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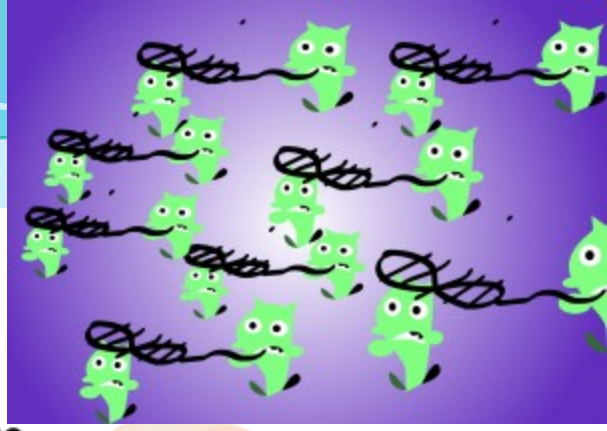
MICROBIOTA E TUMORE



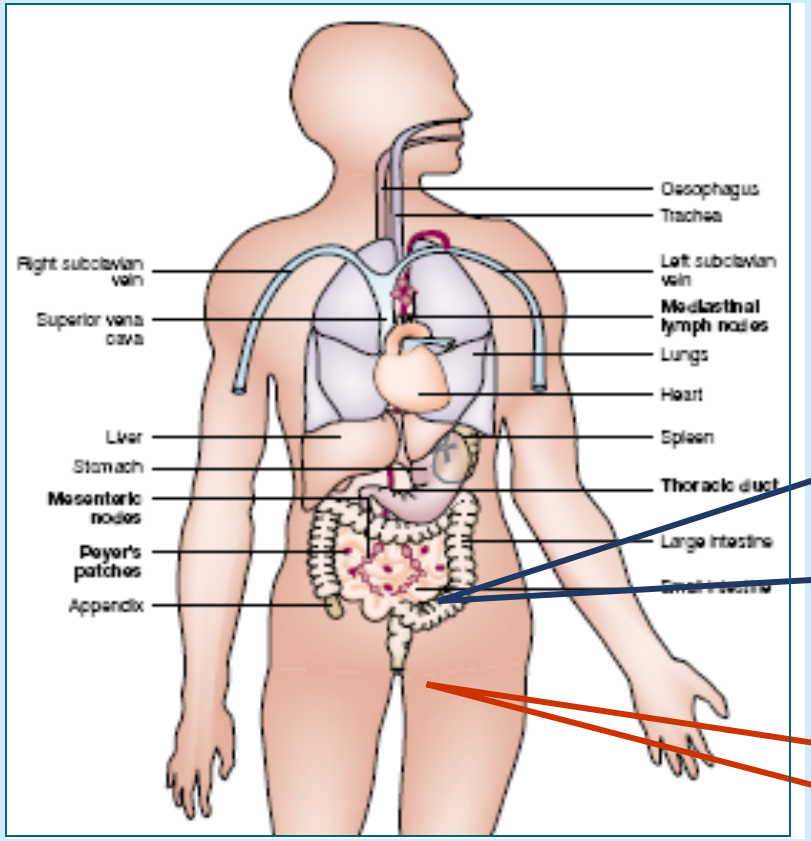
Agenda

1. MICROBIOTA
2. MICROBIOTA e OBESITA’
3. MICROBIOTA e CANCRO :
   - azione anticarcinogenetica
   - in chemio e radioterapia
   - nel Ca colon-retto

"THE HUMAN MICROBIOTA SUPERORGANISM"

pubMed 9040 pubblicazioni

FLORA BATTERICA INTESTINALE

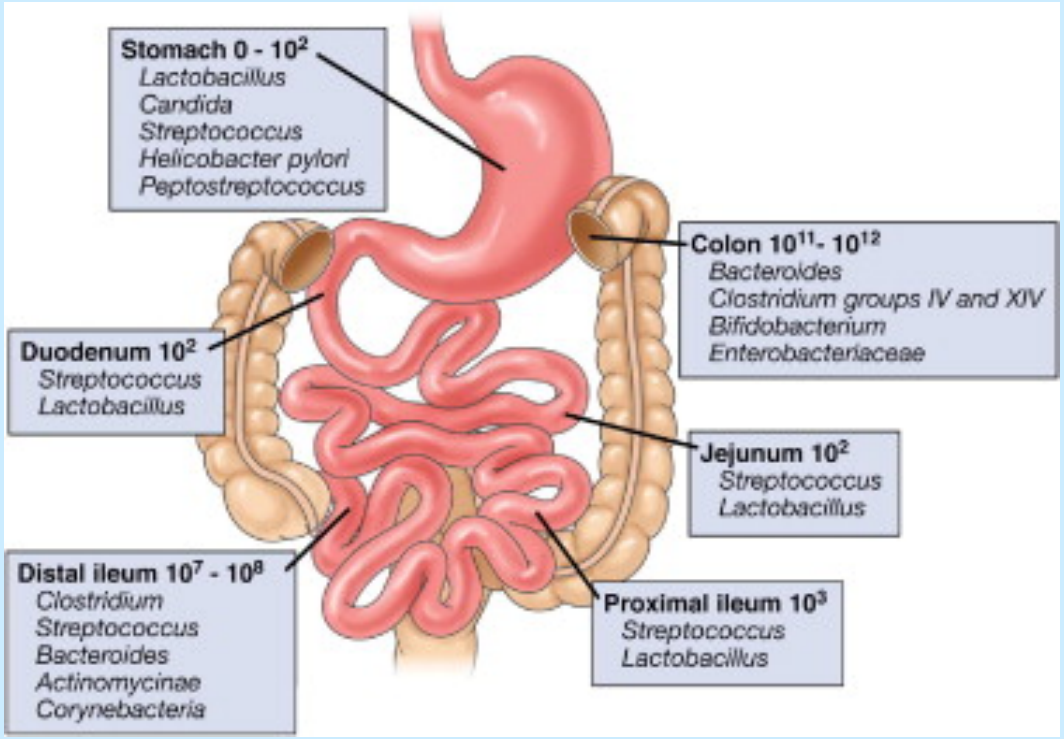


- più di 800 specie
- 100.000 miliardi di batteri
- Oltre 2Kg di massa biologica
- 70% del peso delle feci

80% delle cellule del sistema immunitario

IL MICROBIOTA INTESTINALE:

l'insieme di microrganismi simbiontici nell'apparato digerente MICRIOBIOMA: l'insieme del patrimonio genetico e delle interazioni ambientali che si trovano nell'intestino

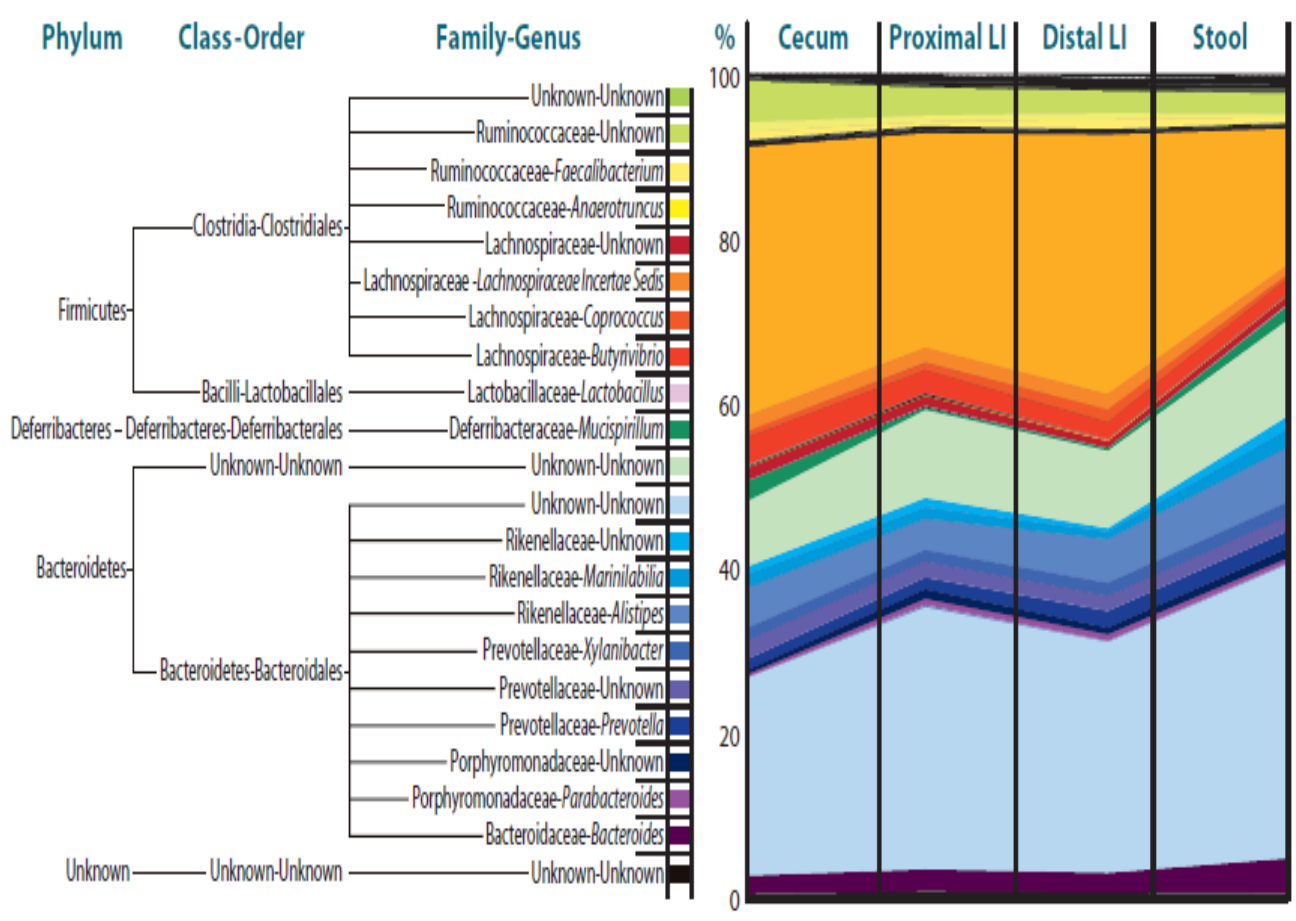


Composizione della concentrazione delle specie microbiche diverse presenti nelle vari parti del tratto gastrointestinale.

