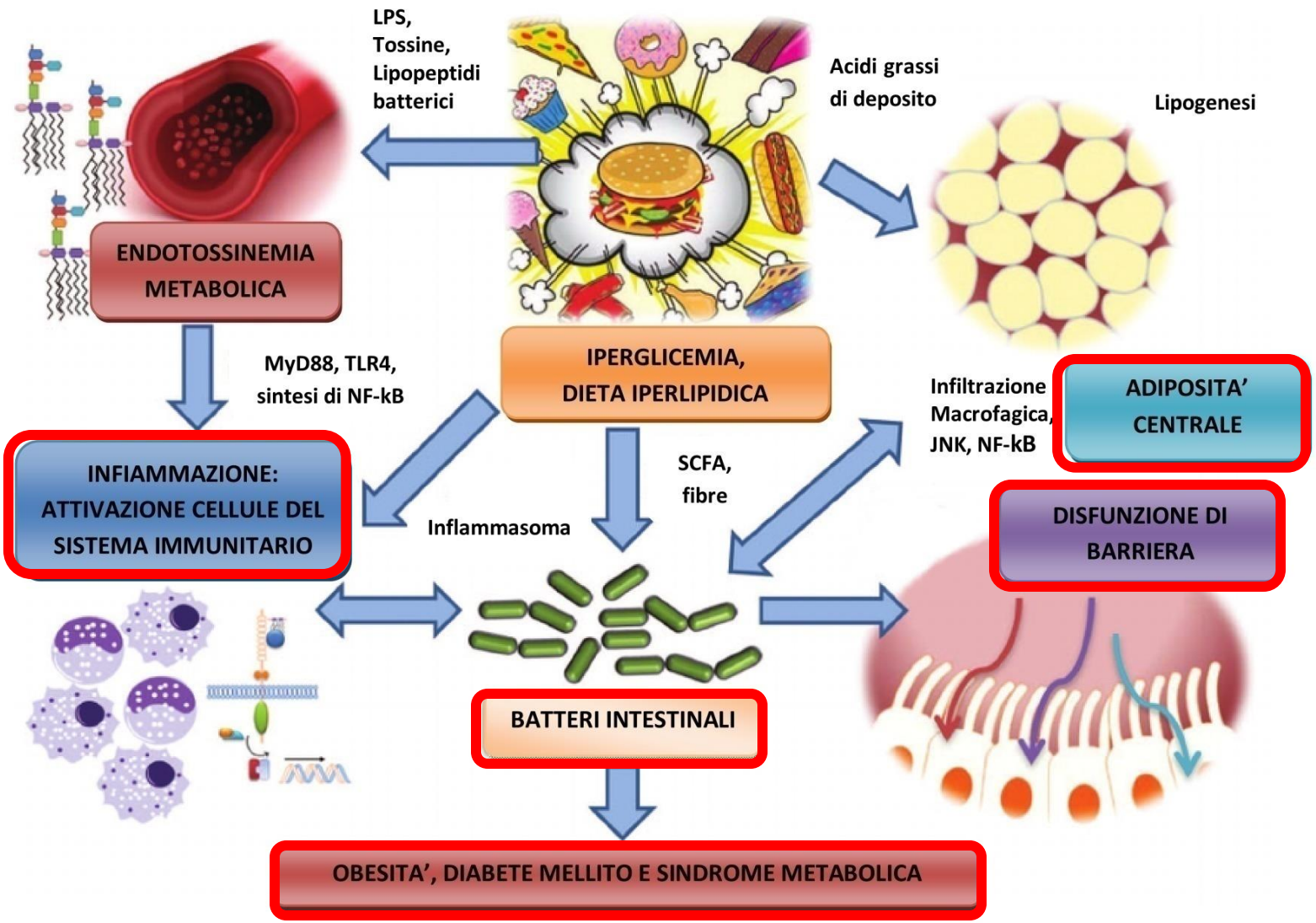
American Institute for Cancer Research
1759 R Street NW, Washington DC
Phone: 202.328.7744 · Email: Communications@aicr.org · www.aicr.org

AICRblog Twitter @aicrtweets Facebook

Microbiota e OBESITÀ

- **Il microbiota intestinale degli obesi risulta essere più ricco di Firmicutes.**
- **E' stato ipotizzato che alcuni microrganismi appartenenti a tale phyla siano in grado di estrarre le calorie dal cibo ingerito con un'efficienza maggiore rispetto agli altri microrganismi;**
- **È stato inoltre osservato che il microbiota dei soggetti obesi presenta una diminuzione di bifidobatteri che generalmente sono in grado di prevenire lo sviluppo dell'obesità (azione specie- e ceppo-specifica).**

IL MICROBIOTA: Patologia



CORRELAZIONE ALTERAZIONE MICROBIOTA-TUMORE

AUMENTATA SINTESI di TRIGLICERIDI e COLESTEROLO

ELEVATI LIVELLI di COLESTEROLO ed ANDROGENI CIRCOLANTI

ECCESSO di TESSUTO ADIPOSO *"ENDOCRINOLOGICAMENTE ATTIVO"*

AROMATASI

CONVERSIONE/ NEO-SINTESI di ESTROGENI

INSULINO-RESISTENZA

OBESITA'/SOVRAPPESO/ SINDROME METABOLICA

ALTERAZIONI del MICROBIOMA INTESTINALE

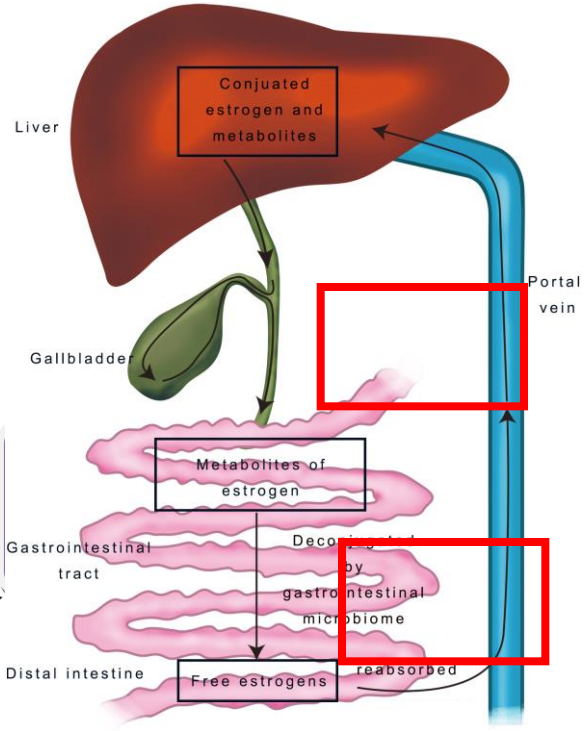
CITOCHINE PRO-INFIAMMATORIE

AUMENTATO RICIRCOLO ENTERO-EPATICO degli ESTROGENI CIRCOLANTI

AUMENTATO RISCHIO di RECIDIVE nel FOLLOW-UP

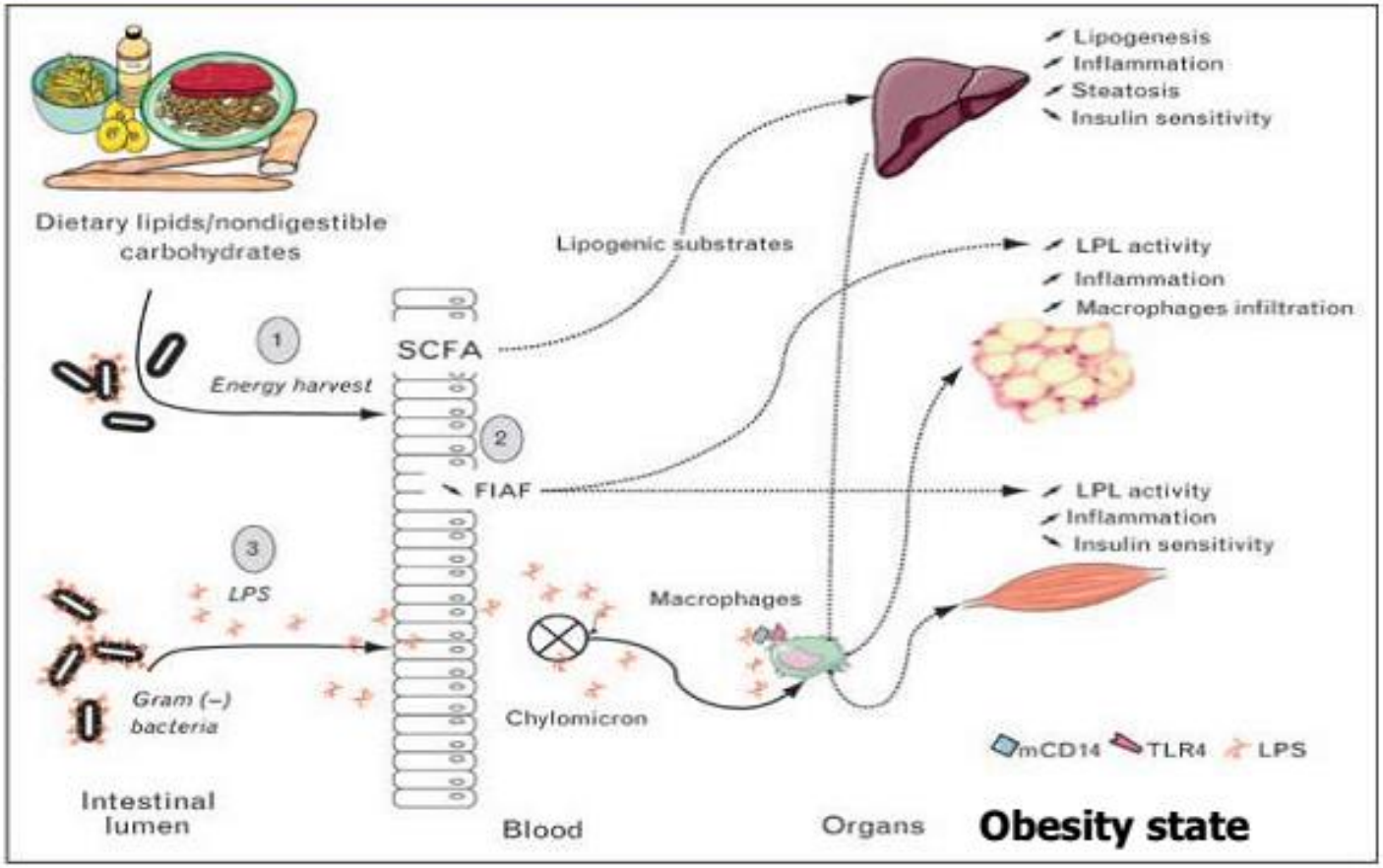
DISMETABOLISMI + INFIAMMAZIONE SISTEMICA di BASSO GRADO

