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How fermentation turns raw foods into functional fermented foods

Gwénaél Jan

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INRAE



➤ How fermentation turns raw foods into functional fermented foods

Gwénaél JAN

UMR1253, INRAE Agrocampus-Ouest, Science et Technologie du Lait et de l'Œuf

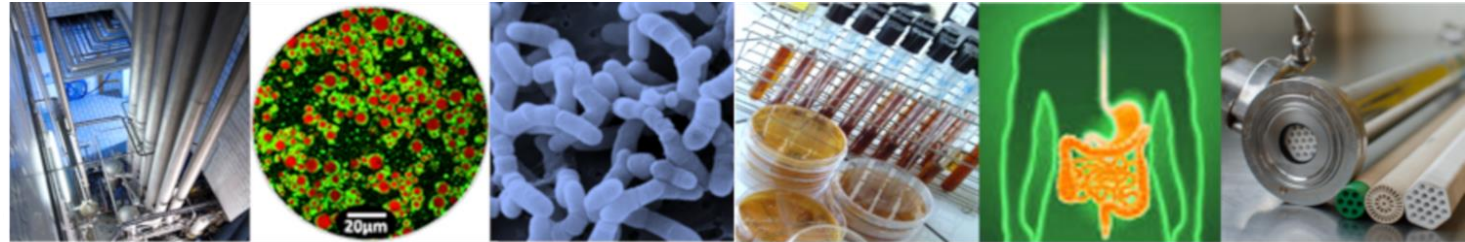
Rennes

Gwenael.jan@inrae.fr

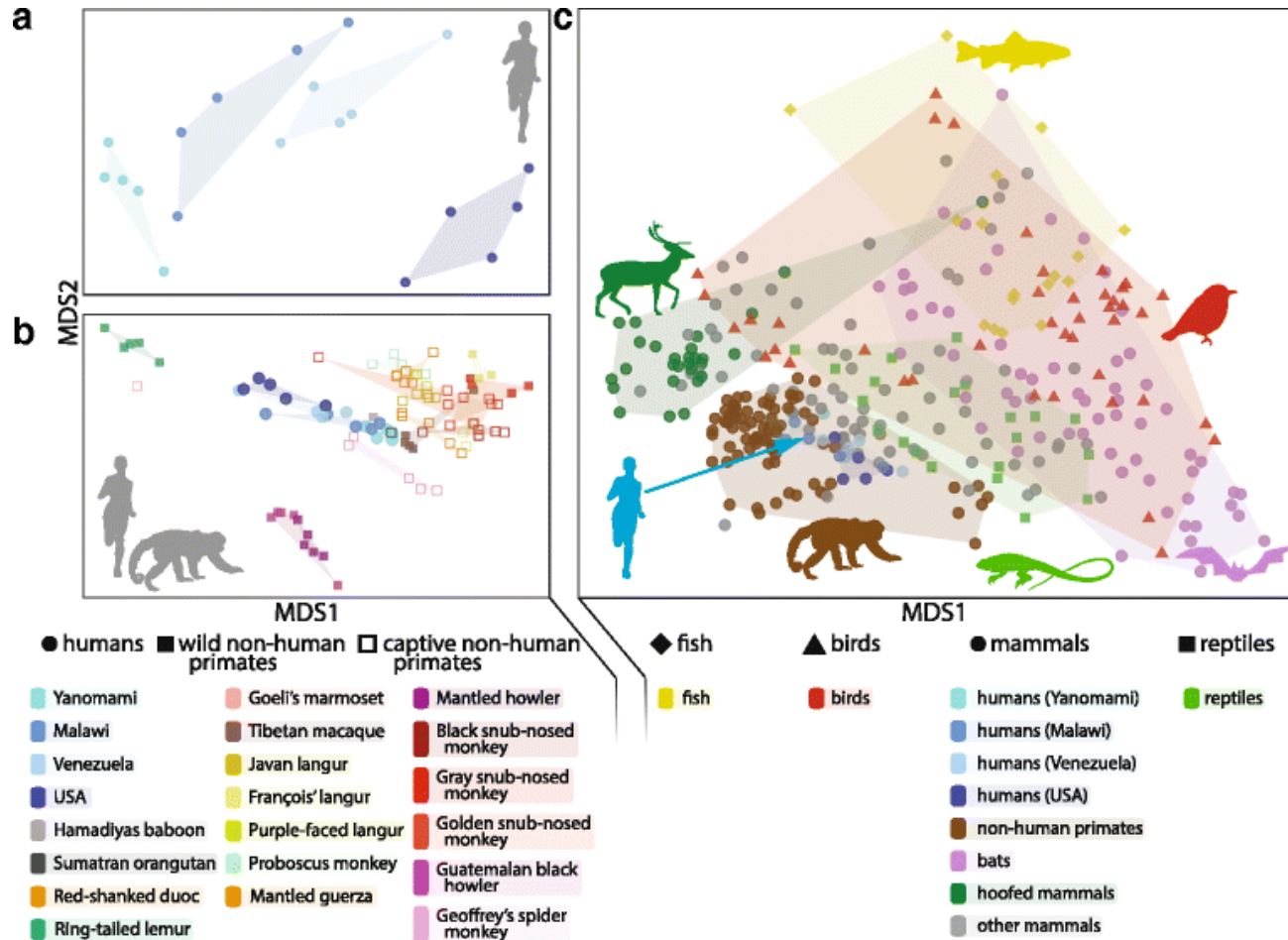
<https://www6.rennes.inrae.fr/stlo>



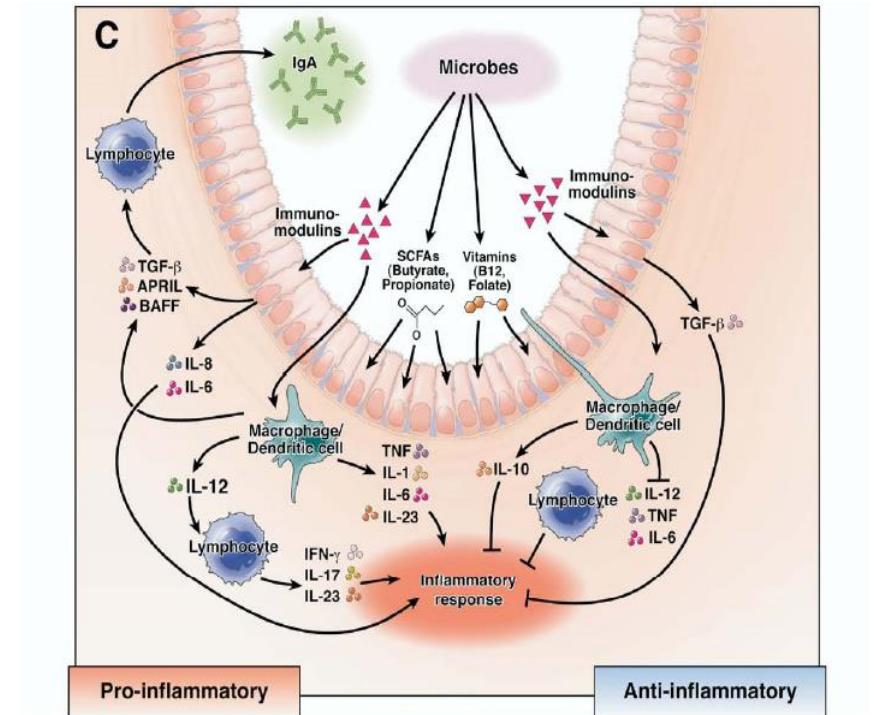
➤ The microbiota and the host, an old story



➤ Coevolution and dependence



Davenport *et al.* BMC Biology (2017)



O'Flaherty *et al.* Gut Microbes (2010)

➔ Our microbiota evolves with us

➔ And we adapt to its products



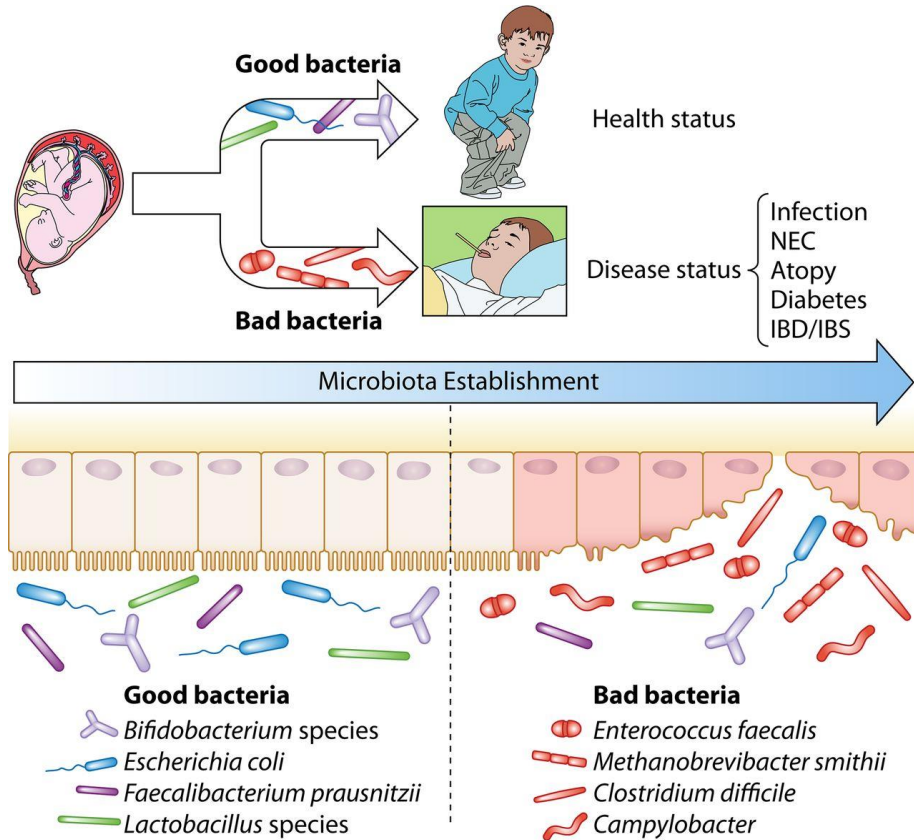
INRAE

Microbiote ingéré, microbiote humain

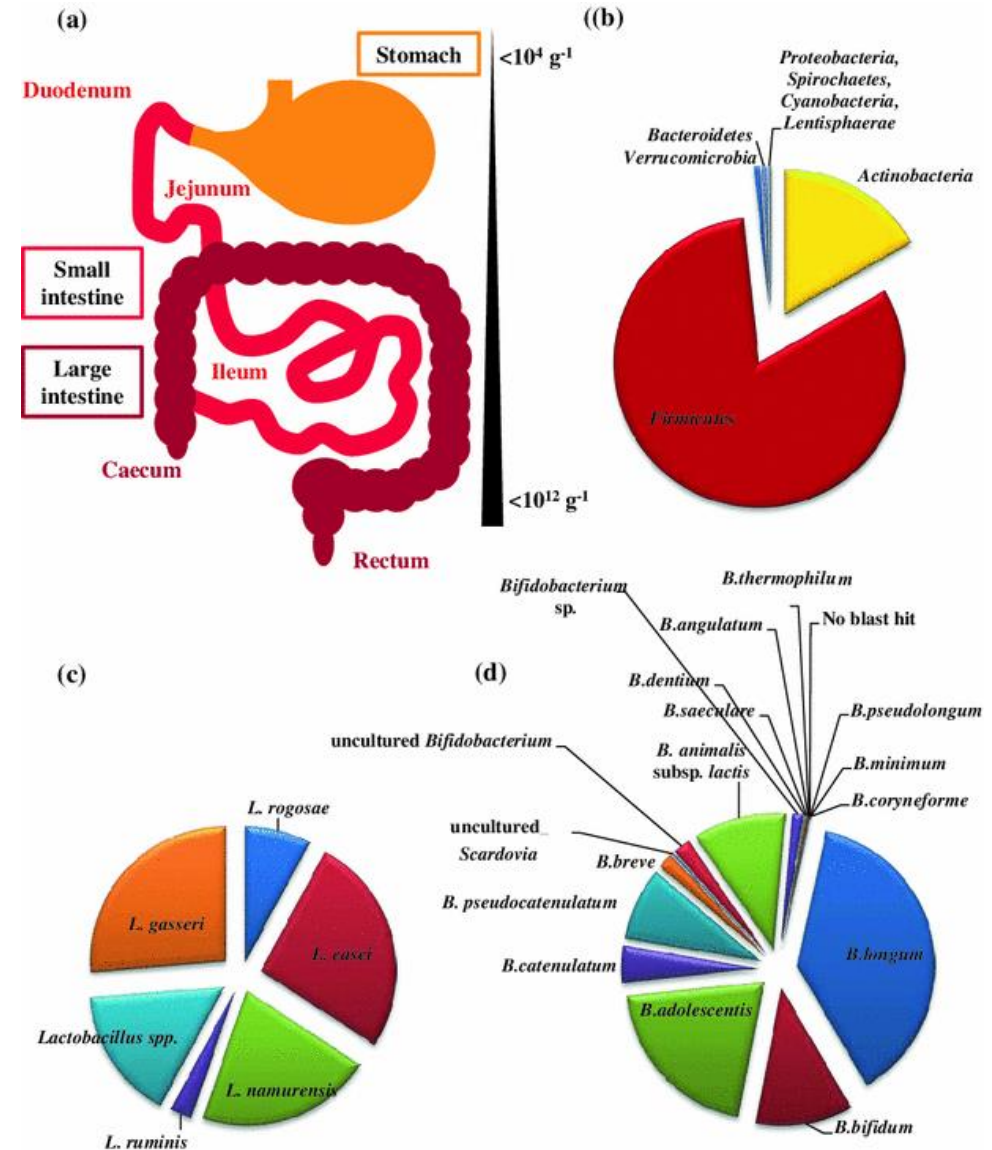
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➤ Our main inhabitants and actors of our health

Good bugs and bad bugs...