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.

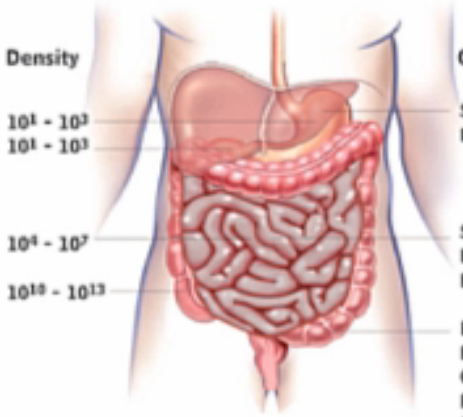
Il microbiota intestinale



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

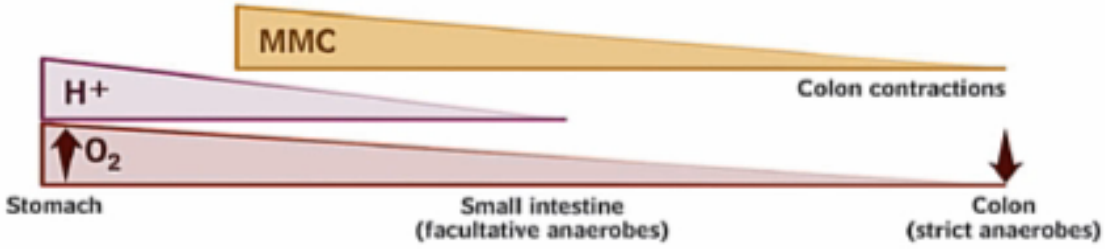
FATTORI CHE INFLUENZANO IL MICROBIOTA INTESTINALE

Microbiota intestinale
Fattori che ne influenzano la distribuzione e la composizione



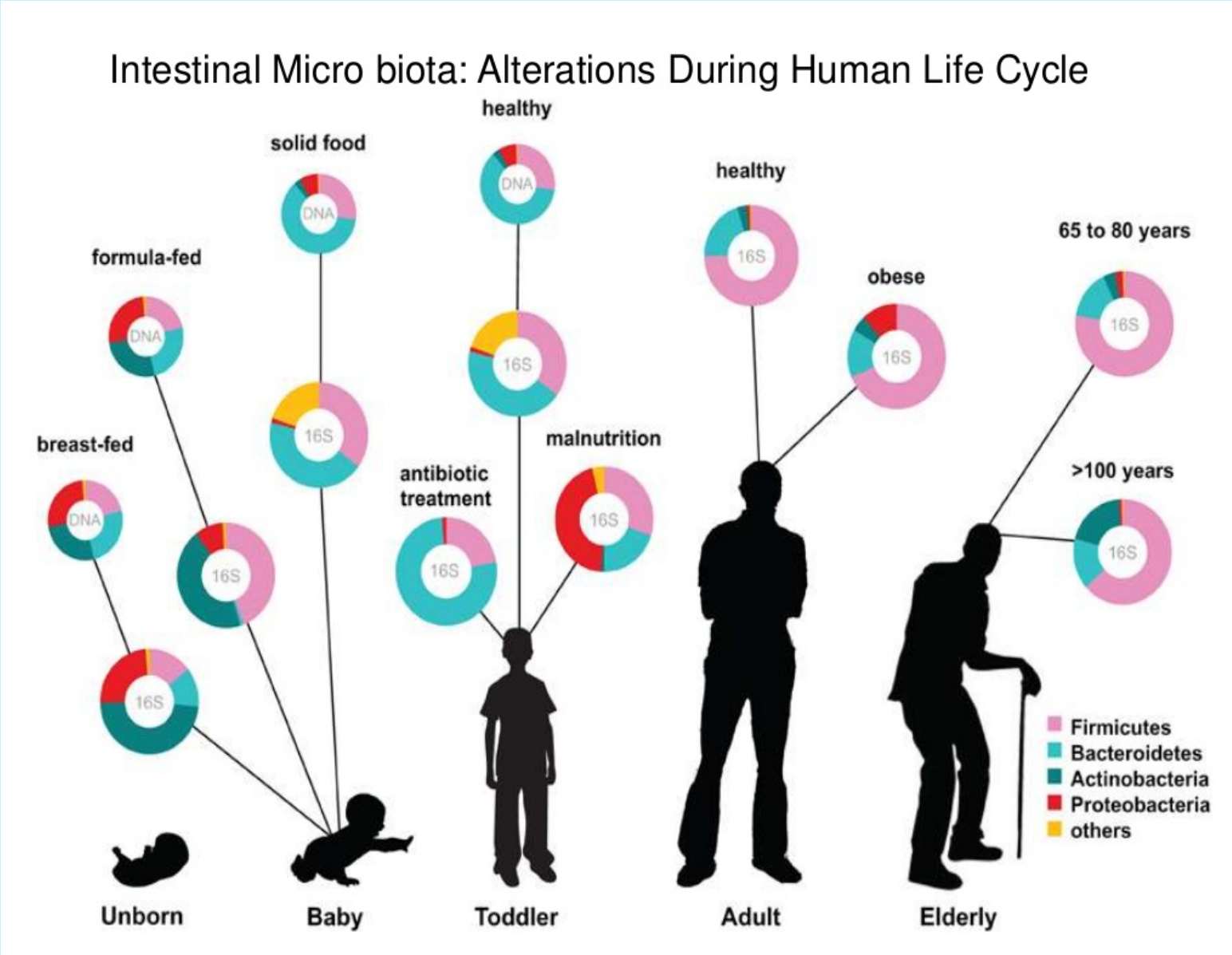
Density	Composition
$10^1 - 10^3$	Streptococcus
$10^1 - 10^3$	Lactobacillus
$10^4 - 10^7$	Streptococcus
	Lactobacillus
	Enterobacteriaceae
$10^{10} - 10^{13}$	Bacteroides
	Eubacterium
	Clostridium
	Ruminococcus
	Bifidobacterium

Intrinsic factors	Extrinsic factors
Gastric acid	Diet, Pre and probiotics
O_2	PPIs, H2 blockers
Motility	Antibiotics
Mucus	Prokinetics
GI secretions	Laxatives
Antimicrobial peptides	Opioids
Immunity (sIgA)	NSAIDs

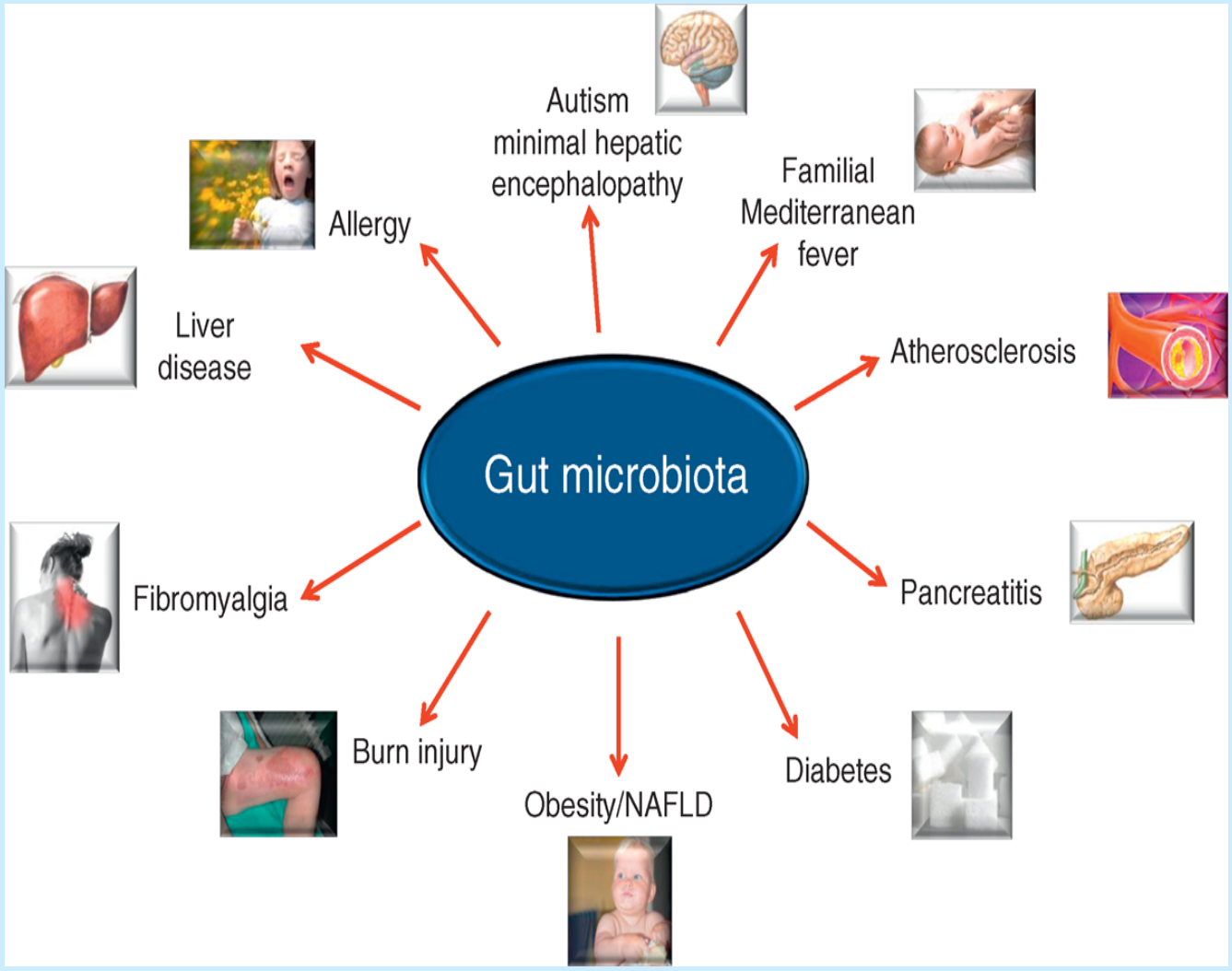


(Simren M, GUT 2013)

Il microbiota si modifica con l'età



Microbiota è correlato con varie patologie



La disbiosi intestinale è spesso associata a diverse patologie (non limitate esclusivamente all'ambiente intestinale).