ALTERATA REGOLAZIONE del DISPENDIO ENERGETICO e dei SISTEMI di CONTROLLO FAME-SAZIETA'



Microbiota-host interactions in obesity & related complications

Gut Microbiota ?



FIAF, fasting-induced adipose factor; LPL, lipoprotein lipase; LPS, lipopolysaccharide; SCFA, short chain fatty acid.

Cani PD and Delzenne NM. Curr Opin Clin Nutr Metab Care 2007; 10:729–734

IVYSPRING INTERNATIONAL PUBLISHER

Journal of Cancer

2017; 8(17): 3378-3395. doi: 10.7150/jca.20497

Review

Linking Gut Microbiota to Colorectal Cancer

Hans Raskov[1]✉, Jakob Burcharth[2], Hans-Christian Pommergaard[3]

Dysbiosis favors invasion and growth of pathogenic species and disrupt homeostasis of the immune system and mucosal barrier. The subsequent inflammatory process results in increased permeability allowing gut microbes to drive a continuous state of inflammation.[66, 86, 96-98]

Abstract

Pre-clinical and clinical data produce mounting evidence that the microbiota is strongly associated with colorectal carcinogenesis. Dysbiosis may change the course of carcinogenesis as microbial actions seem to impact genetic and epigenetic alterations leading to dysplasia, clonal expansion and malignant transformation. Initiation and promotion of colorectal cancer may result from direct bacterial actions, bacterial metabolites and inflammatory pathways. Newer aspects of microbiota and colorectal cancer include quorum sensing, biofilm formation, sidedness and effects/countereffects of microbiota and probiotics on chemotherapy. In the future, targeting the microbiota will probably be a powerful weapon in the battle against CRC as gut microbiology, genomics and metabolomics promise to uncover important linkages between microbiota and intestinal health.

The gut microbiota is an ecologic system of diverse commensal microorganisms metabolizing food remnants, intestinal secretions, digestive juices and exfoliated colonocytes. The colon produces vitamins (vitamin K, B12, thiamin, riboflavin), absorbs water and electrolytes and transports waste products (feces) to the rectum for defecation. Proteolytic fermentation increases with high protein intake and results in production of phenolic compounds, amines, ammonia, NOC: N-nitroso compounds; and indoles, all considered to have a carcinogenic impact on epithelial cell differentiation and proliferation.[56]

La mucosa intestinale è separata dal microbiota da un sottile strato di cellule epiteliali che rappresentato la superficie della mucosa. Le cellule epiteliali sono protette da potenziali patogeni dal film mucosale e dal sistema immunitario. Una breccia di questo film può rappresentare un'iniziale stato di cronica infiammazione

In una stato di eubiosi le interazioni tra i batteri commensali e le cellule del sistema immunitario sono in una situazione di delicato bilanciamento: da un lato i geni proinfiammatori e dall'altro i geni antinfiammatori che agiscono con un'azione di repressione del tumore

Plaza-Diaz J, Gomez-Llorente C, Fontana L, Gil A. Modulation of immunity and inflammatory gene expression in the gut, in inflammatory diseases of the gut and in the liver by probiotics. World J Gastroenterol 2014; 20:15632-49.
Maukonen J, Saarela M. Human gut microbiota: does diet matter? Proc Nutr Soc 2015; 74:23-36.

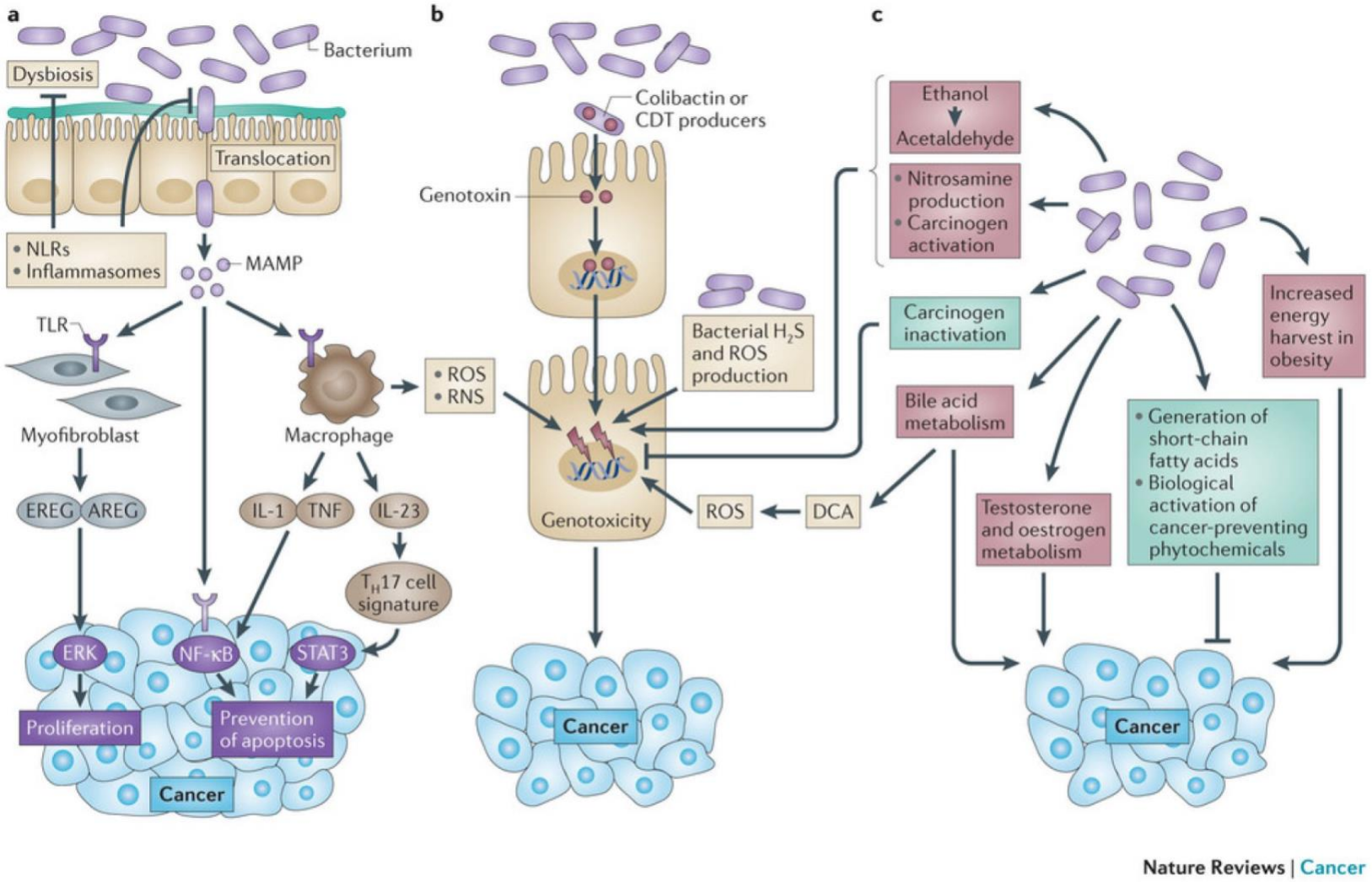


Figure 3. Mechanisms by which the bacterial microbiome modulates carcinogenesis. The microbiota promotes carcinogenesis through different mechanisms. **A** | Dysbiosis and inflammation induced by MAMP activating TLR and other PPR (e.g. NLR). **B** Detrimental effects are mediated by bacterial toxins such as colibactin and CDT: Cytolethal Distending Toxin, ROS, Reactive Nitrogen Species and H_2S. **C** Metabolic actions activating toxins such as acetaldehydes and nitrosamines. The microbiota mediates preventive effects (in green) through inactivation of carcinogens and production of SCFA: short chain fatty acids; such as butyrate and propionate. From Schwabe RF, Jobin C. Nature Reviews Cancer 2013;13:800-12. With permission from Macmillan Publishers Ltd.