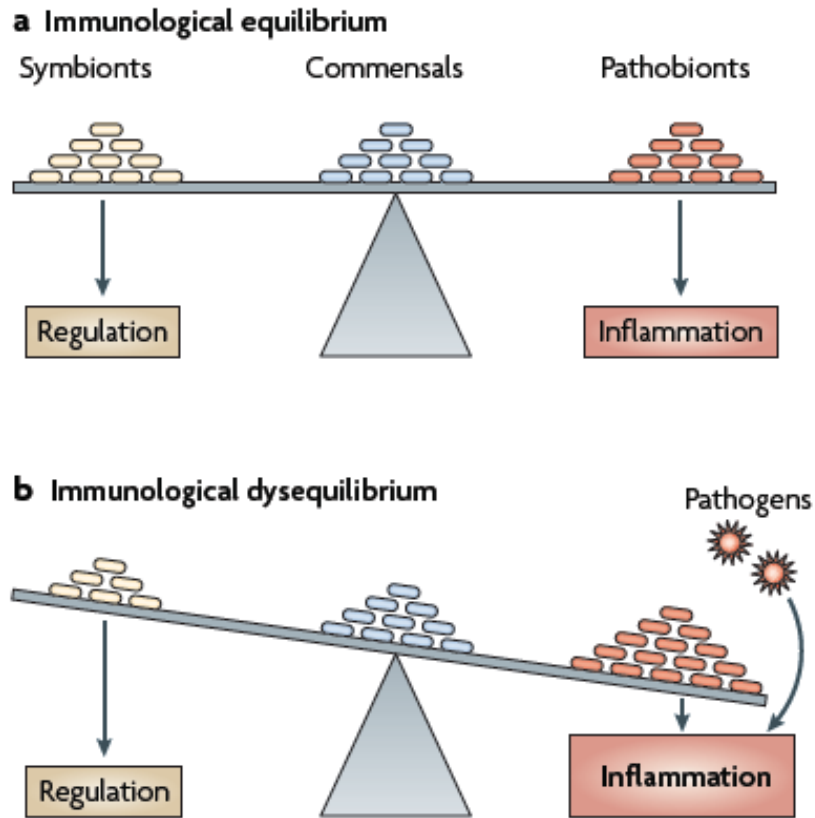


Milani et al. Microbiol.Mol.Biol.Rev. (2017)

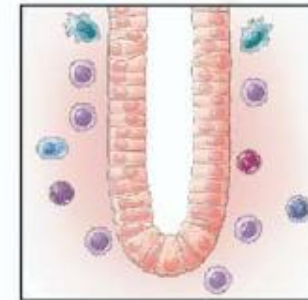


Turroni et al. Cell.Mol.Life Sci. (2014)

➤ A delicate balance



Iannitti & Palmieri. Clinical Nutrition (2010)



“Physiological” or “controlled” inflammation



Inflammatory Bowel Disease

➤ The drama of absence...

nature publishing group

Review

***Bifidobacterium longum* subspecies *infantis*: champion colonizer of the infant gut**

Mark A. Underwood^{1,2}, J. Bruce German^{3,5}, Carlito B. Lebrilla^{2,4} and David A. Mills^{2,3,5}

Oligosaccharides are abundant in human milk. Production of these highly diverse structures requires significant energy expenditure by the mother and yet these human milk oligosaccharides offer no direct nutritive value to her infant. A primary function of human milk oligosaccharides is to shape the infant's intestinal microbiota with life-long consequences. *Bifidobacterium longum* subspecies *infantis* (*B. infantis*) is unique among gut bacteria in its prodigious capacity to digest

***B. infantis* : an anti-inflammatory activity**

and co result c of glyco in other bacterial species. *In vitro*, *B. infantis* grows better than other bacterial strains in the presence of human milk oligosaccharides, displays anti-inflammatory activity in premature intestinal cells, and decreases intestinal permeability. In premature infants, *B. infantis* strains that co-colonize with human milk

***B. infantis* reduces the risk of necrotizing enterocolitis**

B. infantis is also associated with increased vaccine responses. Probiotic organisms have historically been selected based on ease of production and stability. The advantages of *B. infantis*, selected through coevolution with human milk glycans, present an opportunity for focused manipulation of the infant intestinal microbiota.

The colonization of the fetal gut begins *in utero* with swallowing of amniotic fluid. At that point, infants begin a life-long relationship with a community of microorganisms (microbiota) and the gut microbiome) and presumably the health consequences of the phenotype of the gut microbiota occur with rupture of the fetal membranes, birth, initiation of feeding, addition of solid foods, weaning, and interventions such as antibiotics, acid-suppression, and probiotic or probiotic dietary supplements. The predominance of "bifid" microbes in the stools of healthy infants was described more than 100 y ago, prompting the

***B. infantis* enhances the vaccinal response**

hypothesis that human milk contained "bifidogenic factors" that stimulated the growth of these bifidobacteria (1). Prebiotics are dietary supplements that promote health benefits by stimulating the growth and/or activity in the gut lumen of commensal microbes (ideally without stimulating potential pathogens); they do not contain live organisms. Probiotics are dietary supplements that do contain live organisms and are intended to promote health benefits through a variety of mechanisms, including the coevolution of human milk oligosaccharides found in bacterial subspecies, *Bifidobacterium longum* subsp. *infantis* (*B. infantis*) unique in its capacity to consume these oligosaccharides. Note that the species *B. longum* has two subspecies: *B. longum* subsp. *infantis* and *B. longum* subsp. *longum*. These subspecies will be abbreviated as *B. infantis* and *B. longum*, respectively.

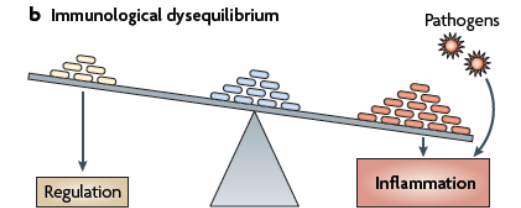
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Prebiotics are dietary supplements that promote health benefits by stimulating the growth and/or activity in the gut lumen of commensal microbes (ideally without stimulating potential pathogens); they do not contain live organisms. Probiotics are dietary supplements that do contain live organisms and are intended to promote health benefits through a variety of mechanisms, including the coevolution of human milk oligosaccharides found in bacterial subspecies,

Bifidobacterium longum subsp. *infantis* (*B. infantis*) unique in its capacity to consume these oligosaccharides. Note that the species *B. longum* has two subspecies: *B. longum* subsp. *infantis* and *B. longum* subsp. *longum*. These subspecies will be abbreviated as *B. infantis* and *B. longum*, respectively.

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Humans stand at the end of the long evolution of mammals, with differences in milk conspicuous for the volume, number of structures, and complexity of milk oligosaccharides (Figure 1) (2–4). Human milk oligosaccharides (HMOs) are the third largest solid component of human milk (after lactose and fat) even in times of famine (5), and yet these free glycans are not digestible by the infant as the human gut does not produce the glycosidases necessary to cleave the HMO linkages. The obvious evolutionary question is: What benefit is provided to the infant that justifies the metabolic expenditure of select gut microbes to deconstruct and consume HMOs (6,7). Among multiple microbial species studied, only two genera, *Bifidobacterium* and *Bacteroides*, are able to comprehensively utilize HMOs as a primary food source (Table 1) (8,9). This relative resistance to microbial consumption allows the HMOs to arrive intact in the distal small bowel and the colon where the largest numbers of commensal bacteria thrive.



RESEARCH ARTICLE

The Journal of Clinical Investigation

Commensal *Propionibacterium* strain UF1 mitigates intestinal inflammation via Th17 cell regulation

Propionibacteria : more frequent in breast-fed infants than in formula-fed ones

Natasha Gomez, Yong Gu, Sridharan Jayaraman, Minghao Song, Morgan Leung, Jennifer E. Brown, Jesse Reed, William C. Fawcett, Elizabeth A. Allen, William H. Miller, David B. Clark, Daniel J. Clark, and Mohammadzadeh^{1,2}

Propionibacteria: mitigate induced necrotizing enterocolitis

¹Department of Pediatrics, University of California, Davis, Sacramento, California, ²Foods for Health Institute, University of California, Davis, Davis, California, ³Department of Food Science and Technology, University of California, Davis, Davis, California, ⁴Department of Chemistry, University of California, Davis, Davis, California, ⁵Department of Virology and Entomology, University of California, Davis, Davis, California. Correspondence: Mark A. Underwood (mark.underwood@ucdmc.ucdavis.edu) of Physiological Sciences, ⁴Division of Neonatology, Department of Pediatrics, and ⁵Interdisciplinary Center for Biotechnology Research, University of Florida, Gainesville, Florida, USA. ⁶Department of Microbiology and Immunology, Loyola University Chicago, Maywood, Illinois, USA. ⁷Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia, USA.

Propionibacteria : regulate Th17 cells

Consumption of human breast milk (HBM) attenuates the incidence of necrotizing enterocolitis (NEC), which remains a leading and intractable cause of mortality in preterm infants. Here, we report that this diminution correlates with alterations in the gut microbiota, particularly enrichment of *Propionibacterium* species. Transfaunation of microbiota from HBM-fed preterm infants or a newly identified and cultured *Propionibacterium* strain, P. UF1, to germfree mice conferred protection against pathogen infection and correlated with profound increases in intestinal Th17 cells. The induction of Th17 cells was dependent on bacterial dihydrolipoamide acetyltransferase (DlaT), a major protein expressed on the P. UF1 surface layer (S-layer). Binding of P. UF1 to its cognate receptor, SIGIRR1, on dendritic cells resulted in the regulation of intestinal phagocytes. Importantly, transfer of P. UF1 profoundly mitigated induced NEC-like injury in neonatal mice. Together, these results mechanistically elucidate the protective effects of HBM and P. UF1-induced immunoregulation, which safeguard against proinflammatory diseases, including NEC.

¹Department of Pediatrics, University of California, Davis, Sacramento, California; ²Foods for Health Institute, University of California, Davis, Davis, California; ³Department of Food Science and Technology, University of California, Davis, Davis, California; ⁴Department of Chemistry, University of California, Davis, Davis, California; ⁵Department of Virology and Entomology, University of California, Davis, Davis, California. Correspondence: Mark A. Underwood (mark.underwood@ucdmc.ucdavis.edu)

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➤ And the healing effect of good bacteria....

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Clinical Investigation

Articles

Probiotics (*Lactobacillus acidophilus* and *Bifidobacterium bifidum*) prevent NEC in VLBW infants fed breast milk but not formula

Andreas Repa¹, Margarita Thanhaeuser¹, David Endress², Michael Weber³, Alexandra Kreissl¹, Christoph Binder¹, Angelika Berger¹ and Nadja Haiden¹



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Microbiology and Molecular
Biology Reviews®

The First Microbial Colonizers of the Human Gut: Composition, Activities, and Health Implications of the Infant Gut Microbiota

Christian Milani,^a Sabrina Duranti,^a Francesca Bottacini,^b Eoghan Casey,^b Francesca Turroni,^{a,c} Jennifer Mahony,^b Clara Belzer,^d Susana Delgado Palacio,^e Silvia Arboleya Montes,^e Leonardo Mancabelli,^a Gabriele Andrea Lugli,^a Juan Miguel Rodriguez,^f Lars Bode,^g Willem de Vos,^{d,h} Miguel Gueimonde,^e Abelardo Margolles,^e Douwe van Sinderen,^b Marco Ventura^{a,c}



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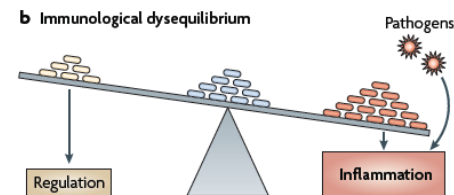
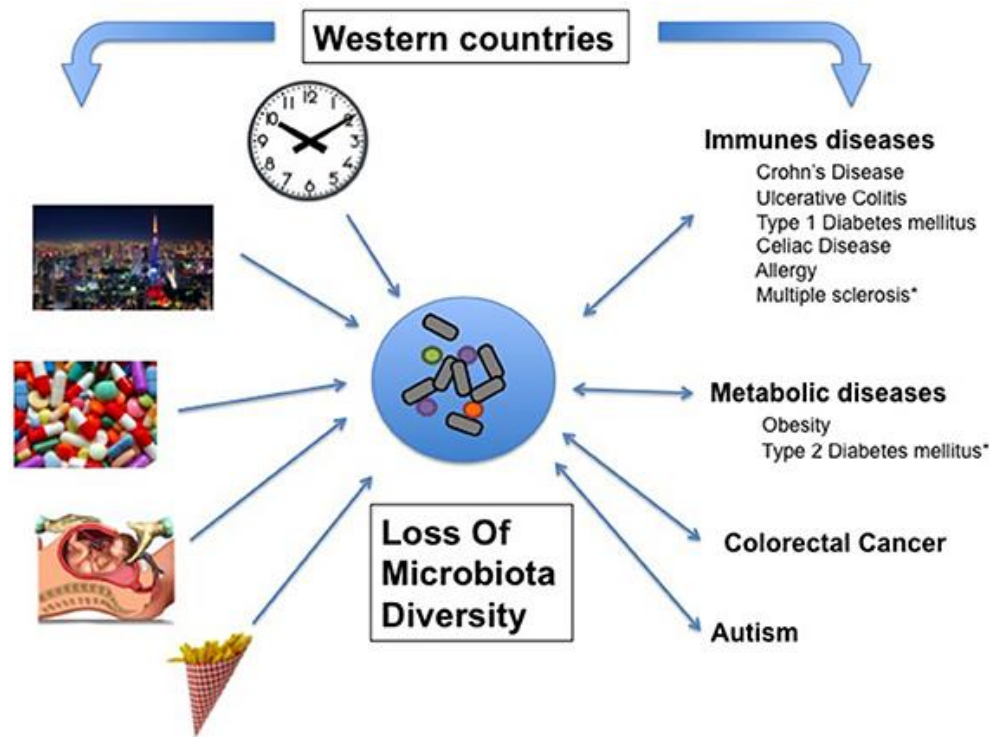
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➤ As in ecology, a key role for biodiversity

➤ A decrease linked to our lifestyle, including a diet from an industrialized country

➤ Reduced biodiversity in many diseases



Disease	LOMD	References	Increased prevalence in western countries	References
IMMUNE DISEASES				
Crohn's Disease	+	Manichanh et al., 2006; Dey et al., 2013; Sha et al., 2013; Matsuoka and Kanai, 2015	+	Lehtinen et al., 2011
Ulcerative Colitis	+	Michail et al., 2012; Sha et al., 2013	+	Lehtinen et al., 2011
Type 1 diabetes mellitus	+	Giongo et al., 2010; De Goffau et al., 2013; Kostic et al., 2015	+	Harjutsalo et al., 2008; Andersson et al., 2014
Multiple Sclerosis	ND	Bhargava and Mowry, 2014	+	Mayr et al., 2003
Celiac Disease	+	Schippa et al., 2010	+	Lohi et al., 2007
Allergy	+	Wang et al., 2008; Ismail et al., 2012; Abrahamsson et al., 2014	+	Latvala et al., 2005; Eder et al., 2006
METABOLIC DISEASES				
Obesity	+	Turnbaugh et al., 2009	+	WHO Obesity and overweight
Type 2 diabetes mellitus	-		+	WHO Diabetes
CANCER				
Colorectal cancer	+	Ahn et al., 2013	+	European Cancer Observatory http://eco.iarc.fr/
OTHERS				
Irritable Bowel Syndrome	+	Carroll et al., 2012; Durbán et al., 2012	-	Lovell and Ford, 2012
Recurrent <i>Clostridium difficile</i> Infection	+	Chang et al., 2008	ND	
Autism	+	Kang et al., 2013	+	Atladdottir et al., 2015
Necrotising Enterocolitis	+	Stewart et al., 2013	ND	
Graft Versus Host Disease	+	Jenq et al., 2012	ND	

WHO | Diabetes WHO. Available at: <http://www.who.int/mediacentre/factsheets/fs312/en/> [Accessed September 29, 2015].

