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# Yoghurts & fermented milks

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Health • Nutrition • Flora

SCIENTIFIC SURVEY • LACTIC ACID BACTERIA • PROBIOTICS

## edito The intestinal microbial ecosystem still has some surprises for us

**Pierre Bourlioux**  
*Professor of microbiology*

In the last twenty years, thanks to the use of molecular biology tools, major breakthroughs have been made in our knowledge of the intestinal ecosystem. The most interesting discoveries are, I believe, those that highlight a real symbiosis between the microflora and the intestinal cells that lead to surprising physiological effects that researchers are only now starting to explain. This should help us to better understand certain functions of the ecosystem as well as certain functional properties of probiotics.

For thirty or so years we have known that the resident microflora has a major influence on the anatomy and physiology of the intestinal cells. However, the last 5 or 6 years have seen a real explosion in the number of works that now form a set of basic data enabling us to know and understand better the functioning of this ecosystem.

The research work of J. Gordon's team is certainly among the most interesting, in particular that focusing on an understanding of the role of colon flora in the working of the intestinal system. These researchers have shown that the expression of more than one hundred genes is modulated by the presence of resident bacterial strains, each strain with a specific action. The genes in question involve the epithelium barrier function, the transport of nutrients, the metabolism of enzymes involved in the production of cellular energy, hormone responses and signal transduction pathways. As each strain has a specific activity and there are a large number of resident bacteria, modulation must necessarily exist within the ecosystem itself via both a "bacteria - bacteria" and "bacteria - cell" dialogue. In both cases, the dialogue is based on an exchange of molecular signals able to modulate the expression of the bacteria's genes and those of the intestinal cells. The effect depends on the concentration of the signal molecule, which itself depends on the number of producing bacteria. This explains why the majority of the observed effects are caused by the ecosystem's dominant bacteria.

The same authors have therefore been able to show that one resident bacterium (*Bacteroides thetaiotaomicron*) was able to emit a signal acting on cellular glycosyltransferases that play a key role in the composition of intestinal glycoconjugates (mucins). This is of paramount importance since all changes to the innate catalogue of intestinal glycoconjugates can cause changes to the bacteria adhesion sites and therefore influence the composition of the microflora.

Last November, the same team published a remarkable work showing that the intestinal microflora should be seen as an environmental factor able to regulate fat storage. This activity occurred via the suppression of Fiaf (Fasting-induced adipocyte factor). Fiaf is a protein belonging to the angiopoietin family that inhibits lipoprotein lipase. Suppressing Fiaf would therefore seem to be behind the increase in the circulating lipoprotein lipase that favours the storage of triglycerides in the adipocytes and therefore increases the body fat content...

There can be no doubt that the more we find out about the intestinal ecosystem, the more interesting it becomes and that we still have a lot to learn.

## Probiotics prevent a weakening of the body's immune defences in situations of stress

It appears to be an established fact that stress situations are often accompanied by a reduction in the immune defences, which may consequently lead to an increase in the likelihood of infection (1). Such a reduction of immunocompetence at a time of stress has been reported, for example, in students at exam time (2-4). A whole range of results, obtained in humans and animals, also support the immunomodulator role of probiotics. This knowledge enabled one research team to formulate the hypothesis that consumption of probiotics may protect against the harmful effects of stress on the immune defences (5).

In this study, the researchers tested the influence of a fermented milk product on the immune parameters in students under stress during their exams.

For 6 weeks (3 weeks before and 3 weeks during the examination period), 136 healthy students were asked to consume either 200 ml of Actimel (test group) or

200 ml of semi-skimmed milk (control group). The Actimel® fermented milk provided  $2 \times 10^9$  cfu of *Lactobacillus bulgaricus*,  $2 \times 10^{10}$  cfu of *Streptococcus thermophilus* and  $2 \times 10^{10}$  cfu of *Lactobacillus casei* DN-114 001 daily.

The state of anxiety (measured by a standard questionnaire\*) and the levels of serum cortisol increased significantly ( $p < 0.05$ ) during the exam period in equivalent fashion in both groups. However, significant differences ( $p < 0.05$ ) between the groups were detected for some immunity markers. Consumption of fermented milk resulted an increase in the number of lymphocytes - whereas this decreased in the control group - and a reduction in the number of CD56 cells (T cytotoxic cells and Natural Killers) whereas this did not change in the control group.

This study shows that the consumption of a fermented milk containing *L. casei* DN-114 001 and yoghurt ferments is able to both modulate the immune response and, in the medium term (6 weeks), to

prevent stress-related damage to certain immunity markers. This beneficial effect means that in the future protection against potential infection need not be affected by stress.

\* Spielberger state-trait anxiety inventory (STAI).