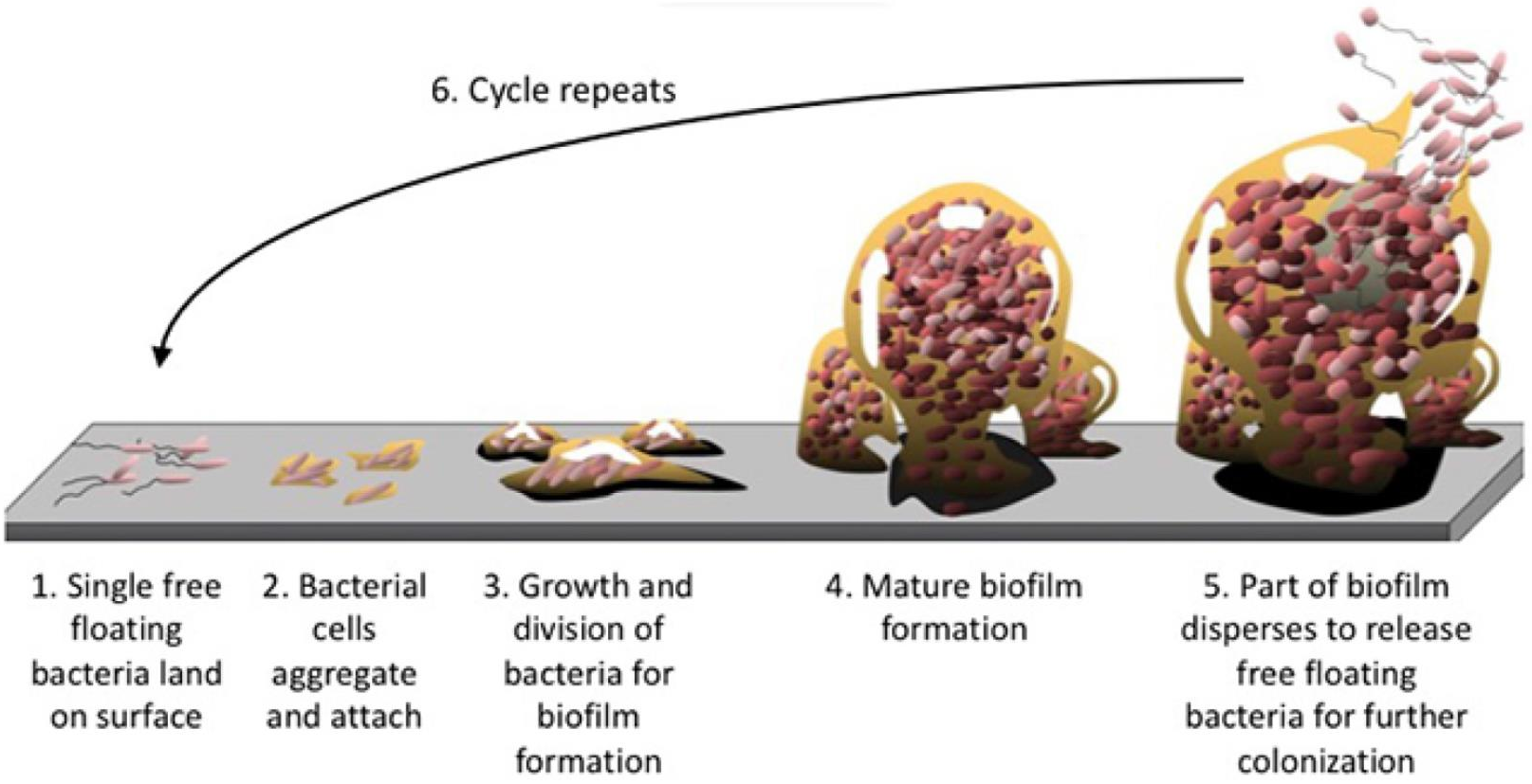


Figure 1. Biofilm formation. The structural components of the extracellular matrix is a highly hydrated, robust structure with high tensile strength and represents up to 90% of the biofilm mass keeping bacteria in close proximity, enabling intimate cell-to-cell interactions and DNA exchange while at the same time protecting the biomass from damaging agents. No copyright.

Efficient DNA repair mechanisms, among others the MMR, the base excision repair system, the nucleotide excision repair system and the double strand break repair systems continuously scan the genome for replication errors. DNA defects are repaired immediately, the base excision repair system alone accounting for more than 10,000 repairs in the colon per day.[43] If time is needed for DNA repair, the G1 cell cycle phase is slowed down or put on stand-by by tumor-suppressor genes, among which the p53 is one of the most important and well known.[44, 45] If mutations are too many or too extensive to repair, apoptosis is initiated through a complex signal pathway shutting down mitochondrial function resulting in immediate cell death.[46]

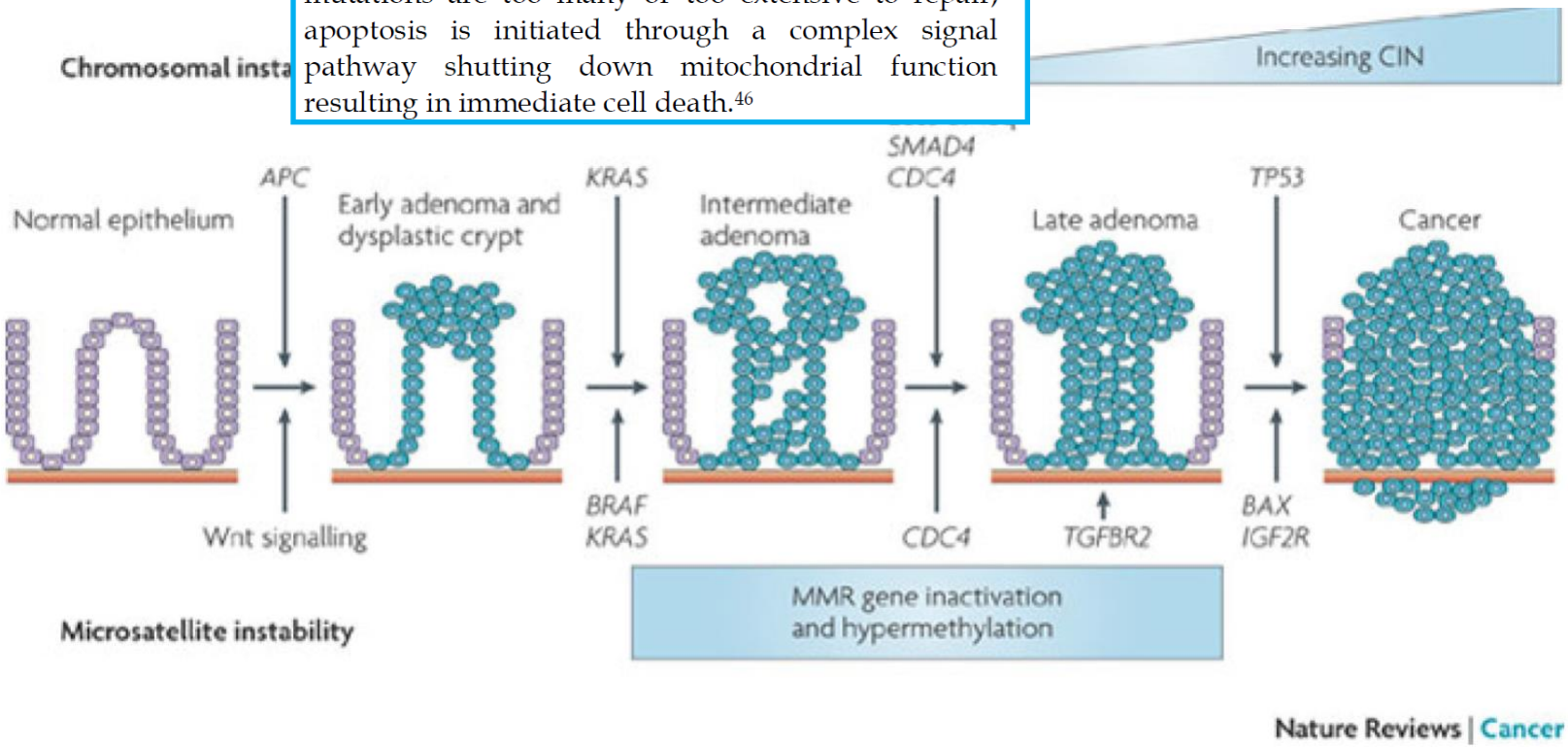


Figure 2. Adenoma-carcinoma sequence. CIS involves loss of APC function and KRAS, followed by loss of chromosome 18q with SMAD4 and mutation in TP53. MSI CRC is characterized by a deficiency of the MMR leading to slippage in microsatellites. CIN: chromosomal instability. From Walther & al. Nat Rev Cancer 2009;9:489-99. Permission from Macmillan Publishers Limited.