WHO | Obesity and overweight WHO. Available at: <http://www.who.int/mediacentre/factsheets/fs311/en/> [Accessed September 29, 2015].

ND, No Data.

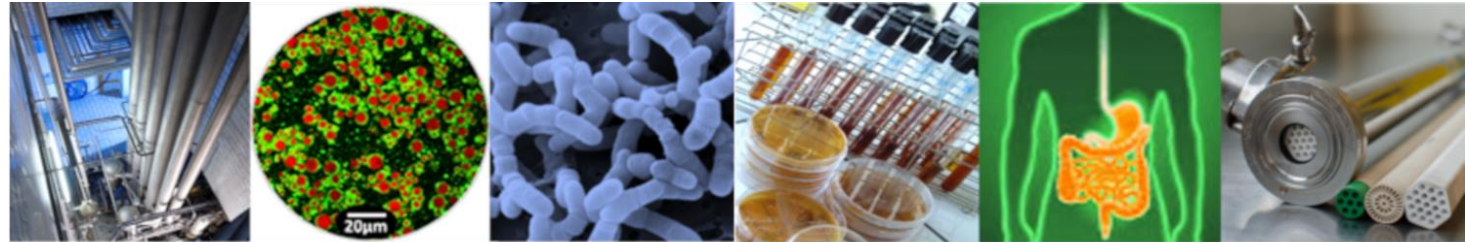


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➤ Diet modulates the microbiota



➤ Diet modulates the microbiota

LETTER

doi:10.1038/nature12820

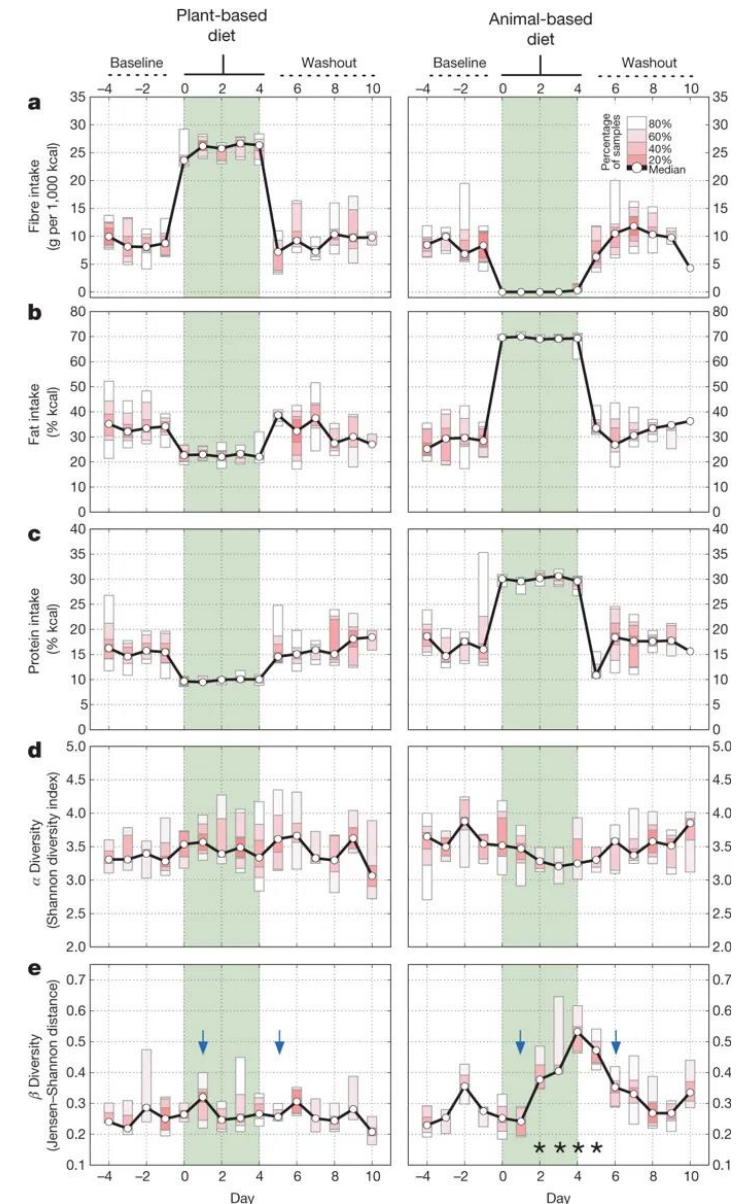
Diet rapidly and reproducibly alters the human gut microbiome

Lawrence A. David^{1,2†}, Corinne F. Maurice¹, Rachel N. Carmody¹, David B. Gootenberg¹, Julie E. Button¹, Benjamin E. Wolfe¹, Alisha V. Ling³, A. Sloan Devlin⁴, Yug Varma⁴, Michael A. Fischbach⁴, Sudha B. Biddinger³, Rachel J. Dutton¹ & Peter J. Turnbaugh¹

A predominantly animal diet increases bile-resistant microbes such as *Bilophila* SP.

A predominantly plant-based diet increases firmicute microbes that degrade plant polysaccharides

Bilophila wadsorthia, a possible link with inflammation

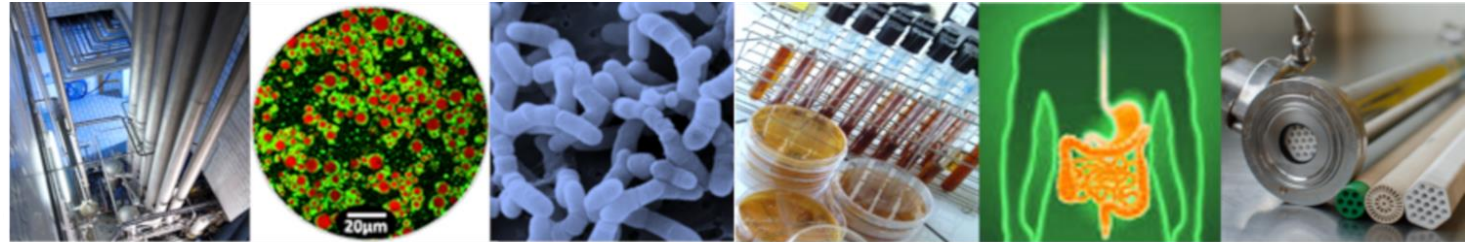


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➤ The diet is a source of microbes



➤ Fermented foods: 30% of our diet



A great gastronomic diversity: 3500 listed in the world

One thing in common:
lactic fermentation
which allows
conservation and
improves hedonic and
nutritional properties!!



➤ A remarkable biodiversity

Pediococcus acidilactici

Lactocobacillus casei

Leuconostoc mesenteroides

Lactococcus lactis

Enterococcus faecium

Lactocobacillus paracasei

Lactocobacillus viridescens



Streptococcus thermophilus

Streptococcus macedonicus

Lactocobacillus plantarum



Lactobacillus bulgaricus

Lactobacillus helveticus



Lactobacillus sakei



Staphylococcus xylosum

Staphylococcus carnosus

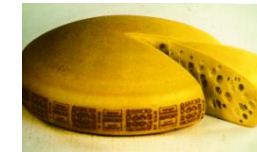


Oenococcus oeni



L. lactis diacetylactis

Propionibacterium freudenreichii



L. lactis cremoris



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YOGURT

Lactic Fermentation

Lactose of lait (glucose+galactose) → lactic acid

Streptococcus thermophilus & *Lactobacillus bulgaricus*



Acidity of the environment, low pH = protection and modification of milk proteins (formation of a gel)

Production of compounds important for the taste

Same composition as milk....i.e. 85% water



125 billion lactic acid bacteria / yogurt

Legislation says: at the expiration date, at least 1 billion must remain alive



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> Cheeses



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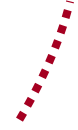
FROMAGES = moyen ancestral de conservation des éléments nutritifs du lait sans aucun conservateur

Bactéries qui se sont
installées spontanément
dans le lait cru



2000 ans
d'expérience ...

Et beaucoup de
bactéries*



Bactéries ajoutées sous
forme de levains, process
contrôlés



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CHEESE = ancestral means of preserving milk nutrients without any preservative

Bacteria originating from the
cow teat, raw milk,
manufacturing environment



2000 years of
experience ...