Journal of Pediatric Gastroenterology & Nutrition. (2013)

OBESITY AND TUMORIGENESIS: INFLAMMATION

The proliferation inducing proinflammatory environment of the obese state alters cellular

Table 1. Hazard ratios for cancer incidence per 5kg/m^2 increase in BMI

Cancer type (incident cases)	HR	CI (99%)	*P*-value
Uterine (2758)	1.62	1.56–1.69	<0.0001
Gallbladder (303)	1.31	1.12–1.52	<0.0001
Renal (1906)	1.25	1.17–1.33	<0.0001
Liver (1859)	1.19	1.12–1.27	<0.0001
Colon (13 465)	1.10	1.07–1.13	<0.0001
Cervical (1389)	1.10	1.03–1.17	0.00035
Ovarian (3684)	1.09	1.04–1.14	<0.0001
Thyroid (941)	1.09	1.00–1.19	0.088
Leukemia (5833)	1.09	1.05–1.13	<0.0001
Pancreas (3851)	1.05	1.00–1.10	0.012
Breast-postmenopausal (28 409)	1.05	1.03–1.07	<0.0001
Rectum (6123)	1.04	1.00–1.08	0.017
Primary brain and CNS (2974)	1.04	0.99–1.06	0.053
Esophageal (5213)	1.03	0.99–1.08	0.056
Stomach (3337)	1.03	0.98–1.09	0.16

CNS, central nervous system; HR, hazard ratio [4▪].

CURRENT OPINION

Obesity and tumor growth: inflammation, immunity, and the role of a ketogenic diet

Christopher Wright[a] and Nicole L. Simone[b]

Università di Filadelfia 2016

KEY POINTS

- Obesity-related cancers will be amongst the most urgent issues that the oncologic field faces over the next decade.
- Obesity creates a state characterized by chronic systemic inflammation and immune dysregulation.
- Leptin is a key adipokine upregulated in the obese state and is intricately involved in the cellular signaling between adipocytes and immunologic cells.
- Dietary intervention has been demonstrated as a feasible adjuvant therapy for a variety of cancers and its impacts on disease progression are a current topic of study.
- Ketogenic diets impede tumor growth through anti-angiogenic, anti-inflammatory, and proapoptotic mechanisms.

Obesità/Immunità/Tumore

L'obesità altera il microambiente del tumore attraverso l'infiammazione e i meccanismi immunologici, curare le disfunzioni metaboliche è comunque una strategia vincente

La leptina promuove la produzione di citokine proinfiammatorie nei macrofagi.

Livelli di leptina inibiscono la produzione di linfociti T mentre le cellule NK presentano una minor citossicità con una riduzione dei T-helper

STUDI SULL'OBESITA' E TUMORE

DIETA E STILE DI VITA in corso

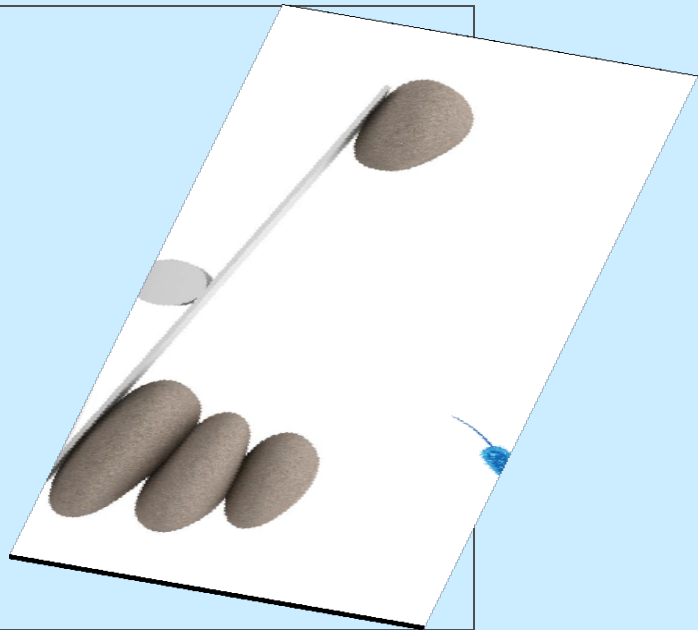
LISA (breast)

CaReFor (breast under therapy)

CHALLENGE (colon)

LiVes (oviarian)

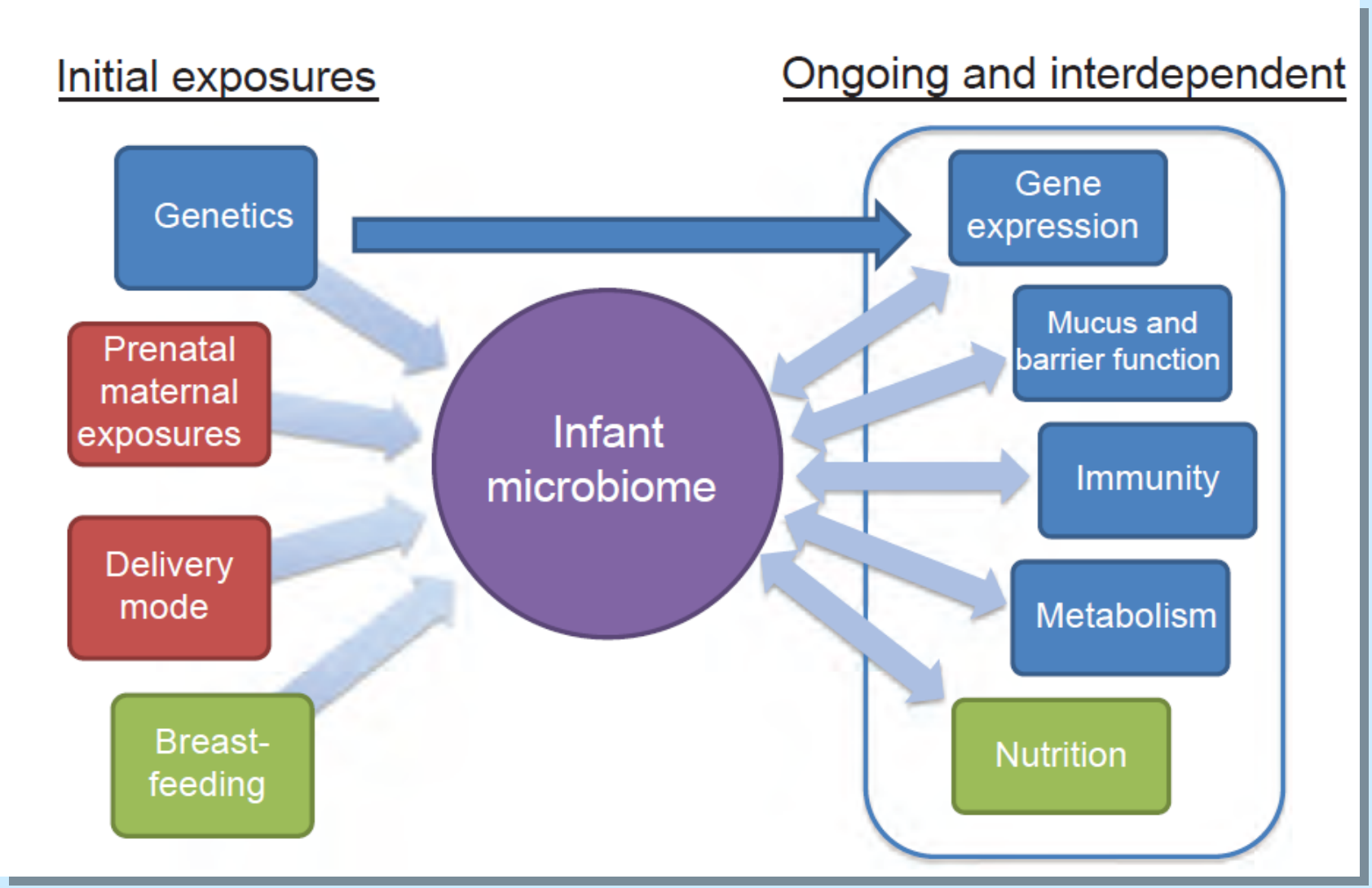
MEAL (prostate)



Why Is Initial Bacterial Colonization of the Intestine Important to Infants' and Children's Health?