In caso di costante infiammazione della mucosa, la prolungata azione del Th17 è stato collegato allo sviluppo di CRC e l'infiltrazione cellulare del Th17 è correlato ad elevati livelli di Th7 citokine mutagene specialmente IL-17 e IL 22 le quali sono associate a peggiore prognosi e sopravvivenza

Possible pathophysiological mechanisms of inflammation also include the oxidative stress caused by an imbalance between the production of ROS: Reactive Oxygen Species; and antioxidant defenses resulting in DNA damage, dysplasia and thus a tumor-supporting environment. Oxidative stress induces NFκB linking chronic inflammation to cancer through the ability of up-regulation of pro-inflammatory and tumor promoting cytokines, such as TNFα, IL-1 and -6 as well as mitogenic and anti-apoptotic signaling. NF-κB directly regulates a complex of genes (including bcl-x and survivin) increasing proliferation and protecting [illegible] from apoptosis.[100, 122] Interestingly, obesity increases NFκB expression in most tissues also increasing the risk of type-2 diabetes. NFκB could be a factor linking obesity, type 2 diabetes, cardio-vascular disease, IBD and cancer.[13, 123]

Drewes JL, Housseau F, Sears CL. Sporadic colorectal cancer: microbial contributors to disease prevention, development and therapy. Br J Cancer 2016; 115:273-80.

Mager LF, Wasmer MH, Rau TT, Krebs P. Cytokine-Induced Modulation of Colorectal Cancer. Front Oncol 2016; 6:96.

RUOLO DELLA DIETA

RUOLO DEI PRE E PROBIOTICI

Microbiota e dieta

La dieta ha un ruolo centrale nella regolazione del microbiota intestinale regolando l'attività metabolica dei batteri:

-eccesso di grassi saturi determina un aumento della permeabilità di membrana e alla suscettibilità degli antigeni microbici

-carenza di acidi grassi polinsaturi alterano la composizione del microbioma

-zuccheri a rapido assorbimento correla con una endotossiemia ed insulino resistenza

-presenza di composti fitochimici protegge il microbioma

L'ossidazione degli acidi grassi determina un aumento dei ROS che a sua volta determina una riduzione della produzione del muco e dell'epitelio intestinale

Inoltre la produzione della malondialdeide, come risultato dell'ossidazione degli acidi grassi, induce un danno dell'epitelio intestinale e aumenta la permeabilità intestinale delle tight junction

CORRELAZIONE OBESITA' E MICROBIOMA

RUOLO DELLA DIETA

E' stato dimostrato che dopo 24 ore di cambiamenti dietetici con dieta ad alto contenuto di fibre e a basso contenuto di lipidi, il microbioma

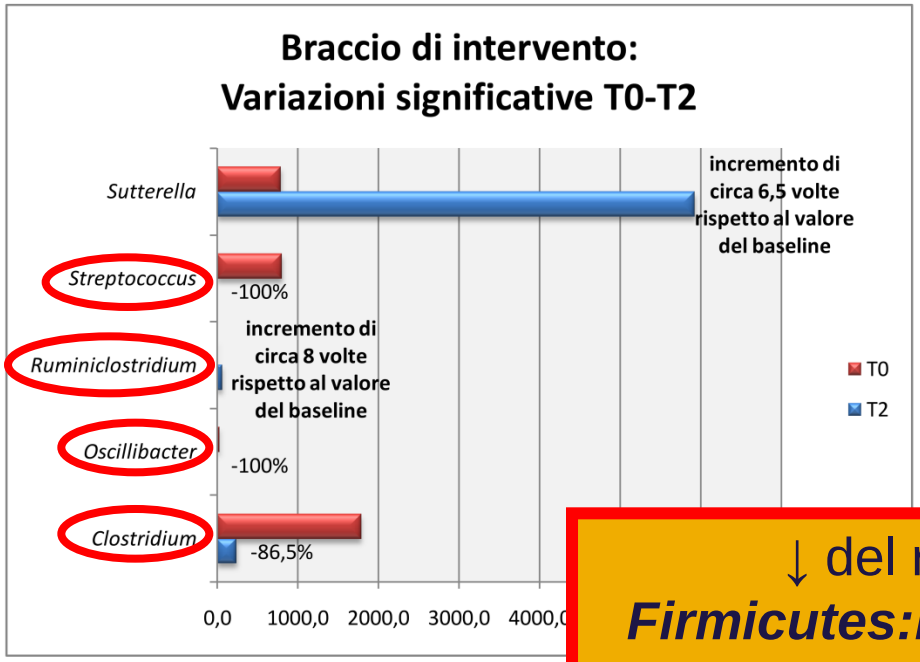
si modifica

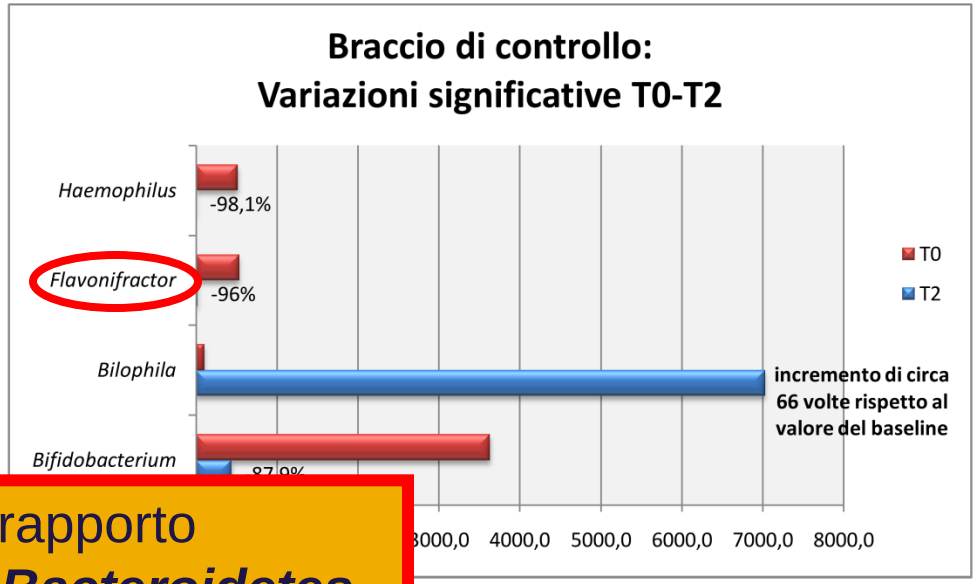
Alcuni nutrienti come le fibre possono fermentare dai batteri intestinali e potrebbero modulare in un periodo breve di tempo il microbioma.

Quindi la modulazione del microbioma intestinale sembra un interessante strumento per il trattamento sia della disbiosi che della sindrome metabolica

Gli strumenti per la modifica possono essere i prebiotici, i probiotici e in futuro il trapianto fecale.

STUDIO SPERIMENTALE:
Microbiota a confronto nei due bracci





↓ del rapporto
Firmicutes:Bacteroidetes

Network complessi tra le diverse specie batteriche

Nel braccio di **intervento:**

-↑ *Sutterella* spp→dubbia interp

-↑*Ruminiclostridium*→ per aumento dell'apporto dietetico di fibre?