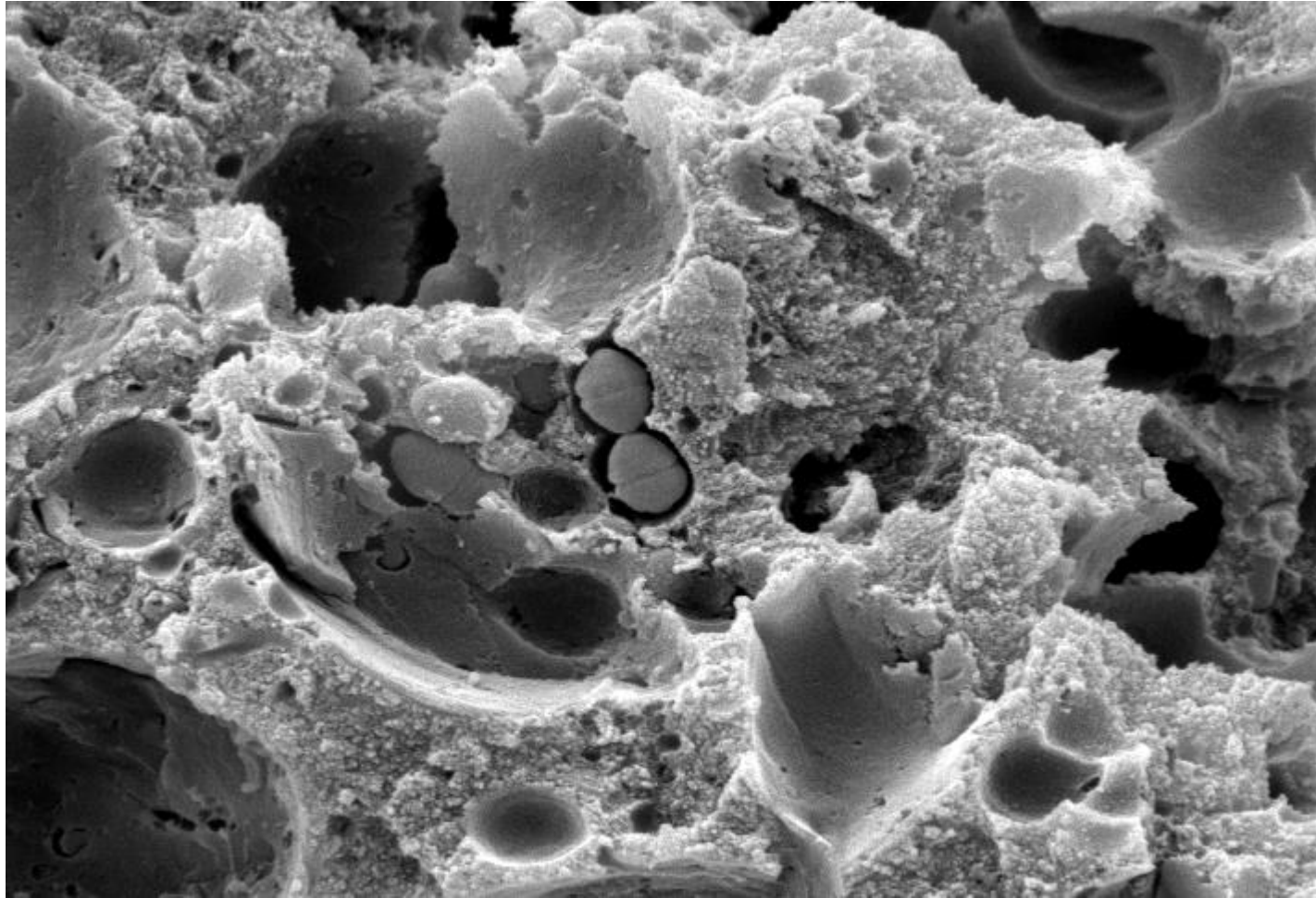
And many
beneficial bacteria



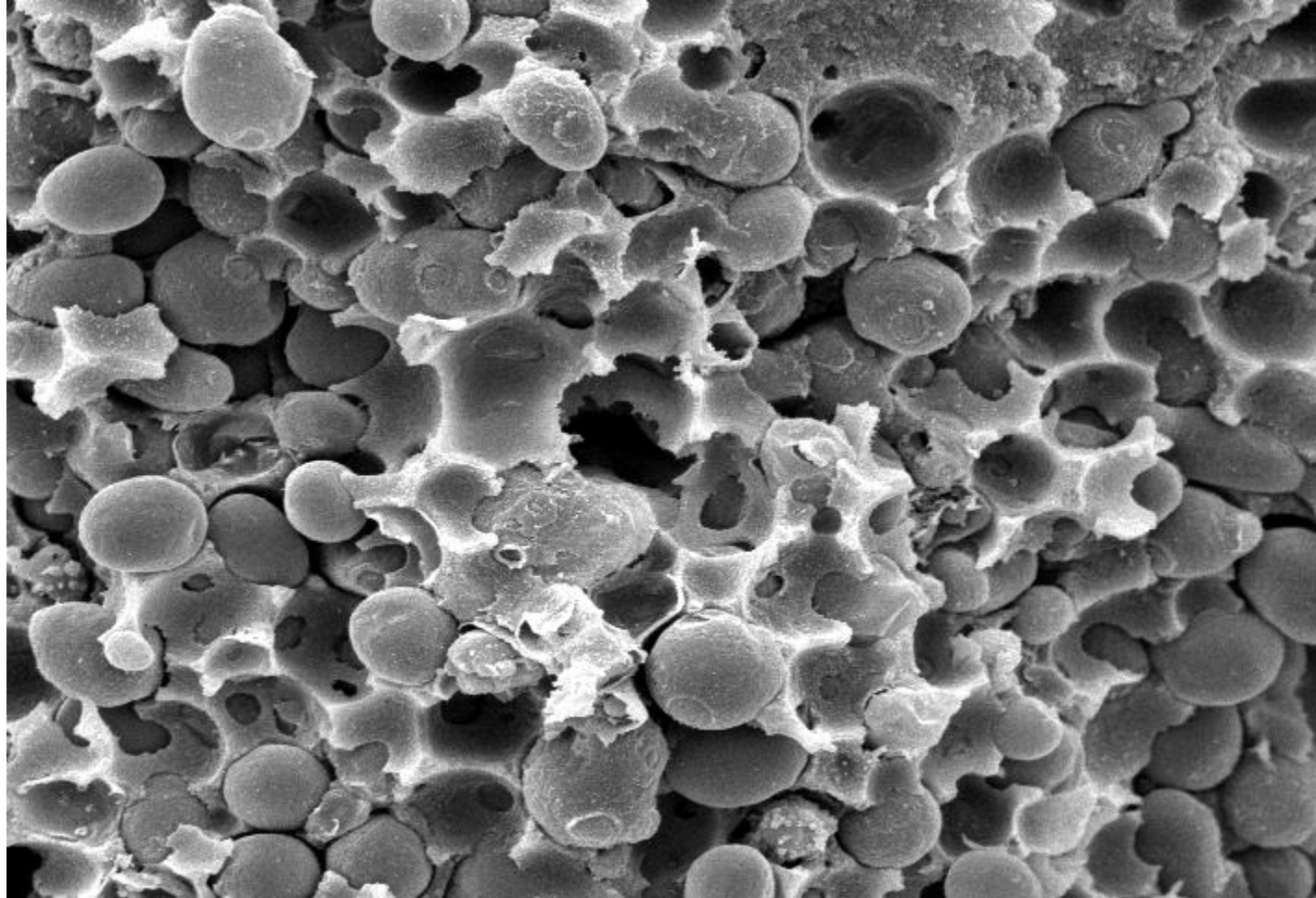
A great
variety of
cheeses

Bacteria now added as
fermentation starters, in a
controlled process

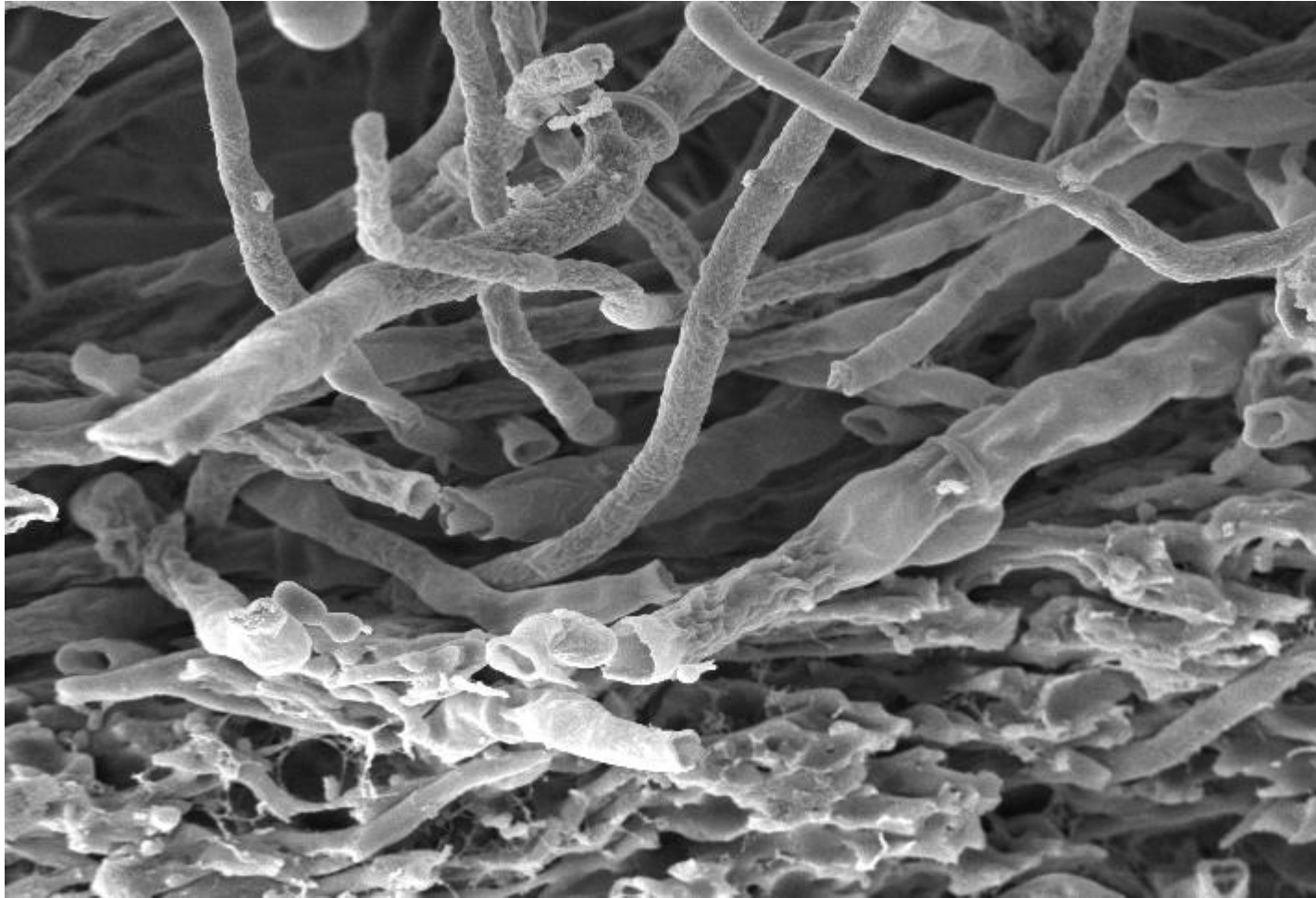
Microorganisms in cheese



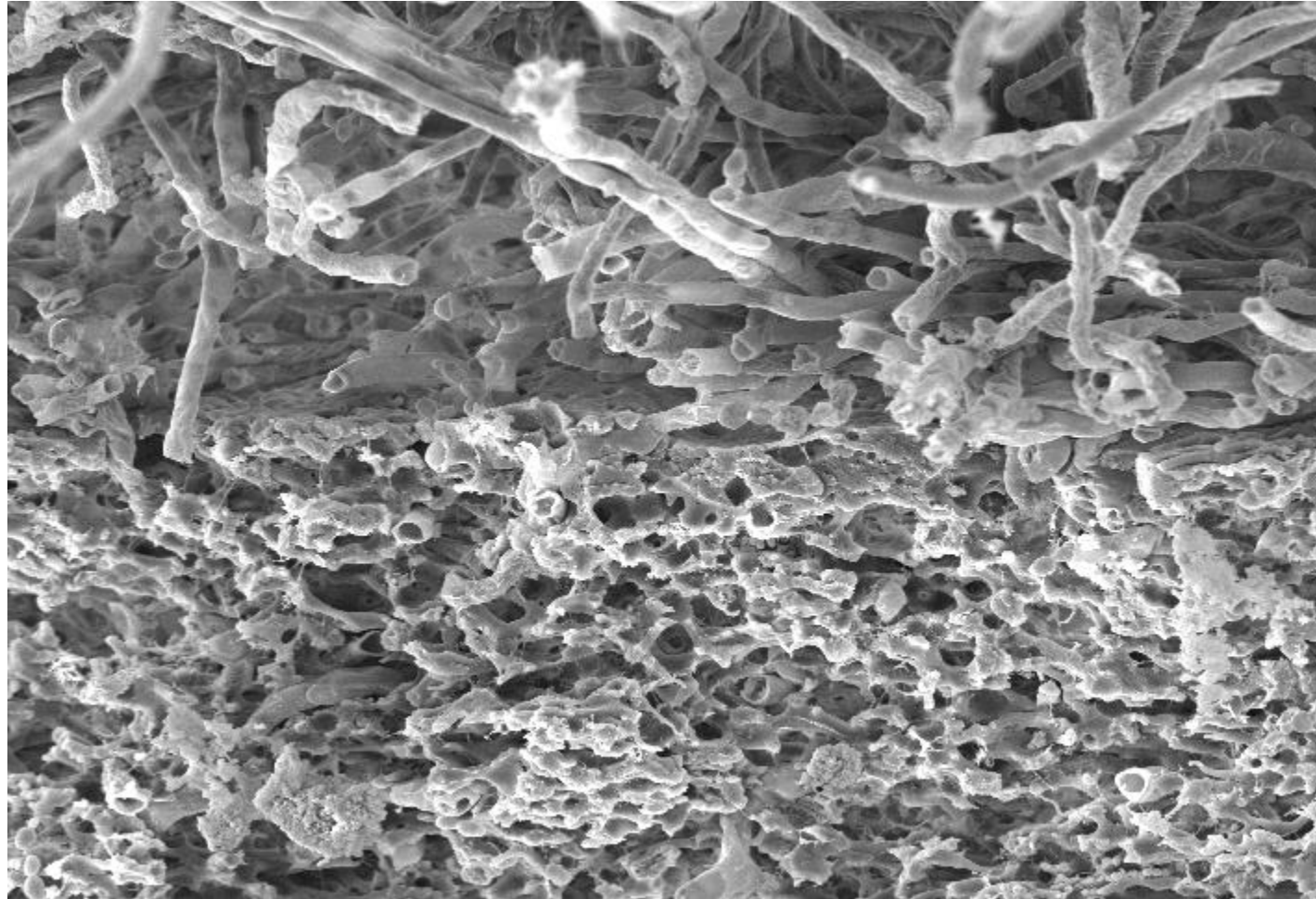
Microorganisms in cheese



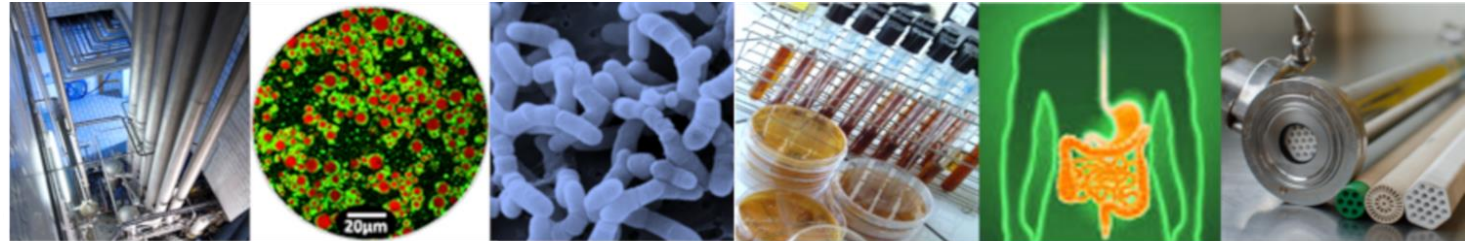
Microorganisms in cheese

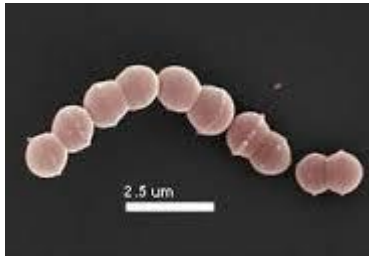


Microorganisms in cheese



➤ Identity Card of the main actors





Streptococcus thermophilus

Genre : Streptococcus

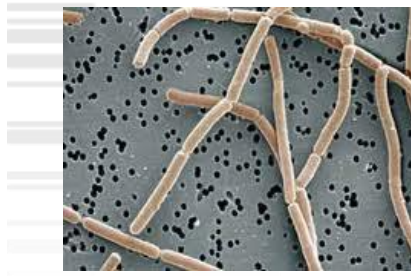
Espèce : thermophilus

Description: coque, Gram+, regroupé en chainettes, non-pathogène, alimentaire, thermophile, bactérie lactique, homofermentaire

Domicile: glande mammaire, lait crû

Terrain de jeux : yaourt, fromages

Profession : acidification, coagulation, protéolyse, saveur



Lactobacillus delbrueckii subsp. *bulgaricus*

Genre : Lactobacillus

Espèce : delbrueckii

Description: bacille, Gram+, non-pathogène, alimentaire, thermophile, bactérie lactique, homofermentaire

Domicile: glande mammaire, lait crû

Terrain de jeux : yaourt, fromages, avec son partenaire *S. thermophilus*

Profession : acidification, coagulation, protéolyse, saveur



Lactobacillus kefiranoficiens

Genre : Lactobacillus

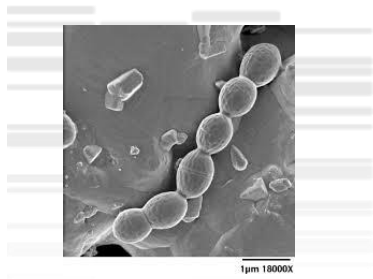
Espèce : *kefiranoficiens*

Description: bacille, Gram+, non-pathogène, alimentaire, thermophile, bactérie lactique, homofermentaire

Domicile: grains de kéfir

Terrain de jeux : kéfir

Profession : acidification, coagulation, protéolyse, saveur



Lactococcus lactis

Genre : Lactococcus

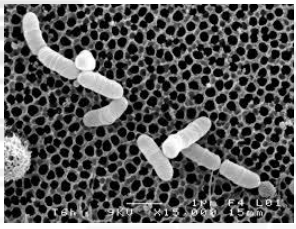
Espèce : lactis

Description: coque, Gram+, non-pathogène, alimentaire, mesophile, bactérie lactique, homofermentaire

Domicile: plantes, tube digestif, glande mammaire

Terrain de jeux : produits laitiers fermentés

Profession : acidification, coagulation, protéolyse, saveur



Propionibacterium freudenreichii

Genre : *Propionibacterium*

Espèce : *freudenreichii*

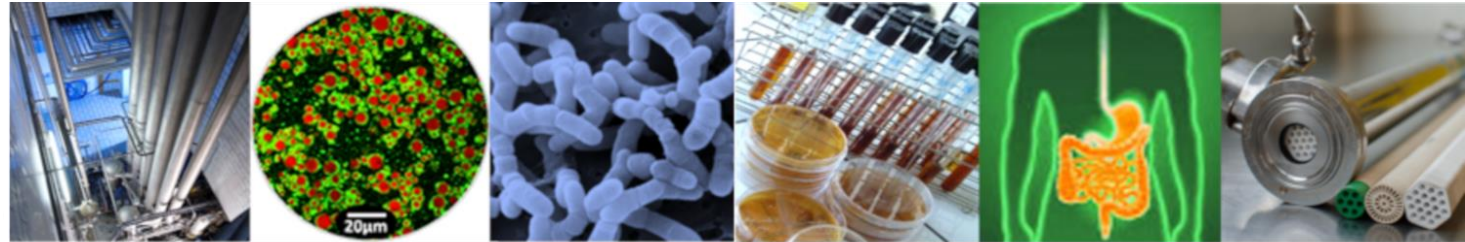
Description: bacille, Gram+, non-pathogène, alimentaire, mesophile, bactérie propionique, hétérofermentaire

Domicile: plantes, tube digestif, glande mammaire

Terrain de jeux : fromages

Profession : aromatiser, texturer

➤ The potent probiotic role of fermented foods



- Did you say probiotic?
Pro : to favour...
Bios : the life?