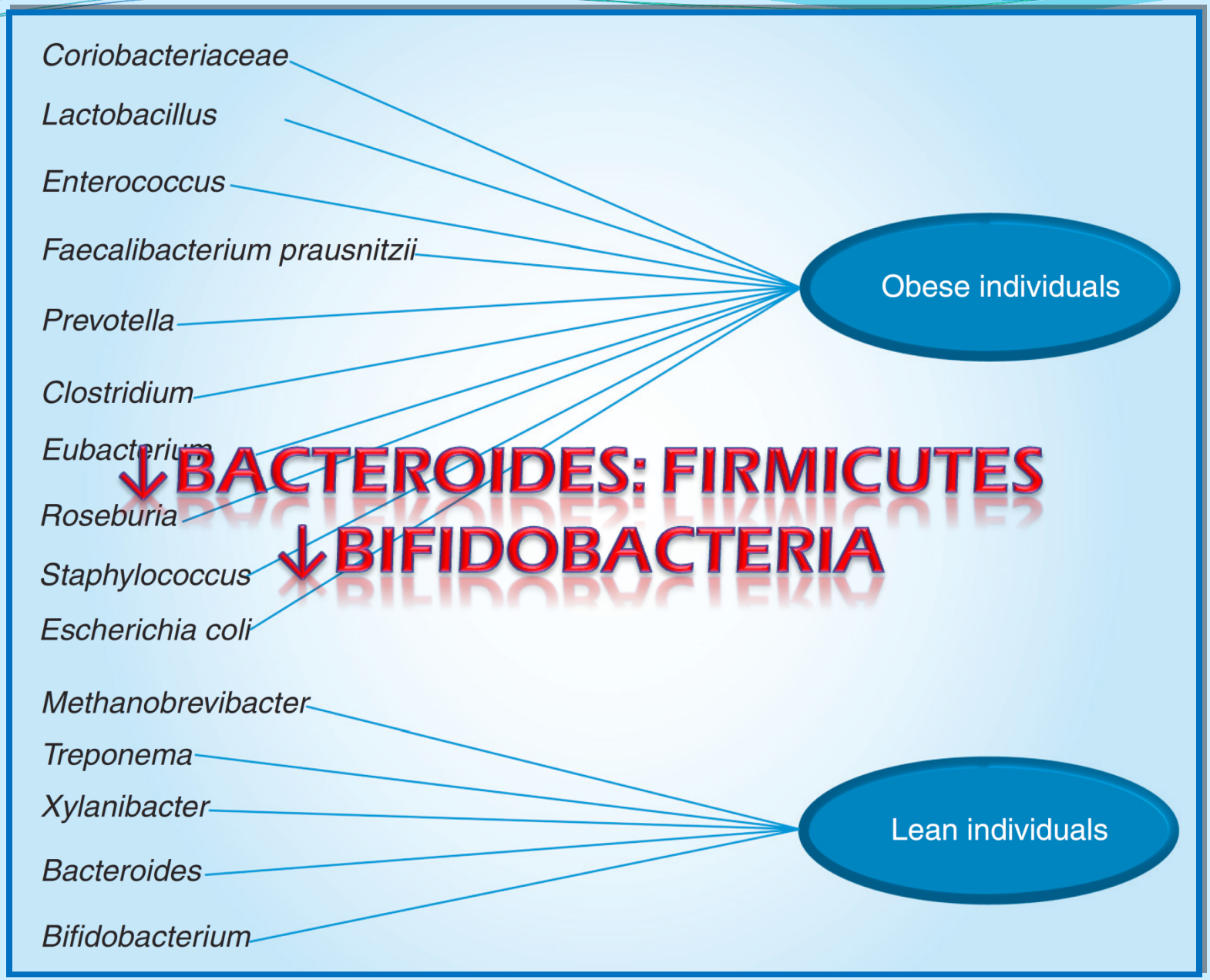
Pearl D. Houghteling and W. Allan Walker

(*JPGN* 2015;60: 294–307)



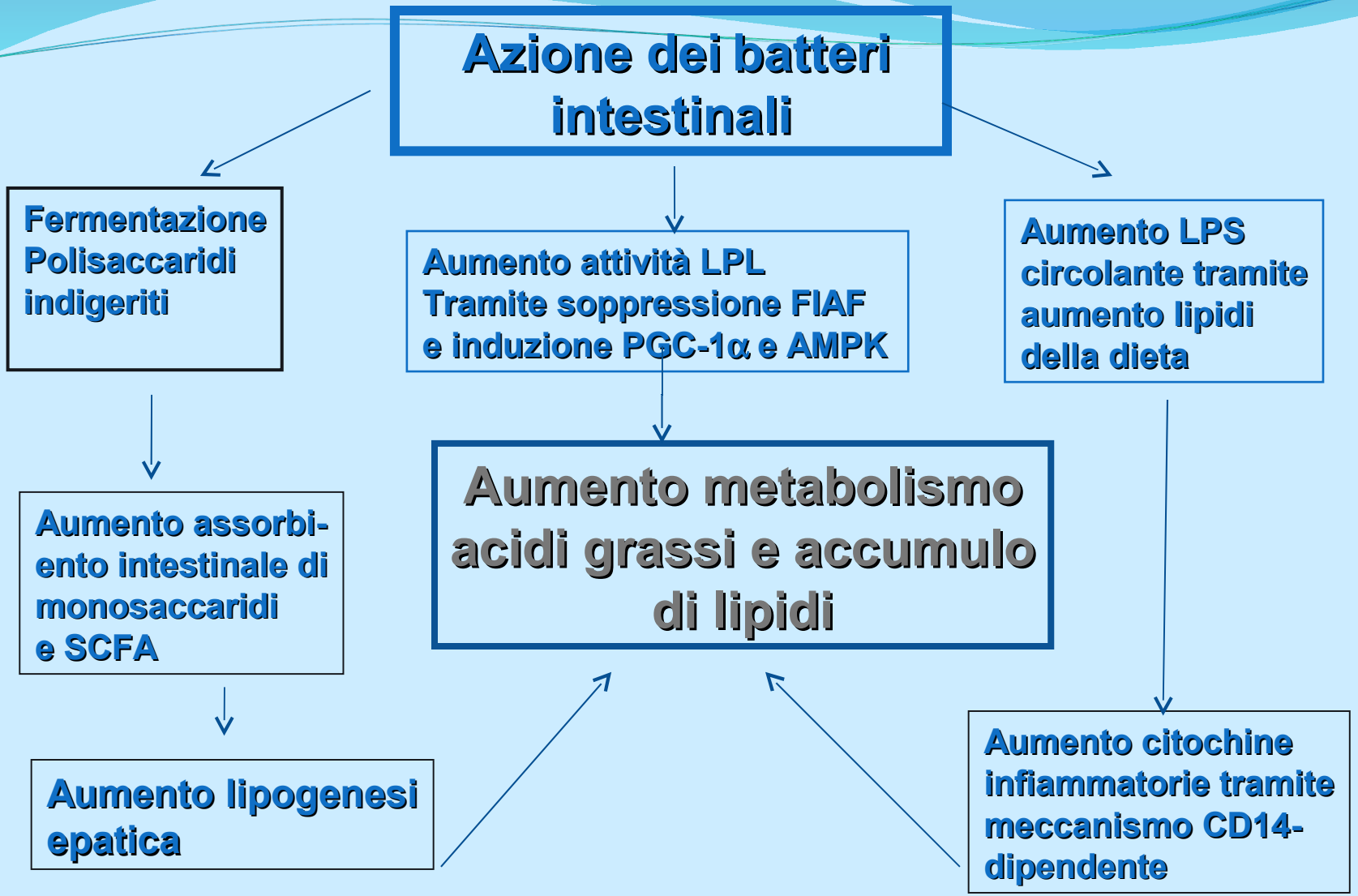
MICROBIOTA NELL'OBESITA'

Angelakis E. et al., 2012



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).


Azione dei batteri intestinali
Fermentazione Polisaccaridi indigeriti
Aumento attività LPL Tramite soppressione FIAF e induzione PGC-1α e AMPK
Aumento LPS circolante tramite aumento lipidi della dieta
Aumento assorbi-ento intestinale di monosaccaridi e SCFA
Aumento metabolismo acidi grassi e accumulo di lipidi
Aumento lipogenesi epatica
Aumento citochine infiammatorie tramite meccanismo CD14-dipendente

Microbioma nella genesi dell'obesità/disbiosi

Nei modelli di topi da esperimento indotti all'obesità da una dieta ed elevato contenuto di grassi e dalla genetica, la disbiosi del microbioma determina un' aumentata permeabilità con alterazione delle tight junction con conseguente stato di endotossiemia, un basso grado di infiammazione e una insulino-resistenza a livello epatico, muscolare e nel tessuto adiposo.