-Positiva ↓ *Streptococcus, Clostridium* spp*;*

-↓*Oscillibacter* spp→ per minore apporto dietetico di "amido resistente"?

ollo:

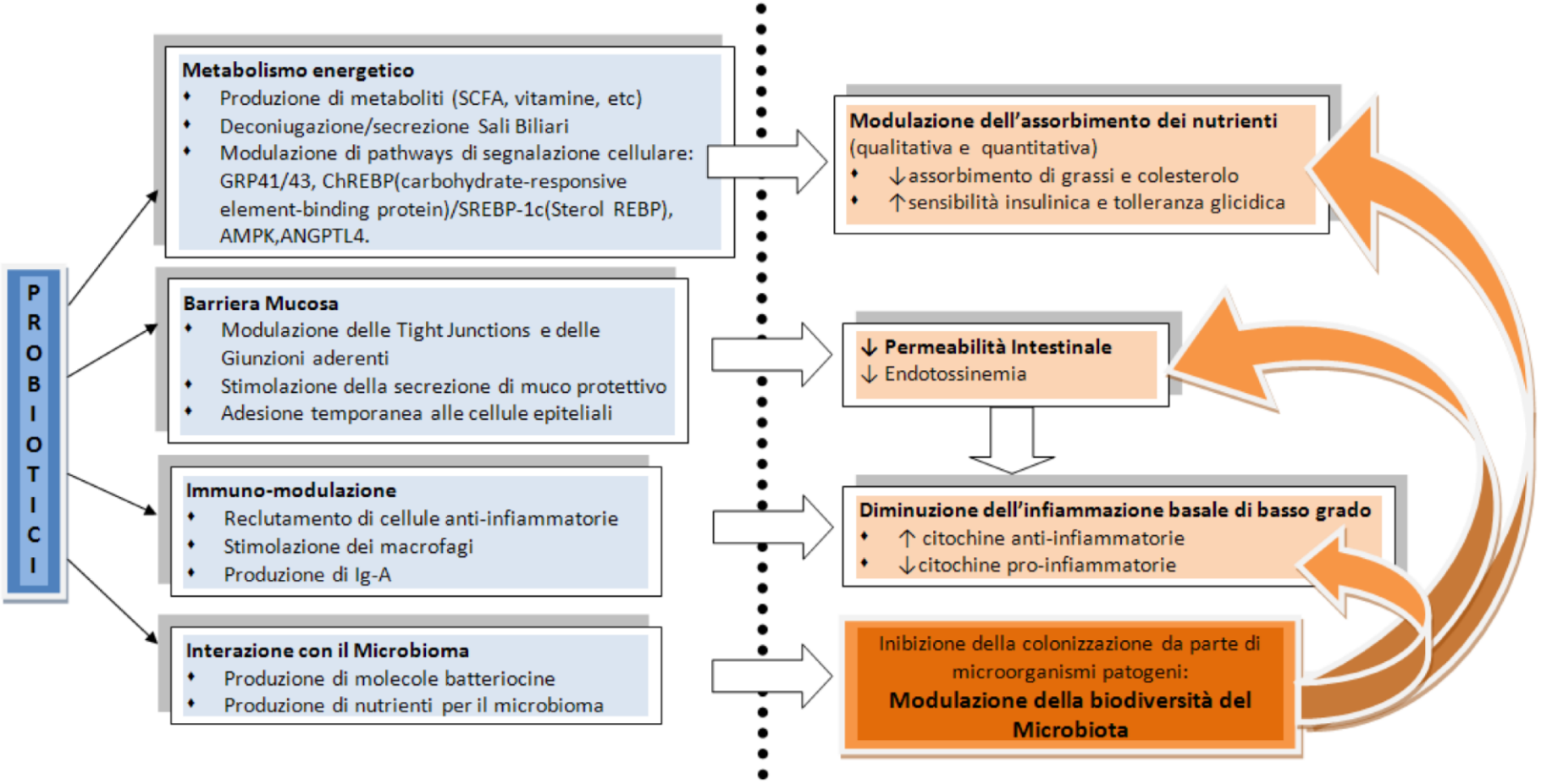
phylus spp*;*

-↓del genere *Flavonifractor* spp*;*

-Forte ↑ *Bilophila* spp→ per maggiore contributo percentuale lipidico?

-↓ dei *Bifidobacterium* spp→ dubbia interpretazione.

IL MICROBIOMA:
Ruolo dei probiotici



AZIONE DEI PROBIOTICI

I probiotici possono modulare la composizione del microbiota in un modo complesso in risposta ad una dieta obesogena. Il trattamento con probiotici diminuisce la permeabilità di membrana e l'endotossiemia metabolica e la sensibilità insulinica. Uno dei meccanismi che spiega questo fenomeno è l'aumentata produzione del GLP-2 endogeno, che determina un recupero della funzione di barriera intestinale

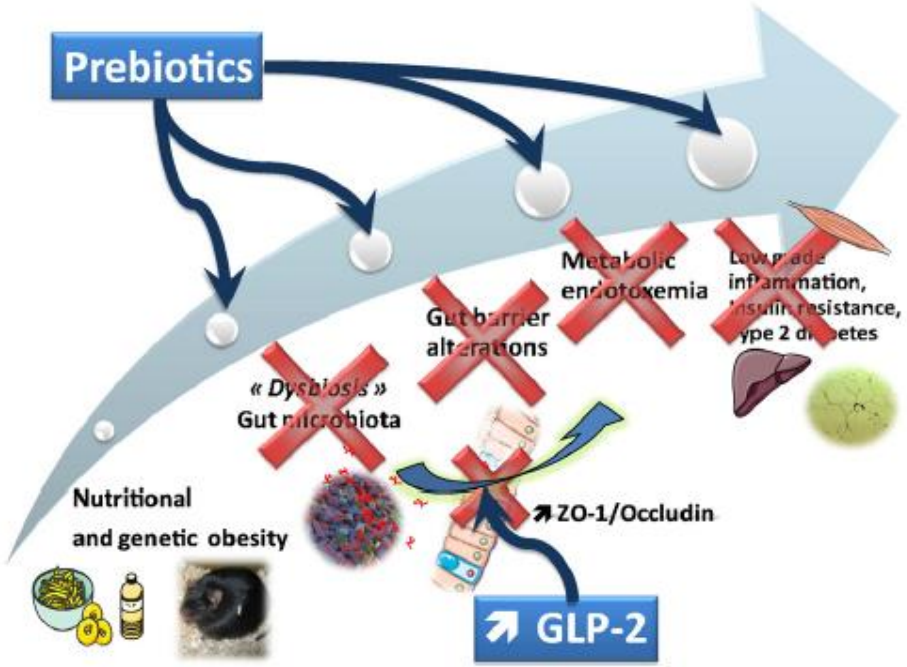


Fig. 4. Prebiotic-induced changes in the gut microbiota can abolish obesity-associated metabolic features. Prebiotics modulate the composition of the gut microbiota in a complex way in response to a high-fat diet or genetic obesity (i.e., increased *Bifidobacterium* spp.). Prebiotic treatment decreases gut permeability and metabolic endotoxaemia but improves insulin sensitivity, steatosis and low-grade inflammation. One of the mechanisms explaining this phenomenon is increased endogenous GLP-2 production, which restores gut barrier function.

Changes in Human Fecal Microbiota Due to Chemotherapy Analyzed by TaqMan-PCR, 454 Sequencing and PCR-DGGE Fingerprinting

Table 1. Number of bands observed in PCR-DGGE fingerprinting in oncology patients before chemotherapy (T_0), immediately after chemotherapy (T_1) and 5–9 days after chemotherapy (T_2) and healthy controls averaged over all time points.

Time point	All bacteria	*Clostridium* cluster *IV*	*Clostridium* cluster *XIVa*
T_0	18.9±4.6	14±7.0	8±3.2
T_1	19.7±4.9	10±6.0	4.9±3.6
T_2	19.6±3.6	15±6.0	5.2±2.6
control	19.2±3.5	12.0±5.0	8.9±3.0

doi:10.1371/journal.pone.0028654.t001

CHEMIOTERAPIA

Chemotherapeutic treatment with or without antibiotics decreases absolute bacterial numbers in comparison to healthy controls

Conclusions/Significance: Despite high individual variations, these results suggest that the observed changes in the human gut microbiota may favor colonization with *C.difficile* and *Enterococcus faecium*. Perturbed microbiota may be a target for specific mitigation with safe pre- and probiotics.

NUTRITION AND CANCER
2016, VOL. 68, NO. 4, 535–544

The Potential Role of Probiotics in Cancer Prevention and Treatment

Ai-Qun Yu[a,b,c] and Lianqin Li[d]

Anticancer effects of probiotics in cancer cells/cell lines

Substantial research using human cancer cells/cell lines has demonstrated that probiotics possess antiproliferative or proapoptotic activities in these cells, among which colonic cancer cells and gastric cancer cells were most commonly studied. According to the report by Lee et al., the cytoplasmic fractions of *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium longum* showed significant antitumor activities in some cancer cell lines

Anticancer effects of probiotics in experimental models

To further investigate the anticancer effects of probiotics, researchers have conducted animal model experiments using rats and mice. The outcomes of most studies turned out to be encouraging and showed potential clinical applications. As indicated in Table 2, treatment with *Lactobacillus acidophilus, Butyrivibrio fibrisolvens, Bacillus polyfermenticus, Lactobacillus plantarum, Lactobacillus fermentum*, or combination of *L. acidophilus* and

Table 2. Preventative effects of probiotics on animal tumors induced by various agents.