➤ Probiotics, it's an old story

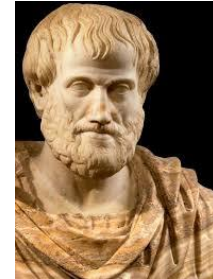
Aristote (384-355 avant JC) in his natural history of animals

✓ Describes the « Kikéon », made from fermented products and qualifies them as « **medicinal magic beverage** »

Pline the elder (23-79 ap JC)

✓ Describes tribes of barbarians « who know how to thicken milk into a matter with a pleasant acidity »

✓ Cites this ancestor of yogurt as “being of a divine nature and serving as a **remedy to many troubles** »



➤ Probiotics, it's an old story

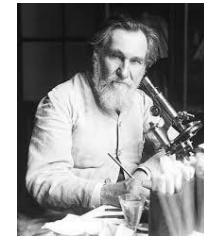
Louis Pasteur

✓ 1860 : Describes **lactic and butyric fermentations** by recently discovered microorganisms



Henry Tissier

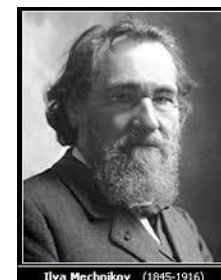
✓ 1889 : Discovers the **bifidobacteria** and recommends consuming them **against diarrhea**



Elie Metchnikov

✓ 1904 : isolates *Lactobacillus bulgaricus*

✓ publishes « **the prolongation of life** »



➤ Probiotics, it's an old story



In 1536, François the 1st had been on the Throne of France for 21 years. The growing rivalry between **François the 1st** (France) and Charles V (Spain) encouraged the former to ally himself beyond the traditional chessboard with the Ottoman Sultan Suleiman the Magnificent



In 1542, **François the 1st** was subject to very severe intestinal disorders. The Turkish sovereign sends him his personal doctor. The latter brings him a yogurt made from sheep's milk. The origin of the word "yogurt" is found in the Turkish word "yogurmark", which means "to knead" or "to thicken". After a cure of several weeks, the sovereign succeeded in putting an end to the gastric problems.



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➤ Probiotics, it's an old story

Product originating from the Balkans

1542, Francis I was cured of intestinal disorders thanks to a sheep's milk yogurt sent by the Ottoman Sultan: Suleiman the Magnificent

1860, discoveries by Pasteur on the role of microorganisms in lactic fermentations

1902, Metchnikoff [1845-1916] isolates the “Bulgarian” lactobacillus specific to this product and the first believes and studies the beneficial role of regular ingestion of yogurt

1930, first industrial production center D. Carasso / Danone

Since 1990, diversification: variety of fermented milks; same fermentation principle + other species added bifidobacteria, other lactobacilli (*Lactobacillus acidophilus*, *Lactobacillus casei*, etc.) “PROBIOTICS”



INRAE

Microbiote ingéré, microbiote humain

Gwénaél JAN, UMR STLO, INRAE, Agrocampus Ouest

➤ Probiotics, what it is ?

2001, Rapport
FAO/WHO:

« Live microorganisms which, when administered in adequate quantities, confer a health benefit to the host »

- micro-organisms: bacteria or yeast**
- living**
- health benefit:**
 - maintaining well-being**
 - preventive action**
 - therapeutic action**
 - via modification of the intestinal flora? not necessarily**



➤ But which bacteria are (or may be) probiotic ?

Lactic acid bacteria

Lactobacillus bulgaricus ; casei ; acidophilus ; johnsonii ; plantarum ; rhamnosus ; reuteri...
Streptococcus thermophilus

Bifidobacteria

B. animalis (lactis) ; B. infantis ; B. longum ; B. bifidum ; B. breve ; B. adolescentis...

But also.....

Escherichia coli (Nissle 1917)

Bacillus

Saccharomyces (*S. cerevisiae* ; *S. boulardii*)

Propionibacteria

Propionibacterium freudenreichii ; Acidipropionibacterium acidipropionici



➤ Which beneficial effects are we talking about ?

In some fields, there are well demonstrated effect:

- Lactose intolerance
 - IBS: irritable bowel syndrome
 - Infectious diarrhea, travellers disease, ATB-associated Diarrhea
 - IBD: Inflammatory Bowel Dideases
- } confort digestif

In others, there are promising tracks:

- Allergies
- Cancer



Sniffen JC, McFarland LV, Evans CT, Goldstein EJC (2018) Choosing an appropriate probiotic product for your patient: An evidence-based practical guide. PLOS ONE 13(12): e0209205. <https://doi.org/10.1371/journal.pone.0209205> <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0209205>

Table 2. Graded recommendations for probiotic formulations for the prevention or treatment of 19 different types of diseases.

Type of disease	No. of study arms	Strong evidence* (no. + RCTs/no. negative RCTs)	Moderate evidence* (no. + RCTs/no. negative RCTs)	Weak to not effective* (no. + RCTs/no. negative RCTs)
Prevention				
Allergy	3	None	None	<i>L. rhamnosus</i> GG (1+/2-)
Antibiotic-Associated Diarrhea (AAD)	61	<i>S. boulardii</i> 1-745 (18+/9-) LaLeLr mix (3+/1-) <i>L. casei</i> DN114001 (2+/0-)	<i>E. faecalis</i> SF38 (2+/1-)	LhLr mix (3+/3-) <i>L. rhamnosus</i> GG (4+/6-) <i>C. butyricum</i> 588 (1+/2-) <i>L. acidophilus</i> La5 + <i>B. lactis</i> Bb12 (1+/5-)
Prevention <i>C. difficile</i> infections (CDI)	23	None	None	<i>S. boulardii</i> (1+/11-) LaLeLr mix (2+/2-) <i>L. rhamnosus</i> GG (1+/4-) <i>L. casei</i> 114001 (1+/1-)
<i>H. pylori</i> (side effects of therapy)	16	<i>S. boulardii</i> 1-745 (7+/2-) LhLr mix (2+/0-)	<i>L. rhamnosus</i> GG (3+/2-)	None
Enteral feed associated diarrhea	3	<i>S. boulardii</i> 1-745 (3+/0-)	None	None
Necrotizing Enterocolitis (NEC)	17	<i>L. rhamnosus</i> GG + lactoferrin (2+/0-) <i>B. infantis</i> + <i>B. lactis</i> + <i>Strept. thermophilus</i> (2+/0-)	None	<i>L. rhamnosus</i> GG (0+/2-) <i>S. boulardii</i> (0+/3-) <i>L. reuteri</i> 17938 (1+/3-) <i>B. lactis</i> Bb12 (0+/2-) <i>L. acidophilus</i> + <i>B. bifidum</i> (1+/1-)
Nosocomial infections	2	None	None	<i>L. rhamnosus</i> GG (1+/1-)
Respiratory tract infections	10	None	None	<i>L. rhamnosus</i> GG (3+/3-) <i>L. casei</i> 114001 (2+/2-)
Surgical infections	8	Synbiotic PpLmLpLp (4+/1-)	None	<i>L. plantarum</i> 299v (1+/2-)
Traveler's diarrhea	7	<i>S. boulardii</i> 1-745 (4+/1-)	None	<i>L. rhamnosus</i> GG (1+/1-)
Urinary Tract Infections	3	None	None	<i>L. rhamnosus</i> GG (0+/3-)
Treatment				
Adult acute diarrhea	9	<i>S. boulardii</i> 1-745 (4+/2-)	<i>E. faecalis</i> SF68 (2+/1-)	None
<i>C. difficile</i> recurrence	4	<i>S. boulardii</i> 1-745 (2+/0-)	None	<i>L. rhamnosus</i> GG (0+/2-)
Colic	4	<i>L. reuteri</i> 17938 (4+/0-)	None	None
Constipation	3	None	<i>B. lactis</i> 173010 (2+/1-)	None
<i>H. pylori</i> eradication	35	LhLr mix (4+/1-)	<i>L. acidophilus</i> La5 + <i>B. lactis</i> Bb12 mix (3+/2-)	<i>S. boulardii</i> 1-745 (4+/11-) <i>L. rhamnosus</i> GG (0+/4-) <i>L. acidophilus</i> LB (1+/2-) <i>C. butyricum</i> 588 (0+/3-)
Inflammatory Bowel Disease (IBD)	25	8-strain mix (8+/2-)	<i>S. boulardii</i> 1-745 (2+/1-)	<i>L. rhamnosus</i> GG (1+/6-) <i>E. coli</i> Nissle (0+/5-)
Irritable Bowel Syndrome (IBS)	23	<i>L. plantarum</i> 299v (4+/1-) <i>B. infantis</i> 35624 (3+/1-)	None	<i>L. rhamnosus</i> GG (2+/2-) <i>S. boulardii</i> 1-745 (2+/2-) 8-strain mix (2+/2-) <i>B. lactis</i> 173010 (1+/1-)
Pediatric acute diarrhea	61	<i>S. boulardii</i> 1-745 (25+/4-) <i>L. rhamnosus</i> GG (10+/3-) <i>L. reuteri</i> 17938 (3+/0-) <i>L. acidophilus</i> LB (3+/1-) <i>L. casei</i> DN114001 (3+/0-) <i>Bac. clausii</i> mix (O/C, N/R84, T84, Sin8 (3+/1-) 8-strain mix (2+/0-)	LhLr (2+/1-)	None

*Strong evidence: net of ≥ 2 more RCT with significant findings; moderate evidence net of 1 more RCT with significant findings; weak, same number of significant and non-significant trials and not effective, net of > 1 RCT with non-significant findings compared to studies with significant findings.

Abbreviations: B., *Bifidobacterium*; Bac., *Bacillus*; C., *Clostridium*; E., *Enterococcus*; H., *Helicobacter*; LaLeLr mix, *L. acidophilus* CL1285 + *L. casei* Lbc80e + *L. rhamnosus* CLR2 (Bio-K+); LhLr mix, *L. helveticus* RS2 (CNCM 1-1722) + *L. rhamnosus* R11 (CNCM 1-1720), Lactidofil; S., *Saccharomyces*; Synbiotic PpLmLpLp, *Pedococcus pentosaceus* 5-33:3, *Leuconostoc mesenteroides* 77:1, *L. paracasei* ssp. *paracasei* F19, *L. plantarum* 2362 and four fibers (inulin, oat bran, pectin, starch); 8-strain mix (*Bifido. longum* BL03, *Bifido. infantis* subsp. *lactis* BJ04, *Bifido. breve* BB02, *L. acidophilus* BA05, *L. plantarum* BP06, *L. paracasei* BP07, *L. helveticus* BD08, *Strept thermophilus* BT01, VSL#3)

<https://doi.org/10.1371/journal.pone.0209205.t002>

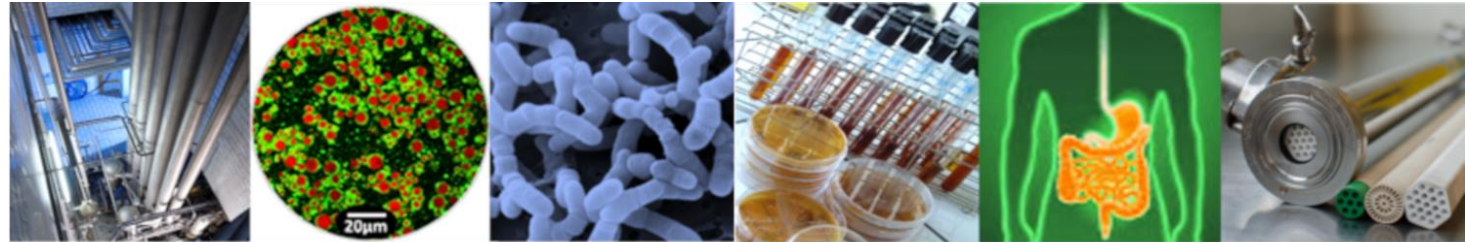


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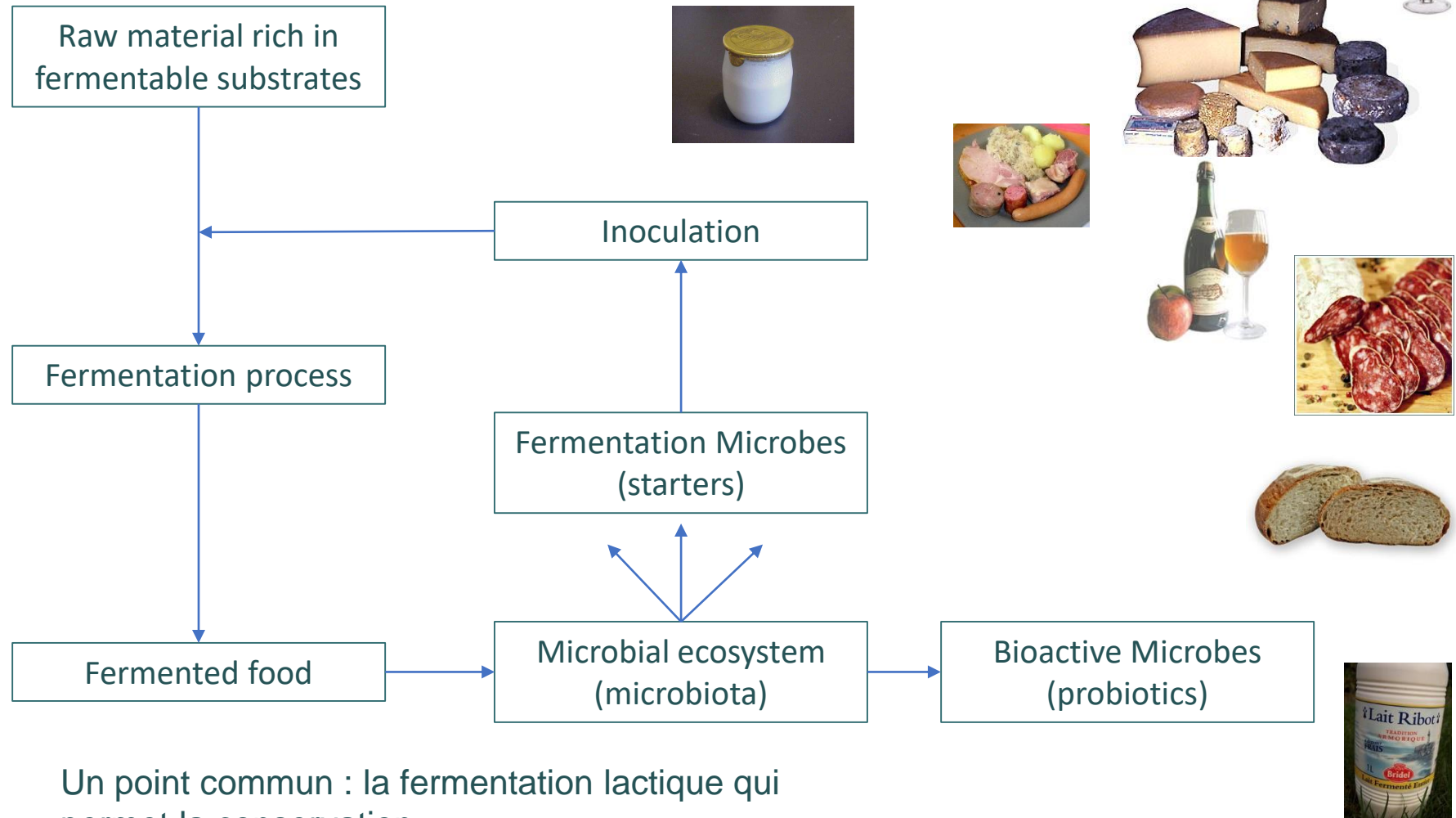
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Gwénaél JAN, UMR STLO, INRAE, Agrocampus Ovest

➤ How Fermentation Makes a Food Probiotic



➤ How does fermentation work?