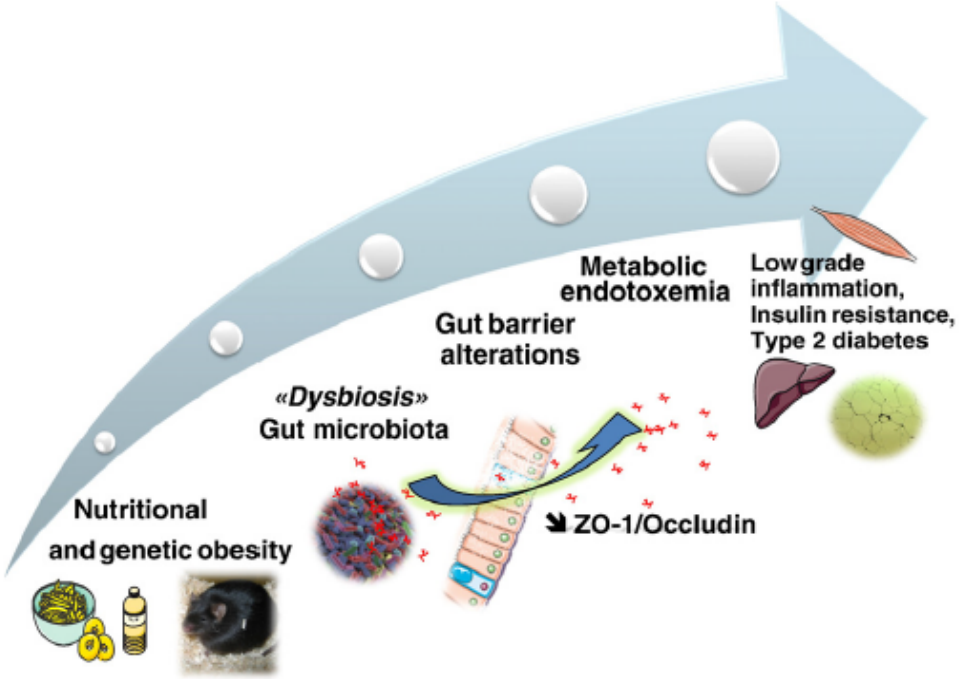
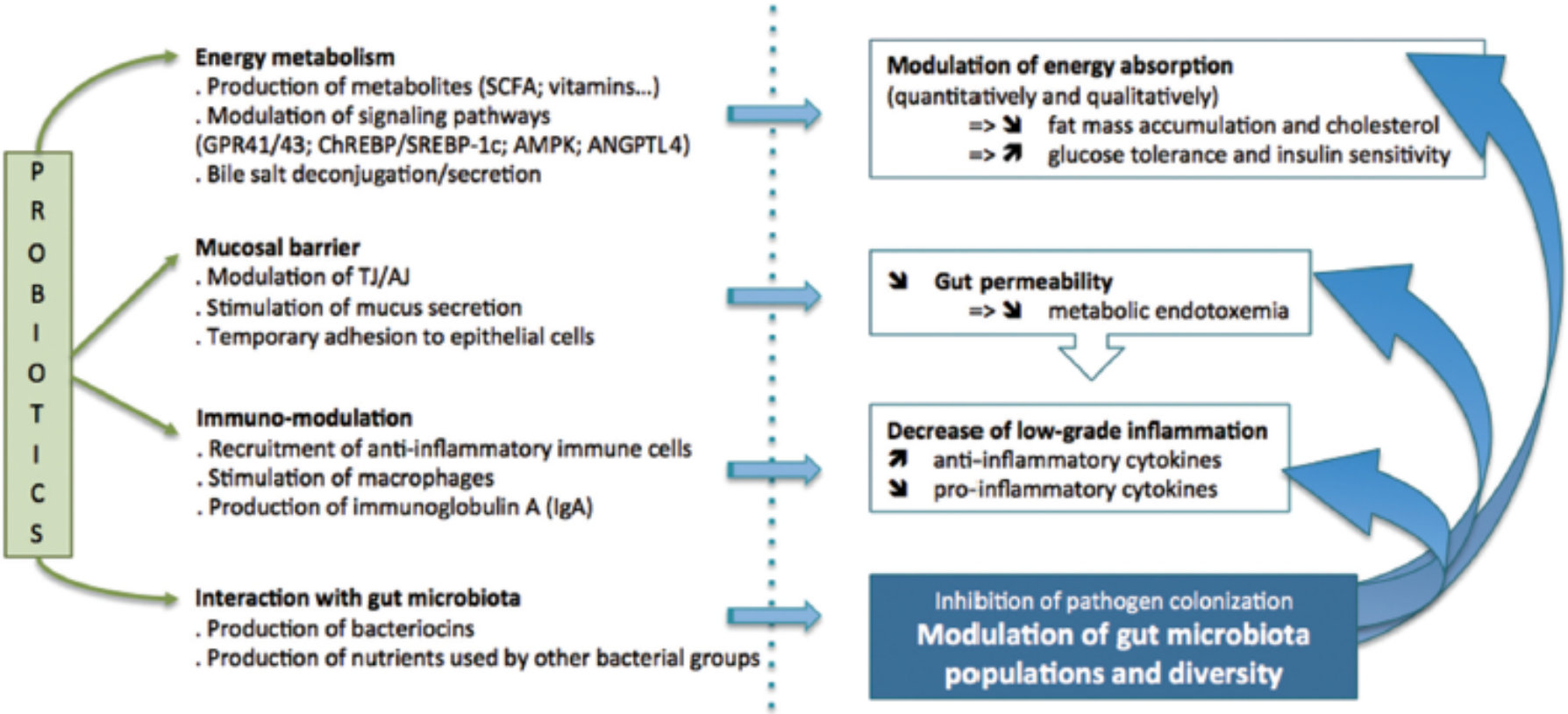


Fig. 3. The gut microbiota are involved in the onset of metabolic disorders associated with obesity: a model. Nutritional (high-fat diet) and genetic (*ob*/*ob* mice) obesity are associated with gut microbiota dysbiosis. This leads to the occurrence of gut permeability (altered distribution of the tight junction proteins ZO-1 and Occludin), promoting metabolic endotoxaemia and initiating the development of low-grade inflammation and insulin resistance in the liver, muscles and adipose tissue.

ALTERAZIONI DEL MICROBIOTA INTESTINALE

- Incremento della capacità d'introitare energia dal nutrimento (attraverso percorsi lipogenetici)
- Alterato metabolismo di acidi grassi e modifica della composizione nel tessuto adiposo ed epatico, alterata formazione della lipoproteinlipasi che favorisce l'accumulo di trigliceridi nel tessuto adiposo
- Modulazione del Peptide YY enterico
- Secrezione del glucagone-1like peptide (GLP-1)
- Attivazione TLR-4 (asse lipopolisaccaridico)
- Modulazione dell'integrità barriera intestinale attraverso l'attività delle GLP-2 (sensibilità insulinica)

AZIONE DEI PROBIOTICI



Le Barz M et al. Diabetes and Metab J, 2015;39:291.303

Azione della 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

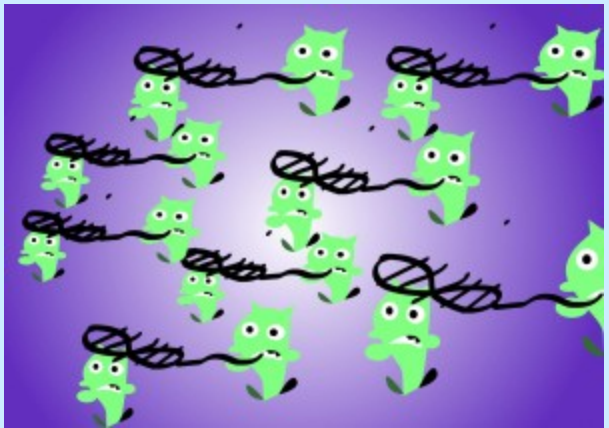
Alcuni ricercatori hanno dimostrato che dopo 24 ore di cambiamenti dietetici con dieta ad alto contenuto di fibre e basso contenuto di lipidi, il microbioma può modificarsi

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 modificazione possono essere i prebiotici,

i probiotici e in futuro il trapianto fecale.



MICROBIOTA E TUMORE

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]

Nutrition and Cancere 2016

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.*

CANCRO COLON-RETTO

Molti studi confermano che il microbioma gioca un ruolo cruciale nel rischio di tumore del colon

La disbiosi favorisce la produzione di metaboliti carcinogenetici **+** l'associazione con il processo infiammatorio cronico intestinale aumenta il rischio di sviluppare Cancro colon

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v20.i48.18121

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ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Dismicrobism in inflammatory bowel disease and colorectal cancer: Changes in response of colocytes

Giovanni Tomasello, Pietro Tralongo, Provvidenza Damiani, Emanuele Sinagra, Benedetto Di Trapani, Marie Noelle Zeenny, Inaya Hajj Hussein, Abdo Jurjus, Angelo Leone

About 1%-2% of CRC patients have a pathological background consisting of intestinal mucosa inflammation[48]. This "inflammatory background" of colonic mucosa can evolve to a less (low-grade) or more severe (high-grade) dysplasia, which through neoplastic transformation gives rise to carcinoma *"in situ"* and finally *"invasive"* carcinoma. Interestingly, many lines of evidence highlighted the importance of intestinal microbiota in the development of CRC[42] and that the type of immune response generated by the gut commensal bacteria could potentially influence tumor immunity[49]. Mice colonized

DOPPIO RUOLO DEL MICROBIOMA: PREVENZIONE O PROMOZIONE DELLA CARCINOGENESI

Gli SCFA particolarmente il butirrato che si forma dalla fermentazione batterica intestinale, sono dei nutrienti per la barriera intestinale e possono giocare un ruolo importante nella prevenzione della carcinogenesi

Meccanismo di azione del butirrato:

↓

Inibizione della deacetilasi dell'istone (HDAC)

che è uno degli approcci terapeutici usati nella terapia antineoplastica

Nelle cellule del Ca colon, il butirrato protegge contro l'inizio della differenzazione del cancro del colon inibisce la proliferazione cellulare, induce l'apoptosi e inibisce l'angiogenesi

DOPPIO RUOLO DEL MICROBIOMA: PREVENZIONE E PROMOZIONE DELLA CARCINOGENESI

Microbial metabolism of cruciferous vegetables or garlic leads to the production of compounds such as sulforaphane N-acetyl-cysteine, allyl mercaptan and butyrate. Thus, microbe-derived metabolites can counteract the carcinogenetic process by triggering cell cycle arrest and apoptosis of tumoral cells through interference with HDAC activity[10,68]. Endoluminal