Probiotics/Synbiotics	Carcinogen	Animal	Antitumor effects			Ref.
			ACF	CRC	Others	
L. acidophilus	DMH	Rat	ND	✓	ND	48
B. fibrisolvens	DMH	Rat	✓	ND	ND	9
B.P.	DMH	Rat	✓	✓	ND	49, 50
L. acidophilus	DMH	Rat	✓	ND	ND	51
L. plantarum	DMH	Rat	ND	✓	ND	52
L. fermentum/L. plantarum	DMH	Mouse	✓	ND	ND	53
L. acidophilus/B. bifidum	DMH	Rat	✓	ND	ND	54
L. casei	AOM	Rat	✓	✓	ND	55
B. lactis/ L. rhamnosus	AOM	Rat	✓	✓	ND	56
L. acidophilus/L. helveticus/B. spp.	AOM	Rat	✓	✓	ND	57
C. butyricum	AOM	Rat	✓	ND	ND	21
B. lactis/RS	AOM	Rat	ND	✓	ND	15
L. brevis/L. paracasei	MNU	Rat	✓	ND	ND	58
L. acidophilus	None	ApcMin/+ mouse	ND	✓	ND	59
S.B.	None	ApcMin/+ mouse	ND	✓	ND	60
L. casei	PhIP	Rat	ND	ND	Breast	62
L. salivarius	4NQO	Rat	ND	ND	Mouth	63
LGG	UV	Mouse	ND	ND	Skin	66

ND = No data; *L. acidophilus* = *Lactobacillus acidophilus*; B.P. = *Bacillus polyfermenticus*; *B. fibrisolvens* = *Butyrivibrio fibrisolvens*; *L. plantarum* = *Lactobacillus plantarum*; *L. fermentum* = *Lactobacillus fermentum*; *L. casei* = *Lactobacillus casei*; *B. lactis* = *Bifidobacterium lactis*; *L. rhamnosus* = *Lactobacillus rhamnosus*; *L.*

Table 3. Immunomodulatory effects of probiotics as evidenced in animals or cell lines.

			Immune and inflammatory parameters				
Probiotic products	Subject	Agent	NK cells	T Cells	Macrophages	Mediators	Ref.
LcS	Rat	AOM	ND	↑	ND	ND	55
LcS	Mouse	3-MC	↑	ND	ND	ND	109
SCM-III	Rat	AOM	ND	↑	ND	ND	57
LABs	Mouse	None	↑	↑	ND	ND	25
SYN	Rat	AOM	↑	ND	ND	IL-10↑	110
L. helveticus	Mouse	None	ND	↑	ND	IL-10↑, IL-6↓	111
B. fibrisolvens	Mouse	DMH	↑	ND	ND	GUS↓	9
B. fibrisolvens	Mouse	3-MC	↑	ND	ND	IFN-γ↑	23
LGG	Caco-2	Flagellin	ND	ND	ND	IL-8↓	11
LcS	Mouse	LPS	ND	ND	ND	IL-6↓	118
L. acidophilus	Mouse	None	ND	ND	ND	IL-12↑	24
B. longum/L. gasseri	Mouse	DMH	ND	ND	↑	ND	115
VSL#3	Rat	TNBS	ND	ND	ND	Angiostatin↑ Alk-Smase↑	119
VSL#3	Mouse	None	ND	↑	ND	IL-17&TNF-α↑ Angiostatin↑	112
L. acidophilus	Mouse	None	ND	↑	ND	IFN-γ, IL-4&TGF-β↑	113
LGG	Mouse	UV	ND	↑	ND	IFN-γ↑	66
L. reuteri	Mouse	None	ND	↑	ND	ND	114
LGG	Caco-2 cells	5-FU	ND	ND	ND	TNF-α, IL-12&MCP-1↑	14

ND = no data; LcS = *Lactobacillus casei* strain Shirota; SCM-III = a probiotic mixture containing *L. acidophilus, L. helveticus*, and *B. lactis* spp. 420; LABs = lactic acid bacteria including *L. acidophilus, L. casei*, and *B. longum*; SYN = Synbiotics containing LGG, *B. lactis* Bb12 and oligofructose-enriched inulin; VSL#3 = a mixture of eight probiotic strains containing *Bifidobacterium breve, Bifidobacterium infantis, Bifidobacterium longum, Lactobacillus acidophilus, Lactobacillus bulgaricus, Lactobacillus casei, Lactobacillus plantarum*, and *Streptococcus salivarius* subspecies *thermophilus*; AOM = azoxymethane; 3-MC = 3-methylcholanthrene; DMH = 1,2-dimethylhydrazine; LPS = lipopolysaccharide; TNBS = trinitrobenzene sulfonic acid; 5-FU = 5-fluorouracil; GUS = β-glucuronidase; IFN-γ = Interferon-γ; TNF-α = tumor necrosis factor-α; TGF-β = transforming growth factor-β; MCP-1 = monocyte chemotactic protein-1.

Ai-Qun Yu[a,b,c] and Liangin Li[d]

MECCANISMI ATTRAVERSO I QUALI I PROBIOTICI ESERCITANO I LORO MECCANISMI

- Migliorano l'omeostasi del microbiota intestinale
- Degradano le sostanze carcinogenetiche
- Modulano l'asse immuno-intestino mediato
- Rinforzano l'attività immunosistemica
- Hanno un effetto positivo sulla translocazione batterica
- Hanno un effetto protettivo sul DNA dell'epitelio intestinale

L'effetto anticarcinogenetico è dato dall'insieme delle varie azioni

Table 2. Beneficial effects of SCFA produced by probiotics

Predominant energy source for colonocytes
Induction of mucin synthesis
Augmentation of tight junction assembly
Mediation of cross-talk between commensals and host immune system for maintenance of gut homeostasis
Conditioning gut epithelial cells to mount protective immunity through MAP kinase signaling
Inhibiting pro-inflammatory cytokines, NFκB and TNFα
Inactivation of mutagens

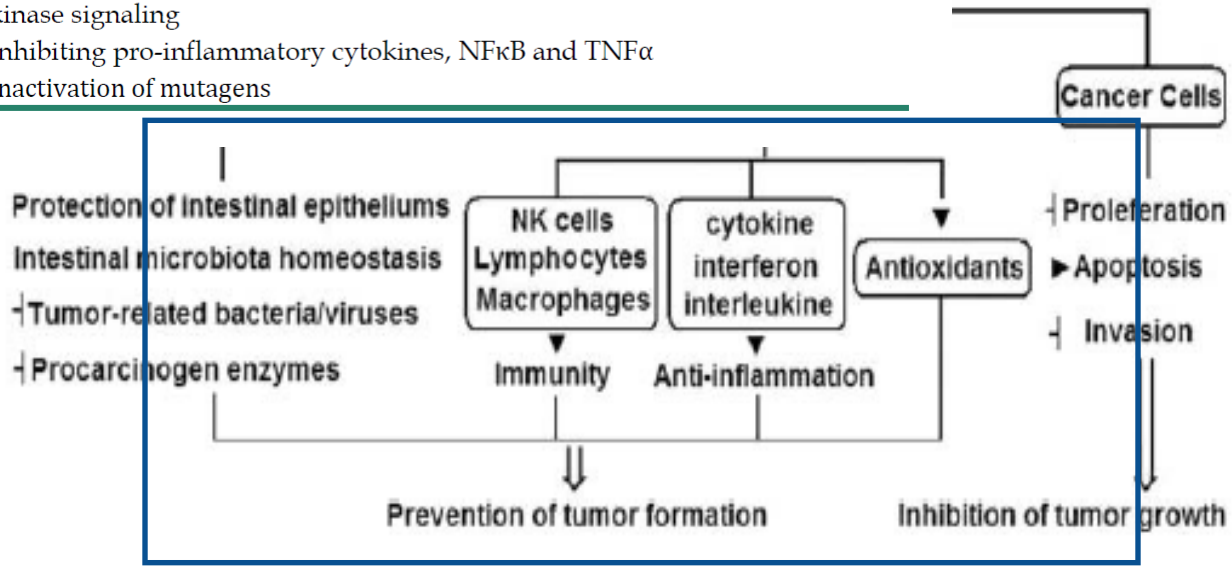


Figure 1. Illustration for the suppressive effects of probiotics on tumor formation and growth. Probiotics can exert their functions locally and systemically. Oral administration of probiotics can provide protection of intestinal epitheliums, modulate the homeostasis of the intestinal microflora, and inhibit the potential pathogens and carcinogenesis in the gut (⊣). Together with the enhancement of antioxidant activities (▼), probiotics can increase the number/activity of immune cells (▼) and control the inflammatory reaction, resulting in the prevention of tumor formation. In addition, probiotics can act on cancer cells by promoting cell apoptosis (►) and inhibiting cell proliferation or invasion (⊣), resulting in the suppression of tumor growth.

The Potential Role of Probiotics in Cancer Prevention and Treatment

Ai-Qun Yu[a,b,c] and Lianqin Li[d]

Utilizzo dei probiotici nelle terapie antineoplatiche

Probiotic *Lactobacillus Acidophilus* and *L. Casei* Mix Sensitize Colorectal Tumoral Cells to 5-Fluorouracil-Induced Apoptosis

CHEMIOTERAPIA

L'uso di L.A e L.Casei sono in grado di aumentare l'apoptosi del 5-FU (il meccanismo non è ancora chiarito)

RADIOTERAPIA

Effects of probiotics on radiation-induced intestinal injury in rats

Table 5
Graded Radiation Injury Scores of histopathologic alterations expressed as percentage of the number of graded scores within each experimental group

	ULC		ATY	SER	VAS	FIB	LYM	ILE
Score	1	2	1	1	1	1	1	1
Group II	15 (71.4%)*	6 (38.6%)	8 (38.1%)	0 (0%)	2 (9.5%)	10 (47.6%)	8 (38.1%)	2 (9.5%)
Group III	8 (38.1%)	13 (61.9%)*	14 (66.7%)	0 (0%)	0 (0%)	16 (69.6%)	7 (33.3%)	3 (14.3%)

ATY, epithelial atypia; FIB, intestinal wall fibrosis; ILE, ileitis cystica profunda; LYM, lymph congestion; SER, serosal thickening; UCL, mucosal ulceration; VAS, vascular sclerosis.
* Significant ($P < 0.05$) by chi-square test.