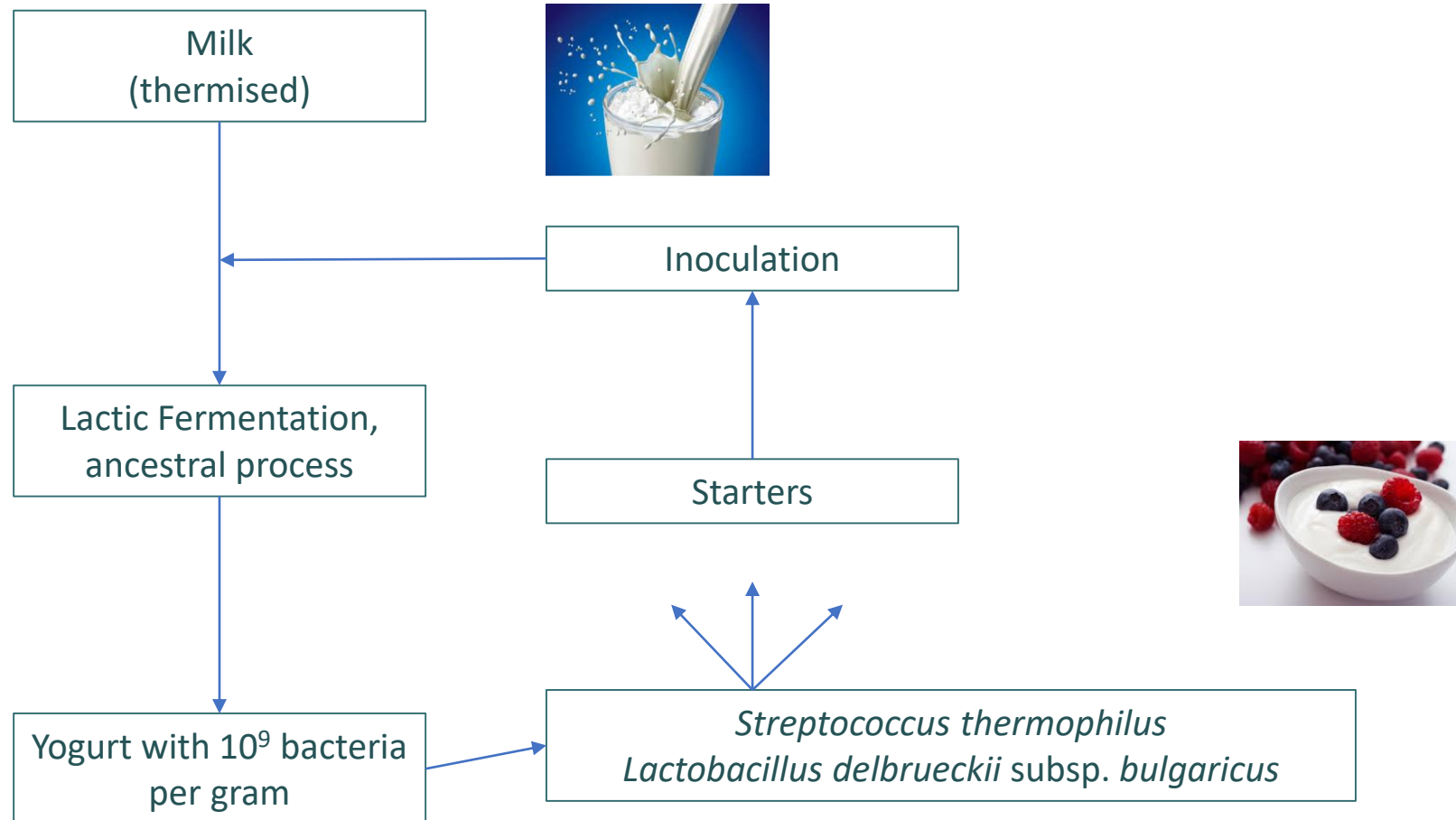


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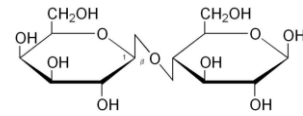
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Gwénaél JAN, UMR STLO, INRAE, Agrocampus Ouest

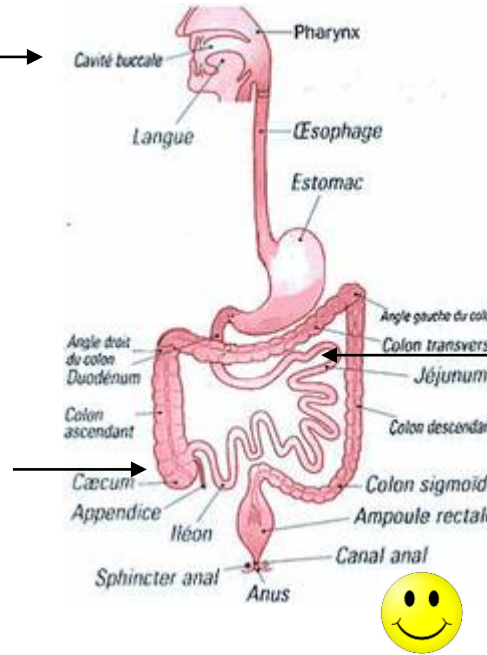
➤ Yogurt, the typical probiotic food



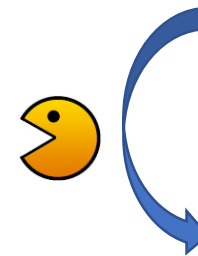
➤ Talking about digestion of lactose



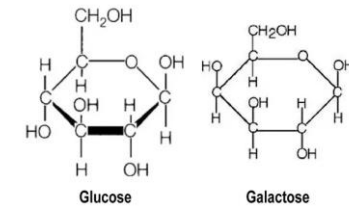
lactose



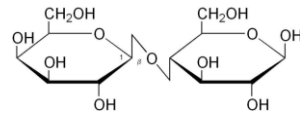
lactase



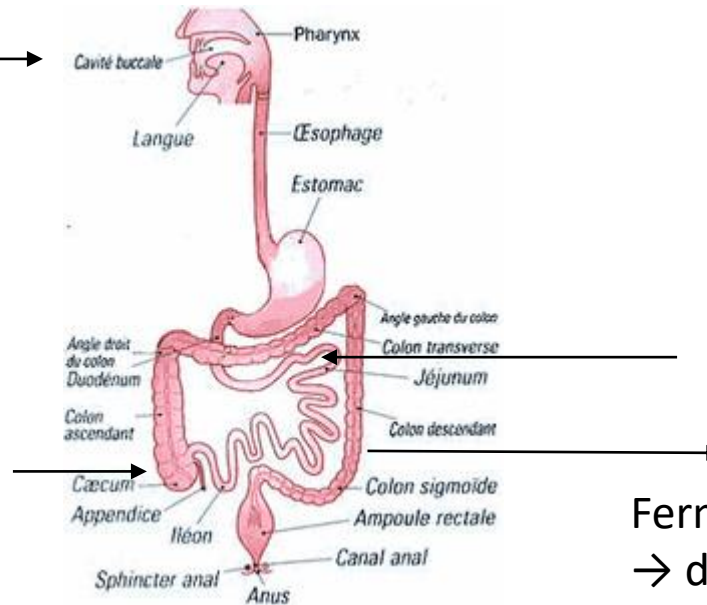
lactose



➤ Lactose intolerance: what is it?



lactose



Lactose in the colon

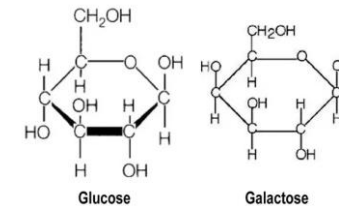
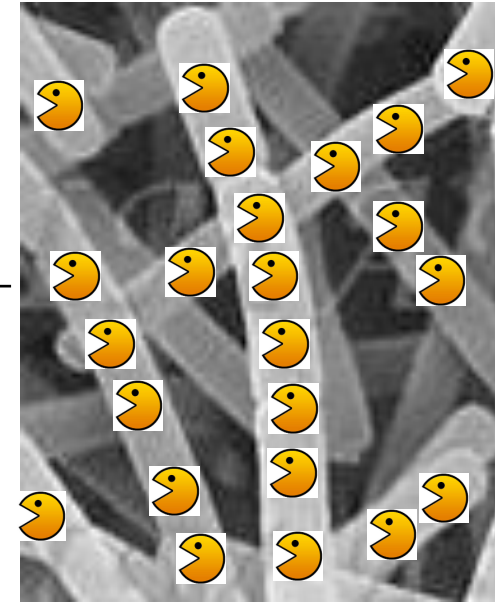
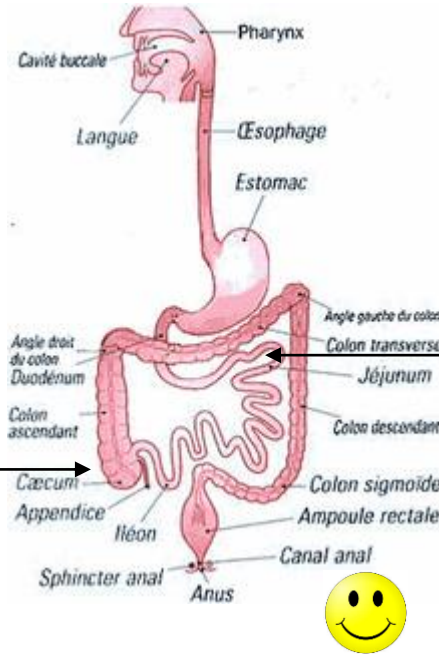
lactase



Fermentation by anaerobes
→ diarrhea
→ nausea
→ bloating
→ flatulence



➤ And, now, the effects of yogurt consumption

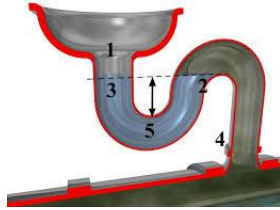


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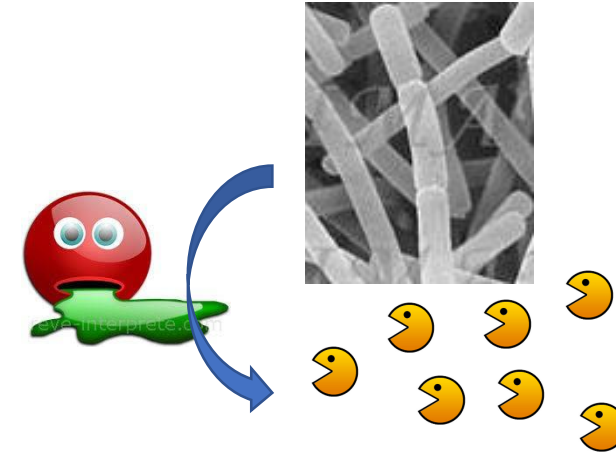
Gwénaél JAN, UMR STLO, INRAE, Agrocampus Ovest

➤ Yogurt, how does it work ?



Slowing of gastric emptying

- Viscosity
- Osmolarity
- Acidity
- Complexity of the food matrix



Restoration of lactase activity

- Intake of β -galactosidase
- Permeabilization by bile
- Release of the enzyme
- Enzyme-substrate meeting
- More lactose in the colon

The consumption of live culture in yogurt improved digestion of lactose in individuals with lactose maldigestion, EFSA, 2010.

Editor's note: there are thermophilic streptococci and lactobacilli in Emmental cheeses too!!!