Sulforafani

HDCA activity

process[69]. Tumorigenesis is a multi-step process in which the damage in the DNA is the essential pre-condition for tumoral induction. *E. coli* has a genic cluster called

Danno del DNA da parte della fermentazione microbica attraverso di poliammine eterociclciche della CARNE

Omega-3

rectal carcinogenesis[70-72]. Experimental data show that consumption of omega-3 polyunsaturated fatty acids is able to decrease the incidence of sporadic colorectal cancer. Eicosapentaenoic free fatty acid reduces polyp formation and growth in models of familial adenomatous polyposis[73]. The intake of docosahexaenoic acid can modify the gut microflora. Breast milk is rich in omega-3

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

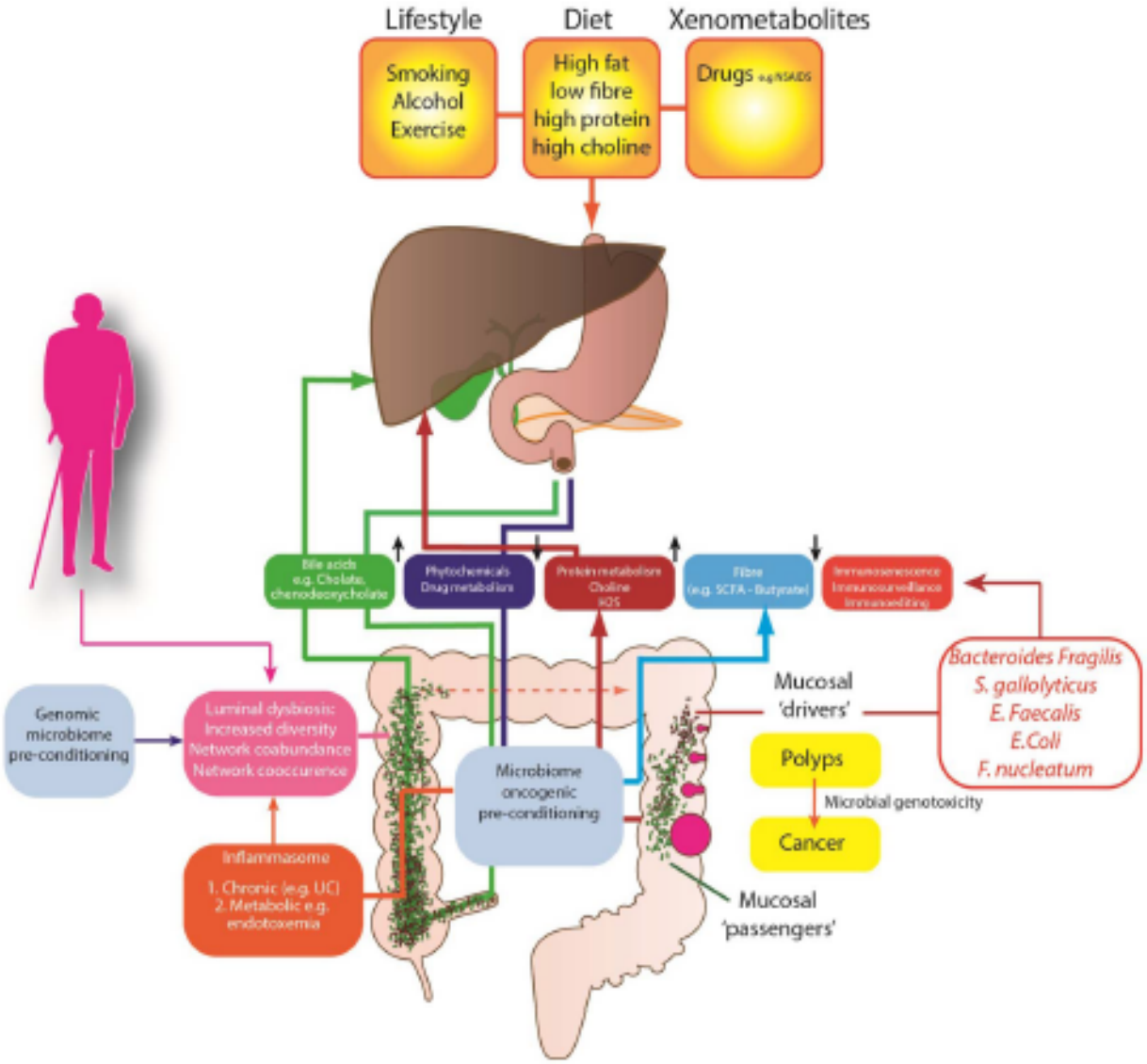

Figure 1 Proposed mechanisms of the gut microbiome in colon cancer aetiology.

Marchesi JR, *et al*. *Gut* 2016;**65**:330–339. doi:10.1136/gutjnl-2015-309990

World J Gastrointest Oncol 2014 December 15; 6(12): 511-530
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REVIEW

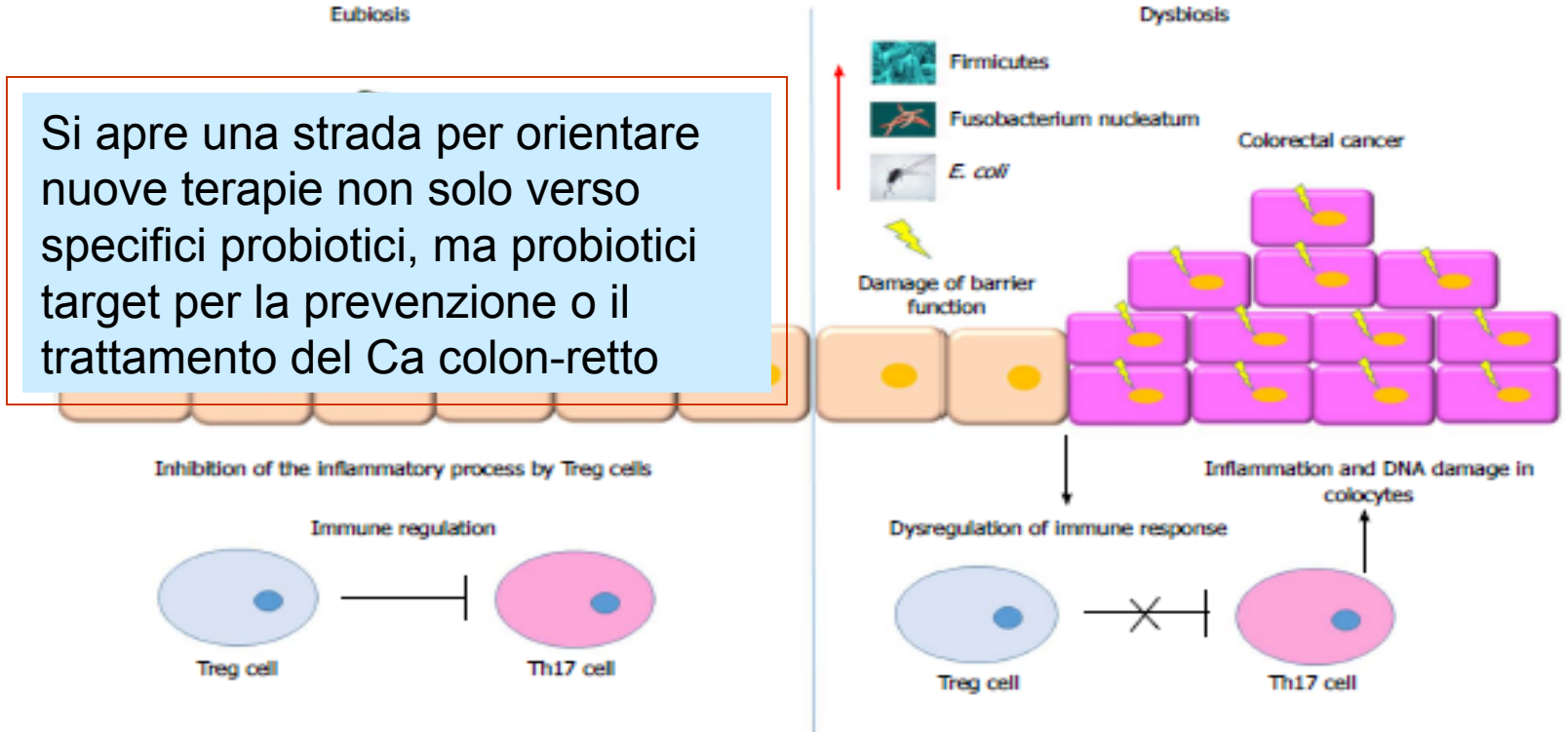
Dismicrobism in inflammatory bowel disease and colorectal cancer: Changes in response of colocytes

Giovanni Tomasello, Pietro Tralongo, Provvidenza Damiani, Emanuele Sinagra, Benedetto Di Trapani, Marie Noelle Zeenny, Inaya Hajj Hussein, Abdo Jurjus, Angelo Leone

Tomasello G *et al*. Eubiosis and dysbiosis in IBD

Eubiosis	Dysbiosis
Protection against inflammatory processes and physiologic mucosa permeability	Promotion of inflammatory processes and increase of mucosa permeability (IBD)
Production of metabolites useful for the trophism of colocytes	Production of procarcinogenic compounds (CCR)
Induction of cytoprotective Hsp	Release of Hsp that trigger immune system response

Figure 2 Eubiosis and dysbiosis exert different biochemical effects in the context of colocytes pathophysiology. IBD: Inflammatory bowel disease.