Results: The results of this study suggest that probiotics may have a protective effect on intestinal mucosa.
Conclusion: Probiotics added as substrates can be given by an oral or enteral route to patients who undergo radiotherapy to prevent radiation-induced enteritis and related malnutrition. © 2006

Nutrition 2006

Lactobacillus supplementation for diarrhoea related to chemotherapy of colorectal cancer: a randomised study

CHEMIOTERAPIA

5-Fluorouracil (5-FU)-based chemotherapy is frequently associated with diarrhoea. We compared two 5-FU-based regimens and the effect of *Lactobacillus* and fibre supplementation on treatment tolerability. Patients diagnosed with colorectal cancer ($n = 150$) were randomly allocated to receive monthly 5-FU and leucovorin bolus injections (the Mayo regimen) or a bimonthly 5-FU bolus plus continuous infusion (the simplified de Gramont regimen) for 24 weeks as postoperative adjuvant therapy. On the basis of random allocation, the study participants did or did not receive *Lactobacillus rhamnosus* GG supplementation ($1-2 \times 10^{10}$ per day) and fibre (11 g guar gum per day) during chemotherapy. Patients who received *Lactobacillus* had less grade 3 or 4 diarrhoea (22 *vs* 37%, $P = 0.027$), reported less abdominal discomfort, needed less hospital care and had fewer chemotherapy dose reductions due to bowel toxicity. No *Lactobacillus*-related toxicity was detected. Guar gum supplementation had no influence on chemotherapy tolerability. The simplified de Gramont regimen was associated with fewer grade 3 or 4 adverse effects than the Mayo regimen (45 *vs* 89%), and with less diarrhoea. We conclude that *Lactobacillus* GG supplementation is well tolerated and may reduce the frequency of severe diarrhoea and abdominal discomfort related to 5-FU-based chemotherapy.

British Journal of Cancer (2007) **97,** 1028–1034. doi:10.1038/sj.bjc.6603990 www.bjcancer.com

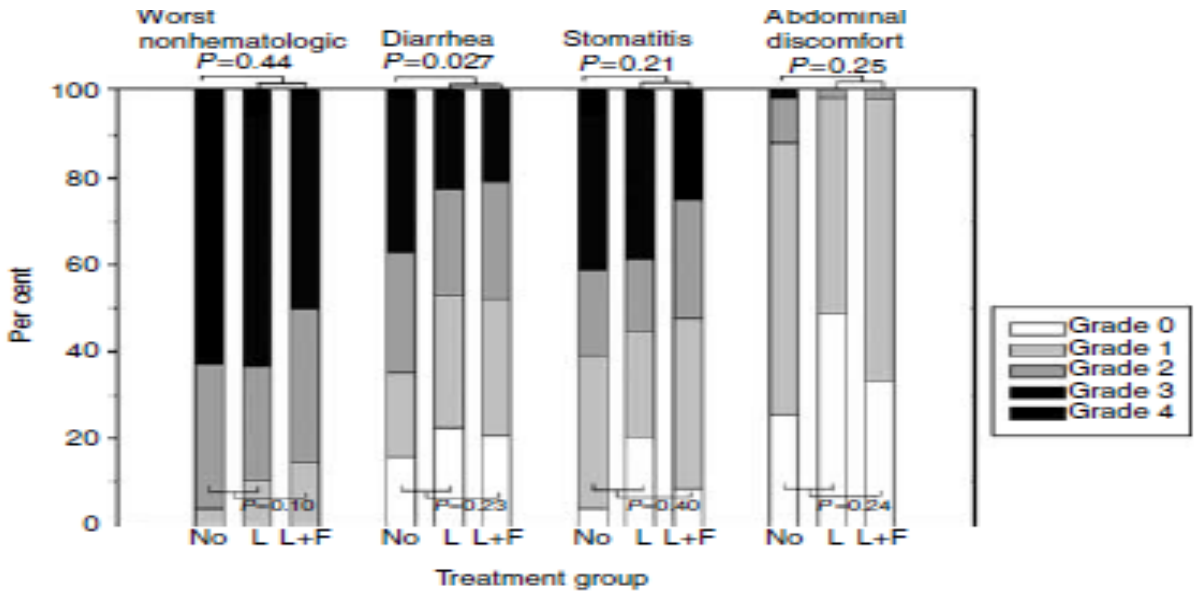


Figure 1 Effect of oral *Lactobacillus rhamnosus GG* (L) and *Lactobacillus rhamnosus GG* plus fibre (guar gum, L + F) supplementation on adverse events recorded during 5-FU-based chemotherapy.

Carcinogenesis vol.31 no.2 pp.246–251, 2010
doi:10.1093/carcin/bgp197
Advance Access publication August 20, 2009

Synbiotic intervention of *Bifidobacterium lactis* and resistant starch protects against colorectal cancer development in rats

The precise mechanisms by which probiotics exert their antitumourigenic influence are uncertain but might involve modifying gut pH and increasing the net production rate of short-chain fatty acid (SCFA) (mainly acetate, propionate and butyrate) (7), antagonizing pathogens through production of antimicrobial and antibacterial co

CARCINOGENESI

L'effetto sinbiotico di una dieta con amido resistenti e altri fattori prebiotici possa essere più prottetiva rispetto al probiotico da solo nello sviluppo del tumore del Ca colonretto

British Journal of Nutrition (2012), **107**, 1006–1016
doi:10.1017/S0007114511003953

Anticarcinogenic effect of probiotic fermented milk and chlorophyllin on aflatoxin-B_1-induced liver carcinogenesis in rats

Lactobacillus Rhamnosus e Casei

Conclusion

The present study indicates that an increase in apoptotic rate in the liver of rats treated with AFB_1 is associated with biochemical disturbances in the oxidant/antioxidant balance system, which may be interlinked with the pathogenic network of AFB_1 toxicity. However, the overall information obtained from the present study indicates that probiotic FM that is administered individually or jointly with CHL to experimental rats possesses a potent protective effect against AFB_1-induced hepatocarcinogenesis.

A randomized double-blind trial on perioperative administration of probiotics in colorectal cancer patients

IN CHIRURGIA

WJG 2010

CONCLUSIONI: 2 gruppi trattati con *Bifidobacterium Longum e Lactobacillus Johnsonii:* solo LJ influenza la mucosa intestinale pre-operatoria riducendo la concentrazione di batteri patogeni e migliorando l'immunità cellulare

International J Food of Microbiology 2010

In vitro screening of probiotics and synbiotics according to anti-inflammatory and anti-proliferative effects

Julien Grimoud [a,b,*], Henri Durand [b], Sarah de Souza [a,b], Pierre Monsan [c], Françoise Ouarné [d], Vassilia Theodorou [e], Christine Roques [a]

treated by the selected synbiotics. Thus, this study demonstrates the ability of probiotics to exert anti-inflammatory effects and shows some anti-proliferative characteristics for a specific synbiotics. These products should be further evaluated in animal models to confirm the *in vitro* results.

Table 4
Summarised results from the inflammation and proliferation models.

Probiotics, synbiotics tested	Anti-inflammatory effects			Anti-proliferative effects		
	HT-29 + LPS + IFNg		Caco-2 (cytokine)	HT-29 proliferation		
	Activated NF-κB	Secreted IL-8	Activated NF-κB	Glucose	OA	OD
Bifidobacterium bifidum LMI 02	+++	+++	++	NS	NS	NS
Bifidobacterium bifidum LMI 20	+++	+++	ND	NS	NS	NS
Bifidobacterium breve R0070	NS	++	++	+	NS	NS
Bifidobacterium longum R0175	NS	+++	NS	NS	NS	NS
Bifidobacterium pseudocatenulatum LMI 14	+++	+++	++	NS	NS	NS
Lactobacillus acidophilus R0240	NS	NS	ND	NS	NS	NS
Lactobacillus buchneri R1102	NS	++	ND	NS	NS	NS
Lactobacillus farciminis CIP103136	NS	+++	+++	NS	NS	NS
Lactobacillus helveticus R0052	+++	+++	++	NS	NS	NS
Lactobacillus plantarum R1012	NS	+++	ND	NS	NS	NS
Lactobacillus rhamnosus R1102	NS	+++	++	++	NS	+
Lactococcus lactis R1058	+++	+++	ND	NS	+	NS
Pediococcus acidilactici R1001	NS	+++	++	NS	NS	NS
Streptococcus thermophilus R0083	NS	+++	ND	NS	NS	NS
Bifidobacterium breve R0070 + *Lactobacillus rhamnosus* R1102				NS	++	++
Bifidobacterium breve R0070 + *Lactococcus lactis* R1058				++	+++	++
Lactobacillus rhamnosus R1102 + *Lactococcus lactis* R1058				++	++	++
Bifidobacterium breve R0070 + *Lactobacillus rhamnosus* R1102 + *Lactococcus lactis* R1058			++	++	++	