➤ Other effects of yogurt consumption

Consumption of fermented and nonfermented dairy products: effects on cholesterol concentrations and metabolism

FREE

Marie-Pierre St-Onge, Edward R Farnworth, Peter JH Jones ✉

The American Journal of Clinical Nutrition, Volume 71, Issue 3, March 2000,

Pages 674–681, <https://doi.org/10.1093/ajcn/71.3.674>

Published: 01 March 2000 Article history ▼

St-Onge et al., 2000, Am. J. Clin. Nutr



« high fat diet » rats

milk

yogurt

↓ Triglycerides
↓ Cholesterol LDL
In the blood



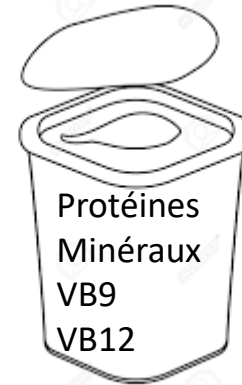
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Current Opinion in
Biotechnology

Bacteria as vitamin suppliers to their host: a gut microbiota perspective

Jean Guy LeBlanc¹, Christian Milani², Graciela Savoy de Giori^{1,3},
Fernando Sesma¹, Douwe van Sinderen⁴ and Marco Ventura²



Bacteria make vitamins

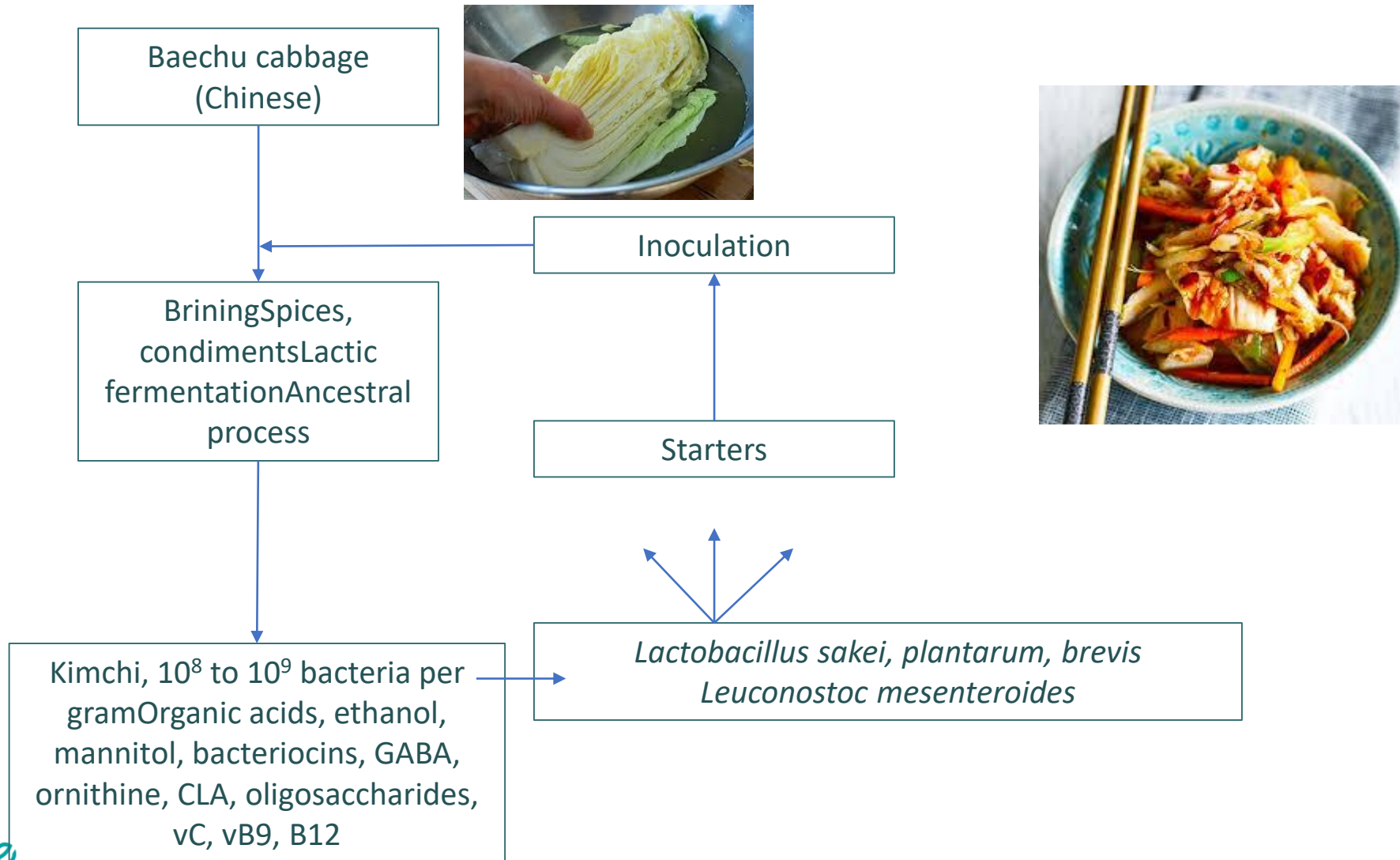


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➤ Kimchi, a traditional fermented plant food



➤ *Lactobacillus plantarum*, the kimchi bacteria known clinically



Online Submissions: <http://www.wjgnet.com/esps/>
wjg@wjgnet.com
doi:10.3748/wjg.v18.i30.4012

World J Gastroenterol 2012 August 14; 18(30): 4012-4018
ISSN 1007-9327 (print) ISSN 2219-2840 (online)
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BRIEF ARTICLE

Clinical trial: *Lactobacillus plantarum* 299v (DSM 9843) improves symptoms of irritable bowel syndrome

Philippe Ducrotté, Prabha Sawant, Venkataraman Jayanthi

IBS, irritable bowel syndrome
Functional disorder
Transit disruption
Abdominal pain
Flatulence

Effect of *Lactobacillus plantarum* consumption

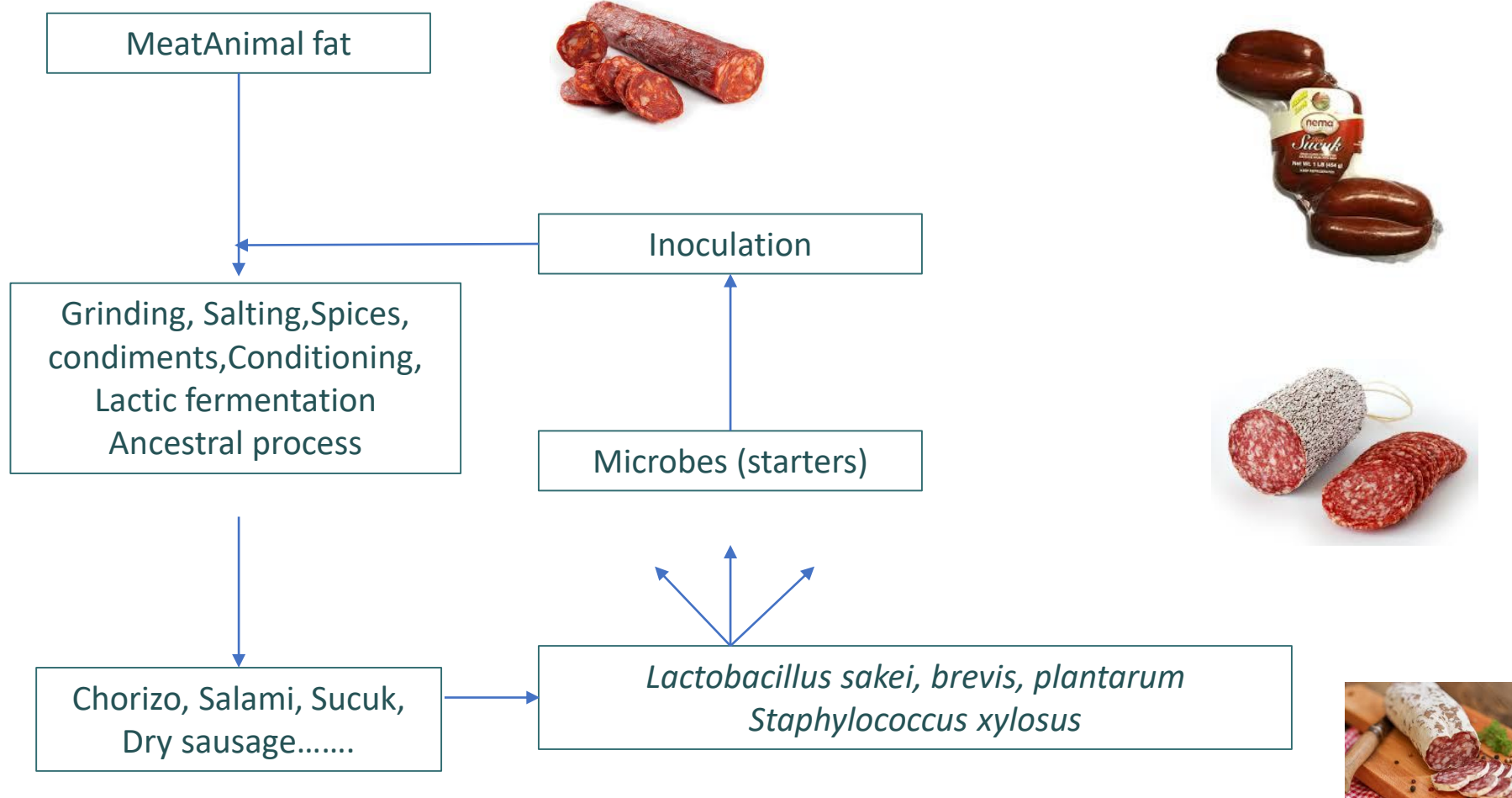
- ↓ severity of visceral pain
- ↓ defecation frequency
- ↓ bloating

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➤ Fermented sausages, meat cheeses



➤ *Lactobacillus sakei*, an emerging probiotic?



Annals of Allergy, Asthma & Immunology

Volume 104, Issue 4, April 2010, Pages 343-348



Original article

Intervention

Effect of *Lactobacillus sakei* supplementation in children with atopic eczema–dermatitis syndrome

Sung-Il Woo MD *, Ji-Yoon Kim MD *, Yong-Ju Lee MD *, Nam-Shik Kim PhD†, Youn-Soo Hahn MD, PhD * 人 ✉

CONCLUSIONS:

Supplementation of *L. sakei* in children with AEDS was associated with a substantial clinical improvement and a significant decrease in chemokine levels, reflecting the severity of AEDS.



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➤ What bacteria can do for us

Vitamines

Hypersensibilité viscérale

Perméabilité intestinale

Inflammation

Immunité

Prolifération

Différenciation

Maldigestion



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➤ Control the microbiota of a cheese by reverse engineering?

Molecular Nutrition
Food Research

Mol. Nutr. Food Res. 2016, 60, 935–948

DOI 10.1002/mnfr.201500580

935

RESEARCH ARTICLE

Combining selected immunomodulatory *Propionibacterium freudenreichii* and *Lactobacillus delbrueckii* strains: Reverse engineering development of an anti-inflammatory cheese

*Coline Plé¹, Jérôme Breton¹, Romain Richoux², Marine Nurdin², Stéphanie-Marie Deutsch^{3,4},
Hélène Falentin^{3,4}, Christophe Hervé⁵, Victoria Chuat^{3,4,6}, Riwanon Lemée⁵,
Emmanuelle Maguin^{7,8}, Gwénaél Jan^{3,4}, Maarten Van de Guchte^{7,8} and Benoit Foligné¹*



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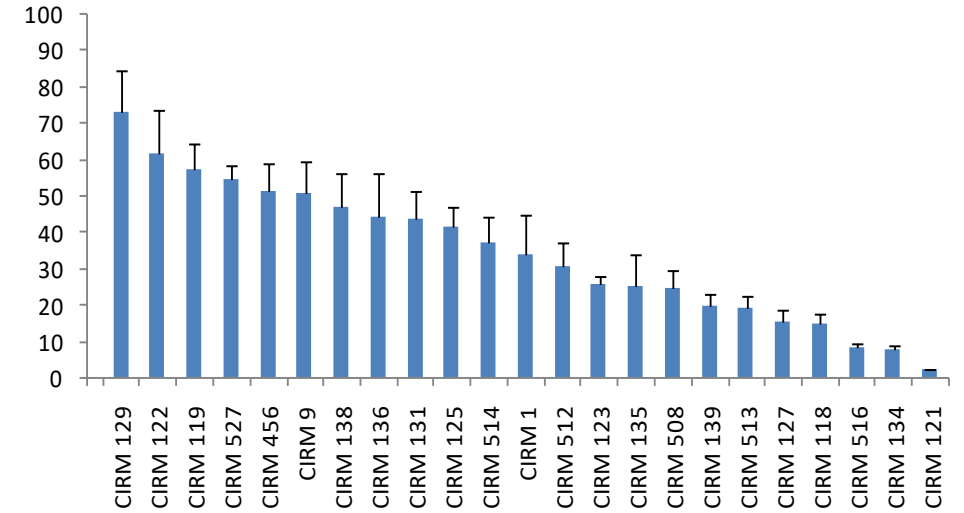
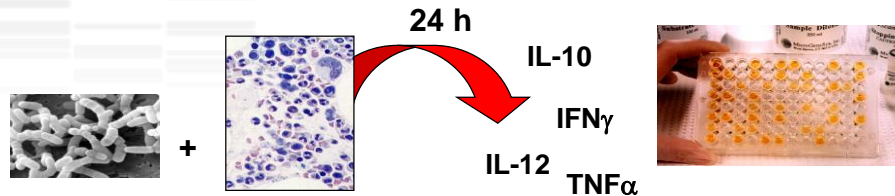
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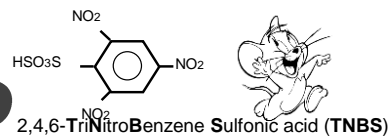


➤ Select probiotic propionic starters

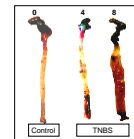
◆ *In vitro*



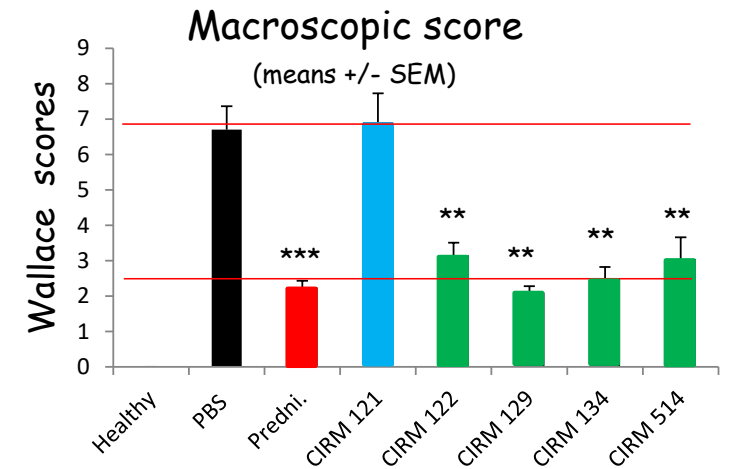
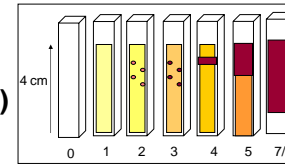
◆ *In vivo*



Acute colitis



Macroscopic score (Wallace)



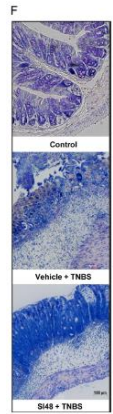
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Gwénaél JAN, UMR

Valorial
OSONS L'ALIMENT, PLUS INTELLIGENT



➤ Making an experimental cheese by reverse engineering



Lait microfiltré

↓
Poudre 100 g/L



↓
Crème 150 g/L

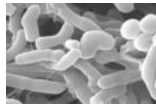


↓
Stérilisation

↓
Culture *P. freudenreichii*

30°C, 72 h

↓
préfromage



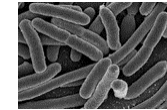
Lait écrémé UHT



↓
Culture *L. delbrueckii*

42°C, 4 h

↓
Lait fermenté



↓
Coagulation, décaillage,
brassage, cuisson, moulage,
pressage, emballage

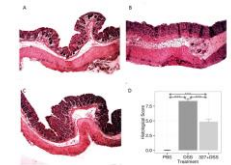


OPEN ACCESS Freely available online



Local and Systemic Immune Mechanisms Underlying the Anti-Colitis Effects of the Dairy Bacterium *Lactobacillus delbrueckii*