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## *Lactobacillus casei* fighting cutaneous inflammation: a study on mice

One of the promising effects of probiotics is their ability to moderate the allergic response (6). This ability has recently been explored in mice (7). The authors analysed the effect of *Lactobacillus casei* DN-114 001 on a model of allergic contact dermatitis and attempted to elucidate the underlying action mechanism.

Mice were sensitised by applying an allergen (2,4-dinitrofluorobenzene, DNFB) to the ear and then subjected to the molecule again five days later (challenge test). The inflammatory skin reaction is evaluated by measuring the thickness of the animals' ears and the specific immune response. The mice were fed daily for 7, 14 or 21 days before sensitisation and during the 12 days following with the probiotic *L. casei* DN-114001 ( $2 \times 10^7$  cfu/j) either in the form of a fermented milk containing yoghurt ferments (Actimel®),

or alone, or as a cell extract containing only the bacterial walls.

Treatment with fermented milk for 14 or 21 days before sensitisation, continued until the challenge test, reduced the skin reaction by 50 % ( $p < 0.05$ ) whereas the 7-day treatment was not sufficient to prevent a reaction. At the same time, the proliferation of allergen-specific CD8 cytotoxic T lymphocytes was inhibited. This inhibiting effect was regulated by the CD4+ T cells that control the CD8 lymphocyte pool. These effects were observed for *L. casei* DN-114 001 lactobacillus, both when it was used alone and live and when it was in the form of cell wall extracts.

This study shows for the first time the ability of *L. casei* to inhibit skin inflammation caused by an allergen by controlling the number of CD8+ cells. It

also shows that the bacterial factors involved in this anti-inflammatory function are, at least partly, located in the bacterial wall.

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## The involvement of the intestinal flora in inflammatory bowel diseases

Ulcerative colitis is a chronic recurring disease characterised by an inflammation of the colon. The aetiology is still unknown but there are strong reasons to believe that the intestinal flora is involved in the onset of inflammation (8, 9). Other studies have shown that the consumption of probiotics, in particular lactobacilli and bifidobacteria, normalises the physiological functions of the colon by increasing the bacterial load (10). An English research team has compared the colon flora of patients suffering from colitis in the inflammatory phase with that of patients in the remission phase (11).

Twelve patients took part in this study, 6 in the remission and 6 in the active phase. Faecal samples were taken from all patients and analysed to count the total number of bacteria, lactobacilli,

sulfate reducing bifidobacteria, *clostridia* and *bacteroides*.

It would appear that the number of lactobacilli is significantly fewer in the active phase than in the remission phase ( $p < 0.05$ ). For the other populations of bacteria, there was no difference between the two phases of the disease.

Analysis of the lactobacillus strains showed that, in the remission phase, *Lactobacillus salivarius*, *Lactobacillus manihottivorans* and *Pediococcus acidilactici* are present whereas they are absent in the active phase.

This study highlights the link between the intestinal flora and the inflammatory process. It also suggests that a reduction in the total number of lacto-

bacilli in the intestine could play a role in the onset of ulcerative colitis.

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## Probiotic DNA is involved in inhibiting the inflammatory reaction

in the colon

Oral tolerance, in other words the host's ability not to trigger an inflammatory response against the bacteria making up the intestinal flora, is a process that is known to happen but whose mechanisms have, as yet, not been explained (12). This ability has been explored in the case of probiotics. Probiotics are not only tolerated in the same way as endogenous bacteria but can, in certain cases, inhibit the inflammatory reaction caused by pathogens. Karen Madsen's team has attempted to define the cellular signals that may well be involved in the tolerance and then tested the responses triggered by the DNA (13).

Murine colon tissue and HT29 epithelial cells from the intestine were placed in contact with the DNA of several different bacteria: pathogenic bacteria (2 strains of *Salmonella*) or probiotics - strains of the VSL#3\* mixture, used in a mixture or individually. The impact of the DNA of the VSL#3 probiotic mixture was also tested on inflamed cells. The inflammation was caused by contact with  $TNF\alpha$  or a strain of salmonella. The inflammatory reaction was evaluated by measuring the secretion of IL8, the activation of  $NF\kappa B^{**}$  and the level of  $I\kappa B^{**}$ . The DNA of the probiotic mixture was

also given orally (for two weeks) to IL-10 deficient mice (who spontaneously developed colitis and produced an excess of  $IFN\gamma$ ), or to normal mice who acted as the control. The production of proinflammatory cytokines by the epithelial cells of the colon and the spread of the colitis were noted.