Si apre una strada per orientare nuove terapie non solo verso specifici probiotici, ma probiotici target per la prevenzione o il trattamento del Ca colon-retto

EFFETTI ANTITUMORALI DEI PROBIOTICI IN TRAIL CLINICI

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 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.

The Potential Role of Probiotics in Cancer Prevention and Treatment

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

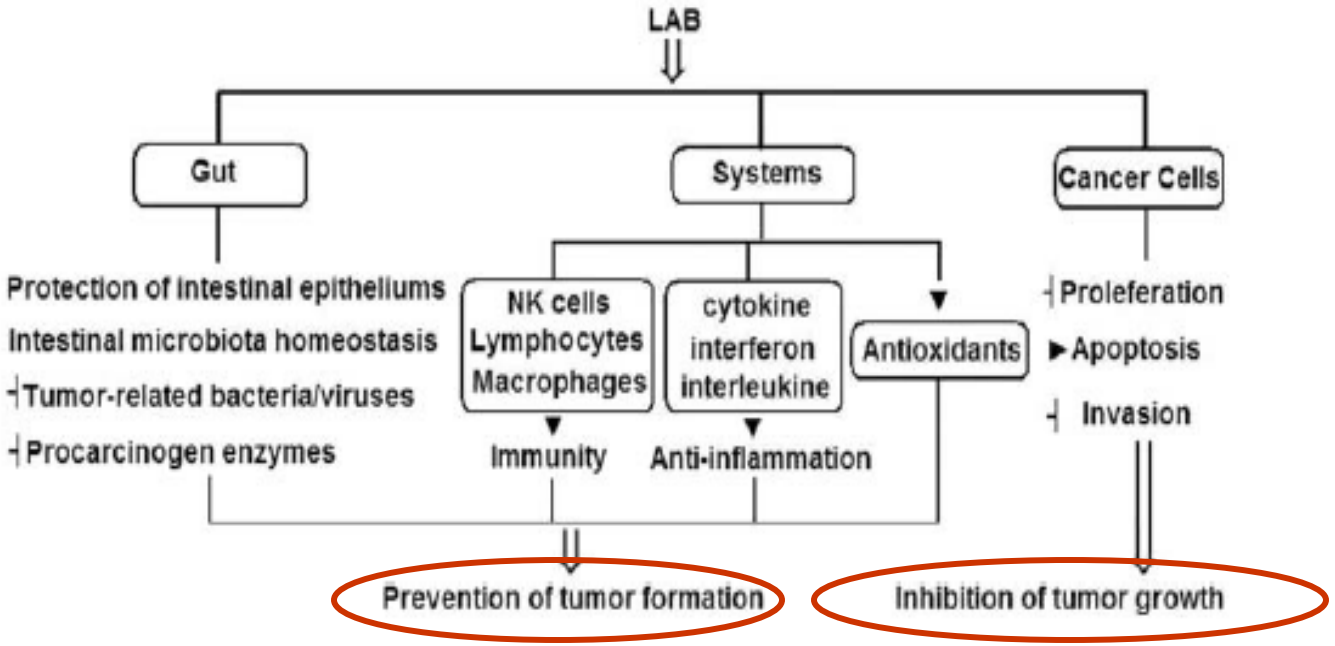


Figure 1. Illustration for the suppressive effects of probiotics on tumor formation and growth. Probiotics can exert their functions locally and systemically. Oral administration of probiotics can provide protection of intestinal epitheliums, modulate the homeostasis of the intestinal microflora, and 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 sugli effetti collaterali delle 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

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.

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

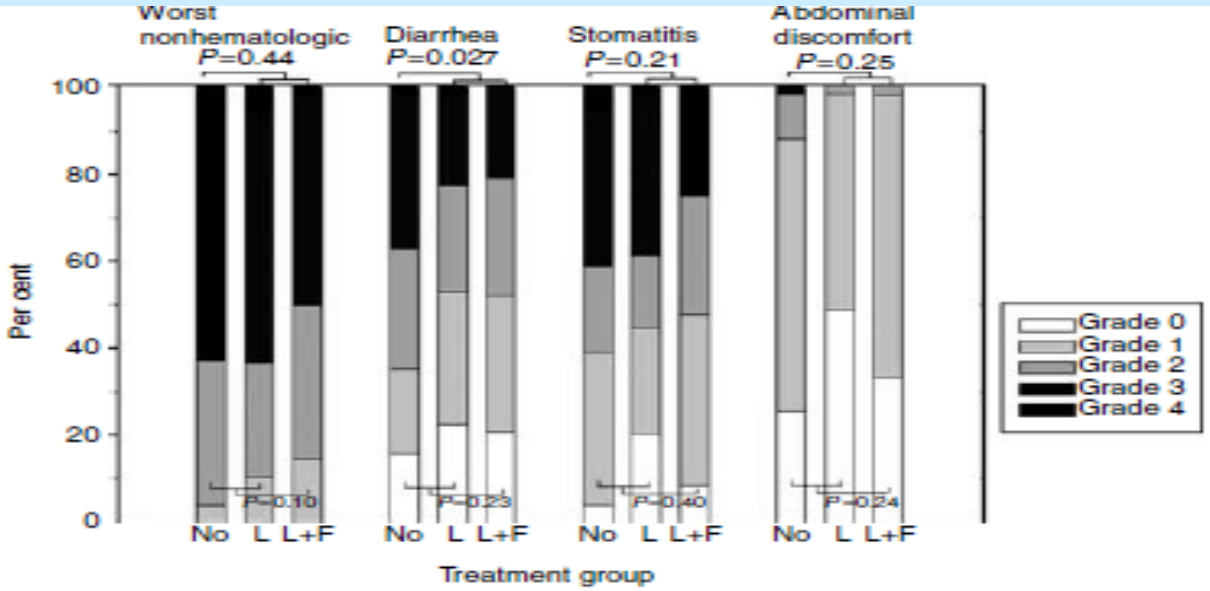


Figure 1 Effect of oral *Lactobacillus rhamnosus GG* (L) and *Lactobacillus rhamnosus GG* plus fibre (guar gum, L + F) supplementation on adverse events recorded during 5-FU-based chemotherapy.

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.

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

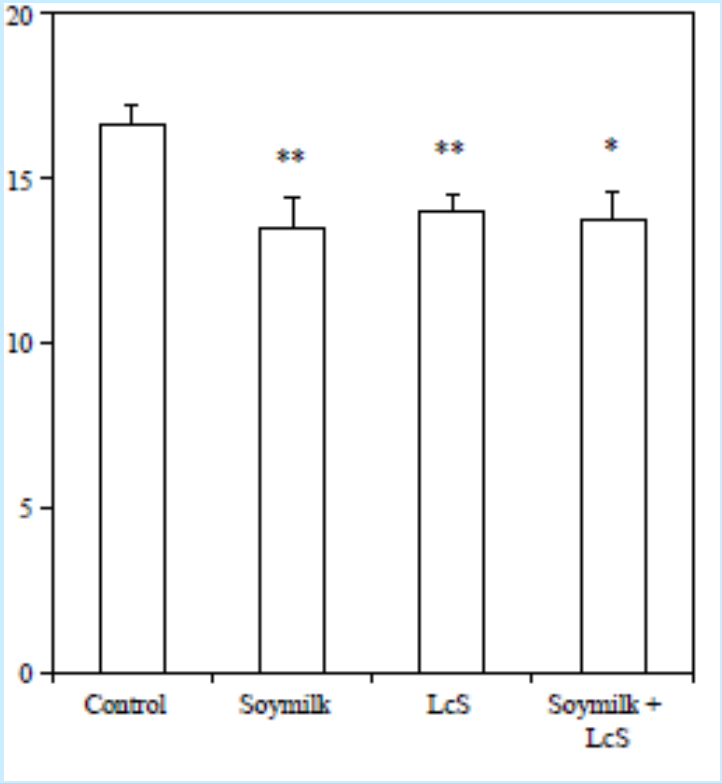
The present study indicates that an increase in apoptotic rate in the liver of rats treated with AFB_1 is associated with biochemical disturbances in the oxidant/antioxidant balance system, which may be interlinked with the pathogenic network of AFB_1 toxicity. However, the overall information obtained 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.

Cancer Science
The official journal of the Japanese Cancer Association
JCA

Lactobacillus casei Shirota enhances the preventive efficacy of soymilk in chemically induced breast cancer

BREAST CANCER

Chiaki Kaga,[1] Akimitsu Takagi,[1,4] Mitsuyoshi Kano,[1] Shoichi Kado,[1] Ikuo Kato,[1] Masashi Sakai,[1] Kouji Miyazaki,[1] Masanobu Nanno,[1] Fumiyasu Ishikawa,[1] Yasuo Ohashi[2] and Masakazu Toi[3]



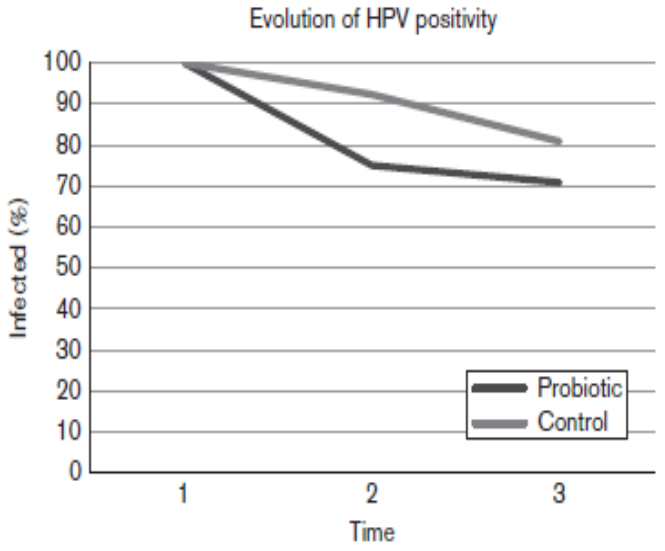
In conclusion, the dietary administration of LcS in combination with soymilk prevented mammary carcinogenesis in PhIP-exposed rats more effectively than that of each component alone. Thus, the habitual consumption of LcS in combination with soymilk might be a beneficial dietary style for breast cancer prevention.