Clarissa Santos Rocha^{1,2,4}, Ana Cristina Gomes-Santos², Thais Garcias Moreira², Marcela de Azevedo¹, Tessalia Diniz Luerce¹, Mahendra Mariadassou³, Ana Paula Longaray Delamare³, Philippe Langella^{1,4}, Emmanuelle Maguin^{3,5}, Vasco Azevedo¹, Ana Maria Caetano de Faria², Anderson Miyoshi^{1,3}, Maarten van de Guchte^{1,4,9}



APPLIED AND ENVIRONMENTAL MICROBIOLOGY, Dec. 2010, p. 8259-8264
0099-2240/10/\$12.00 doi:10.1128/AEM.01976-10
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Vol. 76, No. 24

Promising Immunomodulatory Effects of Selected Strains of Dairy Propionibacteria as Evidenced *In Vitro* and *In Vivo*[†]

Benoît Foligné,^{1,2,3,4} Stéphanie-Marie Deutsch,^{5,6} Jérôme Breton,^{1,2,3,4} Fabien J. Cousin,^{5,6,7} Joëlle Dewulf,^{1,2,3,4} Michel Samson,⁸ Bruno Pot,^{1,2,3,4} and Gwénaél Jan^{5,6*}

**...as a research tool
...but...far from real products**



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Gwénaél JAN, UMR

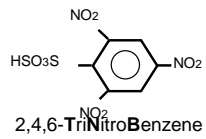
Valorial
OSONS L'ALIMENT, PLUS INTELLIGENT



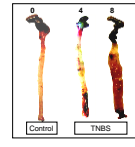
AGENCE NATIONALE DE LA RECHERCHE
ANR

➤ Get the proof of concept

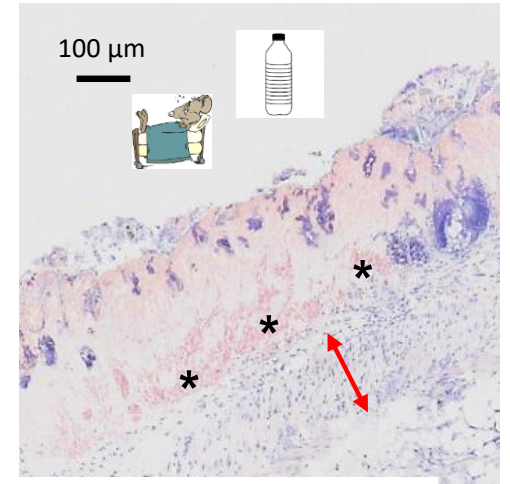
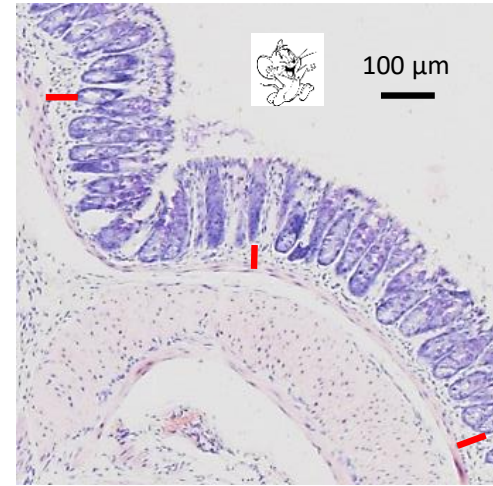
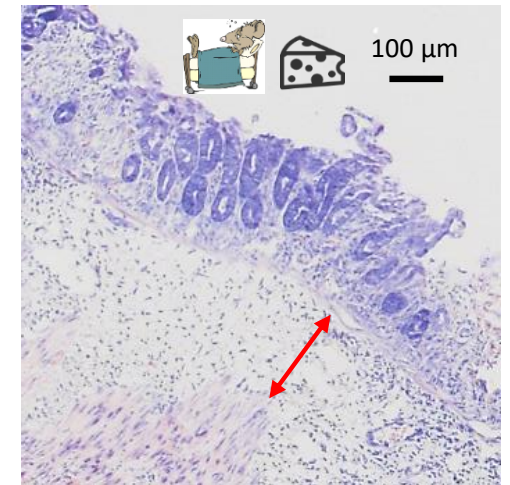
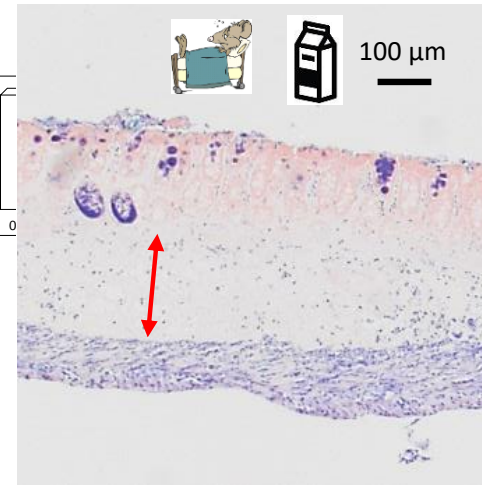
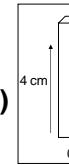
◆ In caseum



Acute colitis



Macroscopic score (Wallace)



> Moving to industrial scale

Let's make a real Emmental cheese!



Propionibacterium freudenreichii

Streptococcus thermophilus

Lactobacillus delbrueckii



➤ And it works!



Method – Pre-treatment with probiotic Cheese

Gavage 100 mg
of probiotic Cheese



C57BL6



Gavage
start

Probiotic Cheese protection

Day 1

Continuous gavage, 10 days



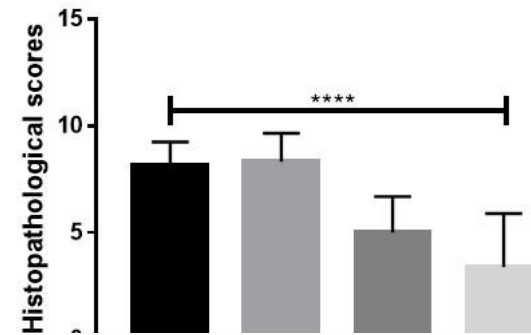
microorganisms

Article

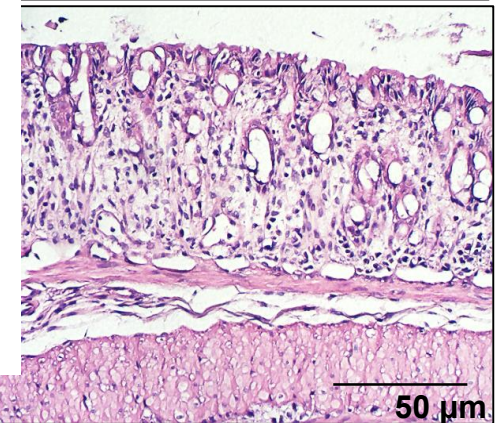
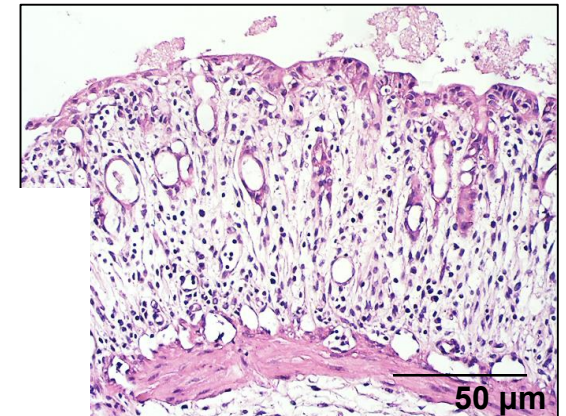
Beneficial Propionibacteria within a Probiotic Emmental Cheese: Impact on Dextran Sodium Sulphate-Induced Colitis in Mice

Houem Rabah ^{1,2,†}, Fillipe Luiz Rosa do Carmo ^{3,†}, Rodrigo Dias de Oliveira Carvalho ⁴, Barbara Fernandes Cordeiro ³, Sara Heloisa da Silva ³, Emiliano Rosa Oliveira ³, Luisa Lemos ³, Denise Carmona Cara ³, Ana Maria Caetano Faria ³, Gilles Garric ¹, Marielle Harel-Oger ¹, Yves Le Loir ¹, Vasco Azevedo ³, Guillaume Bouguen ^{5,‡} and Gwénaél Jan ^{1,*}

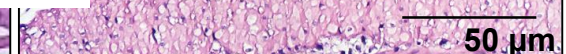
Probiotic Emmental x Colitis



PBS control DSS



Noninflamed control



Probiotic Emmental



➤ Modulatory properties identified in other dairy bacteria



S-Layer Protein Mediates the Stimulatory Effect of *Lactobacillus helveticus* MIMLh5 on Innate Immunity

Valentina Taverniti,^a Milda Stuknyte,^a Mario Minuzzo,^b Stefania Arioli,^a Ivano De Noni,^a Christian Scabiosi,^a Zuzet Martinez Cordova,^c Ilkka Junttila,^{d,e} Sanna Hämäläinen,^{c,d} Hannu Turpeinen,^c Diego Mora,^a Matti Karp,^f Marko Pesu,^{c,g} Simone Guglielmetti^a

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Streptococcus thermophilus NCIMB 41856 ameliorates signs of colitis in an animal model of inflammatory bowel disease

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<https://doi.org/10.3920/BM2016.0110>

Abstract

References

PDF

Clinical & Experimental Immunology
The Journal of Translational Immunology



Clinical and Experimental Immunology ORIGINAL ARTICLE

doi:10.1111/j.1365-2249.2011.04408.x

Lactobacillus rhamnosus GG and *Streptococcus thermophilus* induce suppressor of cytokine signalling 3 (SOCS3) gene expression directly and indirectly via interleukin-10 in human



Takeyuki Takamura¹, Daisuke Harama¹, Suguru Fukumoto¹, Yuki Nakamura¹, Naomi Shimokawa¹, Kayoko Ishimaru¹, Shuji Ikegami², Seiya Makino², Masanori Kitamura³ and Atsubito Nakao¹



OPEN ACCESS Freely available online

L. plantarum, *L. salivarius*, and *L. lactis* Attenuate Th2 Responses and Increase Treg Frequencies in Healthy Mice in a Strain Dependent Manner

Maaike J. Smelt^{1,2}, Bart J. de Haan², Peter A. Bron^{1,3,5}, Iris van Swam^{1,3}, Marjolein Meijerink^{1,4}, Jerry M. Wells^{1,4}, Marijke M. Faas², Paul de Vos^{1,2*}

¹Top Institute Food and Nutrition, Wageningen, The Netherlands, ²Department of Pathology and Medical Biology, University Medical Center Groningen and University of Groningen, Groningen, The Netherlands, ³NIZO Food Research, Ede, The Netherlands, ⁴Department of Host-Microbe Interactomics, Wageningen University, Wageningen, The Netherlands, ⁵Kluyver Centre for Fermentation and Genomics, Delft, The Netherlands

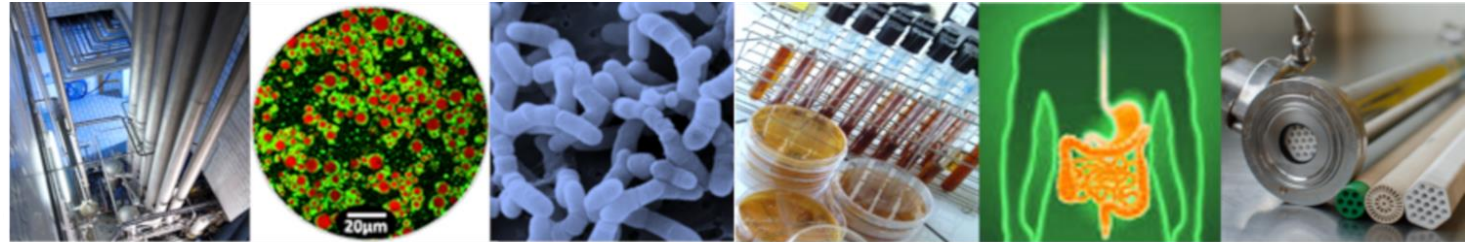


Microbiote ingéré, microbiote hu

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➤ But what does the clinic say?



➤ Meta-analysis on dairy products...

Eur J Epidemiol (2017) 32:269–287
DOI 10.1007/s10654-017-0243-1



META-ANALYSIS

Milk and dairy consumption and risk of cardiovascular diseases and all-cause mortality: dose–response meta-analysis of prospective cohort studies

Jing Guo¹ · Arne Astrup² · Julie A. Lovegrove³ · Lieke Gijsbers⁴ · David I. Givens¹ · Sabita S. Soedamah-Muthu⁴

Pas d'effet de la consommation globale de produits laitiers avec l'incidence des maladies cardiovasculaires

No associations were found for total (high-fat/low-fat) dairy, and milk with the health outcomes of mortality, CHD or CVD

En revanche, association inverse entre la consommation de produits laitiers fermentés, fromages et yaourts, et la mortalité / le risque de maladie cardiovasculaire

Inverse associations were found between total fermented dairy (included sour milk products, cheese or yogurt; per 20 g/day) with mortality (RR 0.98, 95% CI 0.97-0.99; I² = 94.4%) and CVD risk (RR 0.98, 95% CI 0.97-0.99; I² = 87.5%).



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Gwénaél JAN, UMR STLO, INRAE, Agrocampus Ouest

> Literature review.....

Yogurt and other fermented foods as sources of health-promoting bacteria FREE

Car Reen Kok, Robert Hutkins ✉

Nutrition Reviews, Volume 76, Issue Supplement_1, December 2018, Pages 4–15, <https://doi.org/10.1093/nutrit/nuy056>

Published: 16 November 2018



PDF

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Des études épidémiologiques ont montré que la consommation d'aliments fermentés est associée avec un risque réduit de diabète de type 2, de syndrome métabolique, de maladie cardiaque, ainsi qu'avec un meilleur contrôle du poids corporel

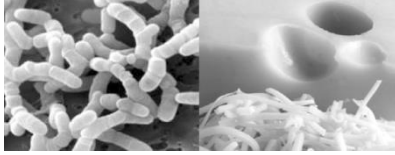
Epidemiological studies have shown that the consumption of fermented foods is associated with reduced risks of type 2 diabetes, metabolic syndrome, and heart disease, along with improved weight management



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Microbiote ingéré, microbiote humain

Gwénaél JAN, UMR STLO, INRAE, Agrocampus Ouest



Conclusion:

- ✓ Our food: a source of bacteria
- ✓ Potentially probiotic bacteria
- ✓ Which modulate the structure and activity of the microbiota
- ✓ With an effect on physiology and health



Fermented foods : 30% of our diet

A major source of bacteria : 10^5 to 10^9 per gram



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A huge variety of bacteria



➤ **Merci de votre attention**