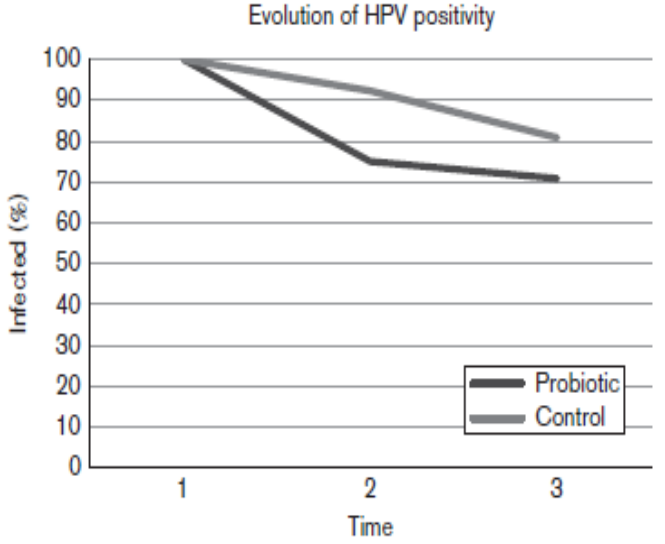
Legend: +++ inhibition of more than 50%, ++ inhibition of more than 20%, + inhibition reaching 20%, NS no significant result, ND not determined.

Probiotics enhance the clearance of human papillomavirus-related cervical lesions: a prospective controlled pilot study

Human Papillomavirus

Probiotics have been proposed for a number of urogenital infectious conditions. In this study, we examine a possible effect on human papillomavirus (HPV)-related precancerous lesions in cervical cytology. We conducted a prospective controlled pilot study, in which 54 women with an HPV + low-grade squamous intraepithelial lesion diagnosis in their PAP smear were followed for 6 months. The intervention group consumed a daily probiotic drink during the study period; the control group received no treatment, according to common care policy. Outcome measures were the control PAP smear and HPV status after 6 months. Probiotic users had a twice as high chance of clearance of cytological abnormalities (60 vs. 31%, $P=0.05$). HPV was cleared in 19% of control patients versus 29% of probiotic users ($P=0.41$). This exploratory pilot study suggests that the probiotic studied promotes the clearance of HPV-related cytological abnormalities. If confirmed, this would represent an entirely new option to manage cervical cancer precursors. *European Journal of Cancer Prevention* 22:46–51

Fig. 2



Evolution of HPV positivity over time in the probiotic and the control group. HPV, human papillomavirus; t_1, at study entry; t_2, after 3 months; t_3, after 6 months.

Dietary synbiotics reduce cancer risk factors in polypectomized and colon cancer patients[1–4]

Results: Synbiotic intervention resulted in significant changes in fecal flora: *Bifidobacterium* and *Lactobacillus* increased and *Clostridium perfringens* decreased. The intervention significantly reduced colorectal proliferation and the capacity of fecal water to induce necrosis in colonic cells and improve epithelial barrier function in polypectomized patients. Genotoxicity assays of colonic biopsy samples indicated a decreased exposure to genotoxins in polypectomized patients at the end of the intervention period. Synbiotic consumption prevented an increased secretion of interleukin 2 by peripheral blood mononuclear cells in the polypectomized patients and increased the production of interferon γ in the cancer patients.

Conclusions: Several colorectal cancer biomarkers can be altered favorably by synbiotic intervention. *Am J Clin Nutr* 2007;85: 488–96.

In pazienti per 12 settimane: possono avere un ruolo nella prevenzione del cancro al colon

MODULAZIONE DEL MICROBIOMA

Dieta e nutrizione:

- quantità calorica, presenza di vitamine e minerali
- composizione della dieta (basso apporto di grassi trans, carne rossa, scarso apporto di fibre)

Rimozione di fattori predisponenti:

- Trattamento del diabete o di altre patologie endocrine
- Evitare obesità, sindrome metabolica, diabete tipo II

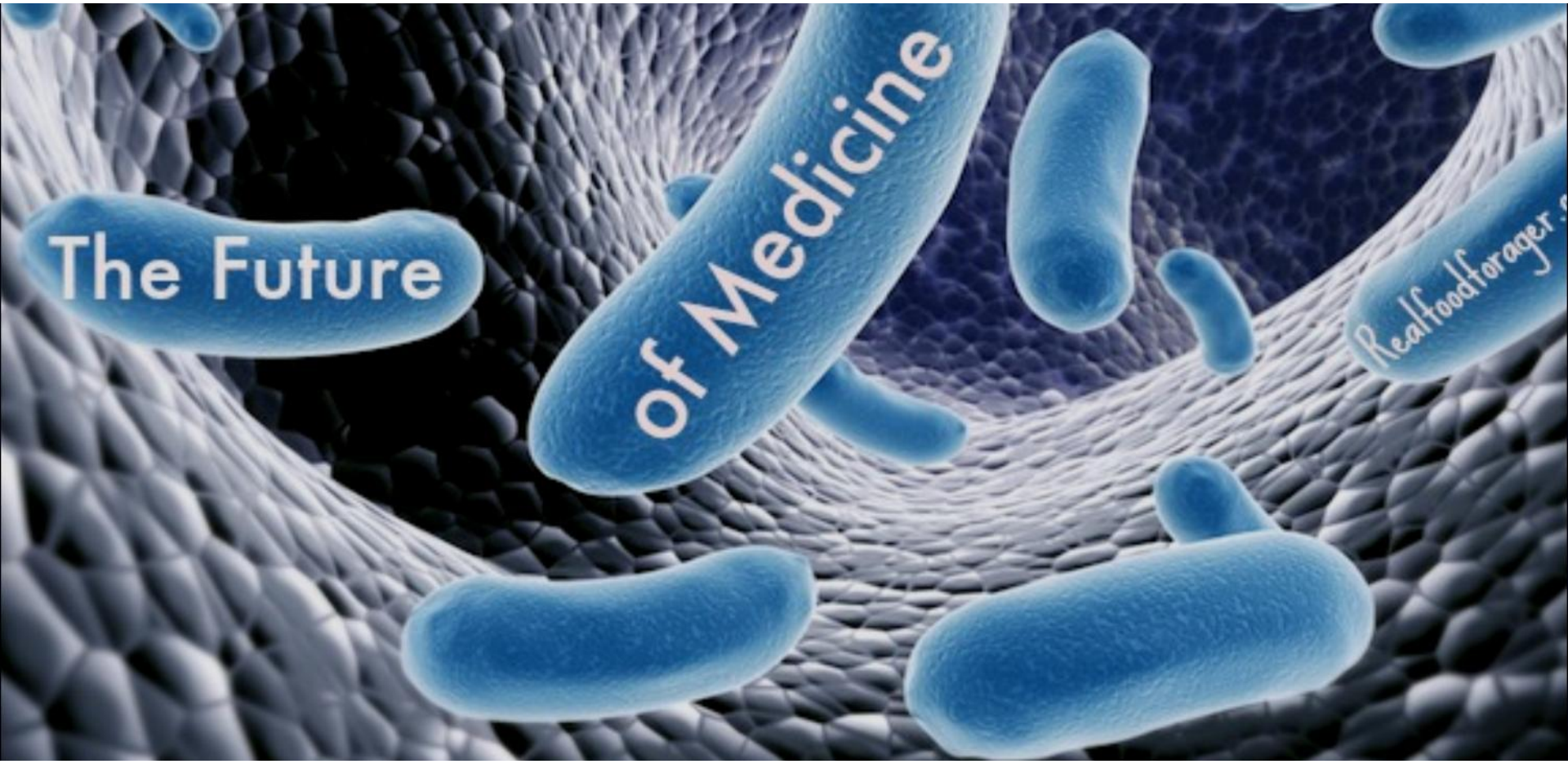
Trattamento: ⟹ DIETA MEDITERRANEA

- Prebiotici
- Probiotici
- Futuro: trapianto fecale

CONCLUSONI

•La ricerca in questo campo servirà a capire meglio l'impatto della dieta e le variazioni individuali (epigenetica) che riveleranno nuove strade per la prevenzione.
•Inoltre le terapie con i prebiotici i probiotici e il trapianto del microbiota serviranno a modificare l'omeostasi del quadro microbico e ridurre la tossicità di alcuni batteri, l'infiammazione le vie mitogenetiche e di antiapoptosi delle cellule mentre l'introduzione di nuovi antibiotici potranno servire a contribuire all'efficacia della chemioterapia.
•La nuova classe di antibiotici potrebbero essere gli strumenti per inibire il biofilm a cambiare la virulenza e resistenza di alcuni batteri e quindi il corso della carcinogenesi

Grazie per l'ascolto e la cortese attenzione



...is the Microbiome