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.

Lipoteichoic acid from *Lactobacillus rhamnosus GG* as an oral photoprotective agent against UV-induced carcinogenesis

SKIN CANCER

British Journal of Nutrition (2013), **109**, 457–466

Probiotics *Lactobacillus rhamnosus GG, Lactobacillus acidophilus* Suppresses DMH-Induced Procarcinogenic Fecal Enzymes and Preneoplastic Aberrant Crypt Foci in Early Colon Carcinogenesis in Sprague Dawley Rats

Angela Verma and Geeta Shukla

Nutrition and Cancer, 65(1), 84–91

Diet makes an important contribution to colorectal cancer (CRC) risk implying risks for CRC are potentially reducible. Therefore, the probiotics have been suggested as the prophylactic measure in colon cancer. In this study, different probiotics were used to compare their protective potential against 1,2 dimethylhydrazine dihydrochloride (DMH)-induced chemical colon carcinogenesis in Sprague Dawley rats. Animals belonging to different probiotic groups were fed orally with 1 × 10^9 lactobacilli daily for 1 week, and then a weekly injection of DMH was given intraperitoneally for 6 wks with daily administration of probiotic. *Lactobacillus GG* and *L.acidophilus* + DMH-treated animals had maximum percent reduction in ACF counts. A significant decrease ($P < 0.05$) in fecal nitroreductase activity was observed in *L.casei* + DMH and *L.plantarum* + DMH-treated rats whereas β-glucuronidase activity decreased in *L.GG* + DMH and *L.acidophilus* + DMH-treated rats. Animals treated with *Bifidobacterium bifidum* + DMH had significant decreased β-glucosidase activity. However, not much difference was observed in the colon morphology of animals belonging to various probiotic + DMH-treated rats compared with DMH-treated alone. The results indicated that probiotics, *L.GG*, and *L.acidophilus* can be used as the better prophylactic agents for experimental colon carcinogenesis.

PROFILASSI CANCRO COLON

Estimation of the Potential Antitumor Activity of Microencapsulated *Lactobacillus acidophilus* Yogurt Formulation in the Attenuation of Tumorigenesis in Apc(Min/+) Mice

Dig Dis Sci 2009

The present study therefore demonstrates that microencapsulated probiotic bacteria in yogurt exert beneficial action by maintaining the constant body weight, minimizing intestinal inflammation, and delaying overall polyp progression in experimental Min mice. This study will have implications for colon cancer, IBD, and other GI diseases.

La somministrazione di probiotici *L. acidophilus* in yogurt in animali da esperimento esercita un'azione antitumore

NAFLD

Lactobacillus rhamnosus GG Protects against Non-Alcoholic Fatty Liver Disease in Mice

Yvonne Ritze[1], Gyöngyi Bárdos[1], Anke Claus[1], Veronika Ehrmann[1], Ina Bergheim[1,2], Andreas Schwiertz[3],

Results: LGG increased beneficial bacteria in the distal small intestine. Moreover, LGG reduced duodenal IκB protein levels and restored the duodenal tight junction protein concentration. Portal LPS ($P \leq 0.05$) was reduced and tended to attenuate TNF-α, IL-8R and IL-1β mRNA expression in the liver feeding a high-fructose diet supplemented with LGG. Furthermore liver fat accumulation and portal alanine-aminotransferase concentrations ($P \leq 0.05$) were attenuated in mice fed the high-fructose diet and LGG.

Conclusions: We show for the first time that LGG protects mice from NAFLD induced by a high-fructose diet. The underlying mechanisms of protection likely involve an increase of beneficial bacteria, restoration of gut barrier function and subsequent attenuation of liver inflammation and steatosis.

EFFETTI DI ALCUNI PROBIOTICI IN CASO DI MODELLI SPERIMENTALI DI NAFLD

Probiotic	Experimental model	Duration of therapy	Results	Reference
VSL#3 1.5×10^{9} CFU/mouse/day	Mice: *ob/ob* mice fed HFD	4 weeks	Improved NAFLD histology and reduction in hepatic total fatty acid content, and serum ALT levels; amelioration of hepatic IR	[Li et al., 2003 [119]
Bacillus polyfermenticus SCD 3.1×10^{6} CFU/day	Rats: high-fat and high-cholesterol diet	6 weeks	Reduction in plasma LDL, cholesterol, and hepatic total cholesterol, and triglycerides	[Paik et al., 2005 [164]
Lactobacillus rhamnosus PL60 1.0×10^{7}–1.0×10^{9} CFU/mouse/day	Mice: HFD	8 weeks	Resolution of hepatic steatosis (at higher dose)	[Lee et al., 2006 [162]
Lactobacillus acidophilus and *Lactobacillus casei*	Rats: high-fructose diet	8 weeks	Reduced liver oxidative stress, improved IR	[Yadav et al., 2007 [163]
VSL#3 1.5×10^{9} CFU/mouse/day	Mice: HFD	4 weeks	Improved HFD-induced hepatic NKT cell depletion, IR, hepatic steatosis and inflammation	[Ma et al., 2008 [122]
Lactobacillus plantarum MA2 1×10^{11} CFU/rat/day	Rats: cholesterol-enriched diet	5 weeks	Reduction in liver and serum cholesterol and triglycerides	[Wang et al.,2009 [161]
VSL#3 1.3×10^{10} CFU/kg	Rats: HFD	4 weeks	Amelioration of the hepatic inflammatory, steatotic and peroxidative factors and reduction in serum aminotransferase levels	[Esposito et al., 2009 [41]
VSL#3 in drinking water	Mice: MCD	9 weeks	No effect on MCD-induced liver steatosis and inflammation, but amelioration of liver fibrosis	[Velayudham et al., 2009 [1
Lactobacillus paracasei B21060 2.5×10^{8} bacteria/kg/diet	Rats:	5 weeks	Ameliorated steatosis, IR and decreased hepatic inflammatory cytokines	Our unpublished data

MCD, methionine–choline-deficient.

Long-Term Use of Probiotic-Containing Yogurts Is a Safe Way to Prevent *Helicobacter pylori*: Based on a Mongolian Gerbil's Model

Background. The suppression of *Helicobacter pylori* (*H. pylori*) decreases *H. pylori*-related diseases. The probiotics have an inhibitory effect on *H. pylori*. *Aim*. We investigated the effects of long-term use of yogurt on *H. pylori* based on Mongolian gerbils' model. *Materials and Methods*. Yogurt (containing a supplement of *Lactobacillus acidophilus, Bifidobacterium lactis, etc.*) was used. Forty-six gerbils were divided into five groups. All groups were inoculated with *H. pylori* for 5 to 8 weeks. The yogurt was given as follows: Group (Gr.) A: from 1st to 4th week; Gr. B from 5th to 8th week; Gr. C: from 17th week to sacrifice; Gr. D: from 5th week to sacrifice. Gerbils were sacrificed on the 52nd week. Histology was evaluated according to the Sydney system. *Results*. The positive rates of *H. pylori* were 60% (Gr. A), 75% (Gr. B), 67% (Gr. C), 44% (Gr. D), and 100% (Gr. E). Gr. D showed lower inflammatory score. Only Gr. E (60%) had intestinal metaplasia. Gr. D showed higher IL-10 and lower TNF-α expression than Gr. E. *Conclusion*. Long-term intake of yogurt could decrease *H. pylori* infection. The long-term use of yogurt would be an alternative strategy to manage *H. pylori* infection.

Su animali da esperimento per 52 settimane

Helicobacter pylori

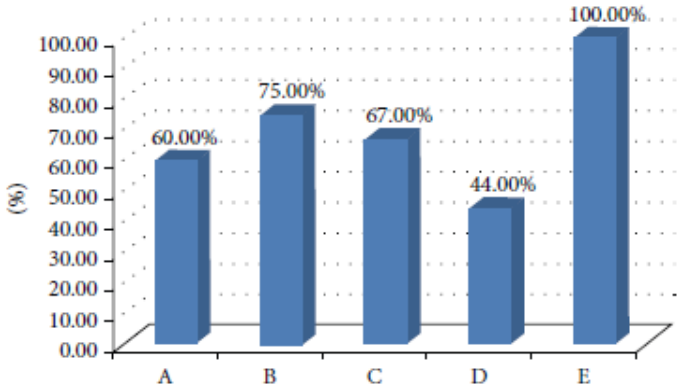


FIGURE 2: All gerbils in control group (*H. pylori* given only) showed positive result of *H. pylori* test in 52th week. Lower positive rates were noted in those yogurt-fed groups. Group D reveals lowest positive rate. It demonstrated that yogurt can prevent *H. pylori* infection and the effect might be related with the duration of yogurt use.

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 o trattamento

Trattamento:

- Prebiotici
- Probiotici
- Trapianto fecale

CONCLUSIONI

Lo studio del microbiota sta trovando sempre più campi di applicazione

L' EQUILIBRIO DEL MICROBIOTA:

- **Migliora la barriera gastrointestinale**
- **Inibisce i potenziali elementi patogeni e carcinogenetici presenti nell'intestino**
- **Rinforza il sistema immunitario**
- **Gioca un ruolo importante nella genesi e nella crescita del tumore**

HUMAN MICROBIOME

FAQ

AMERICAN SOCIETY FOR MICROBIOLOGY