Experiments performed *in vitro* show that, unlike the salmonella tested, the probiotics in the VSL#3 mix, used either together or individually, did not cause an inflammatory reaction. Furthermore, the DNA of these probiotics prevented the inflammatory reaction caused by  $TNF\alpha$  or by a strain of salmonella.

*In vivo*, ingesting the DNA from the strains of the VSL#3 mix caused a reduction in the production of inflammatory cytokines and an improvement in the symptoms of the colitis.

Unlike the genetic material of the pathogenic bacteria, that cause an inflammatory type immune reaction, the DNA from the probiotics in the VSL#3 mixture limits, both *in vitro* and *in vivo*, inflammation of the epithelial cells of the colon. Bacterial DNA may therefore appear here as a signal recognised by

the host's intestinal cells that enables the host to distinguish pathogenic bacteria from non pathogenic bacteria - commensal bacteria or probiotics. However, the mechanisms involved remain unclear, since the only eucaryote receptor as yet identified for the bacterial DNA, the Toll 9 receptor, has an activating effect; the pro-inflammatory signalling cascade being dependant on  $NF\kappa B$ .

\* VSL#3 is a probiotic mix containing *Streptococcus thermophilus*, *Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus casei* and *Lactobacillus bulgaricus*.

\*\* The  $NF\kappa B$  nuclear factor plays a key role in activating the inflammatory response. The  $\kappa B$  inhibitor ( $I\kappa B$ ) is, in normal situations, bound to  $NF\kappa B$ ; its hydrolysis allows the activation of  $NF\kappa B$ .

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## Consumption of fermented formula reduces the severity of diarrhoea in new-born babies

Mothers' milk, apart from its benefits for bonding, protects babies against intestinal infections (14). This effect could be linked to the provision of beneficial endogenous flora where bifidobacteria are in the great majority (15). Since probiotics seem able to influence the composition of the intestinal flora (16), the use of probiotics in babies who cannot be breast-fed is an avenue of research currently being explored.

In a study conducted double blind and placebo controlled (17), a team from Necker Hospital (France) compared the impact on diarrhoea of the consumption of standard formula (Gallia®) and a formula fermented with *Bifidobacterium breve* C50 and *Streptococcus thermophilus* 065 (Calisma®) and whose bacteria were inactivated after fermentation. For a period of at least three months, 913 healthy babies received one or other of the formulas, both of which had iden-

tical nutritional properties. The authors studied the frequency and duration of diarrhoea along with its severity that could be evaluated by the number of times the patients were admitted to hospital, the number of cases of dehydration, diarrhoea related visits to the doctor and prescriptions for oral rehydration solutions.

Neither the frequency nor the duration of the diarrhoea, nor the number of admissions to hospital differed between the two groups of infants. However, the severity of the diarrhoea was considerably reduced in the infants consuming the fermented milk compared to those consuming the standard milk (cases of dehydration: 2.5% vs 6.1%  $p=0.01$ ; visits to doctors' 46% vs 56.5%  $p=0.03$ ; prescription of an oral rehydration solution: 41.9% vs 51.9%  $p=0.03$ ; prescription of a different formula: 59% vs 74.9%  $p=0.0001$ ).

Fermented formula given to healthy babies reduced the severity of diarrhoea compared to standard formula. This benefit to health provided by probiotics promises to be a simple way of fighting diarrhoea - a recurring paediatric problem.

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## Probiotics potentialise the recovery of the intestinal mucosa in rats

Among their several possible gastro-intestinal impacts, probiotics could influence the intestine's absorption capacity and strengthen the intestinal mucosa's role as a barrier (18). Some pathological situations, such as diarrhoea and malnutrition are associated with histological impairment to the intestinal mucosa that take the form of atrophy and inflammation. These compromise the integrity of the intestine's barrier functions (19). The use of probiotics to improve the physiological condition of the intestine has been envisaged.

In a study conducted on rats, researchers examined the effect of ingesting probiotics on intestinal atrophy observed after a protein deficient diet (20). Rats with atrophic intestines were subjected over two weeks to a renutrition programme that was either standard (control group)

or contained probiotics (*Streptococcus thermophilus* and *Lactobacillus helveticus*,  $4 \times 10^6$  cfu/j in total). The histological characteristics and the weight and length of the intestine were evaluated at the end of the renutrition period.

No differences were observed in the animals' weight gain or the size and weight of the intestine and liver. However, the values of certain histological parameters were improved in the group receiving the probiotics compared to the control group. In the jejunum, the size of the villi and depth of the crypt foci were greater in the rats receiving probiotics ( $p=0.04$  and  $p=0.03$  respectively); in the caecum and distal colon, the depth of the crypt foci and the thickness of the walls were increased ( $p=0.05$ ;  $p=0.02$  and  $p=0.03$ ). The spleens also weighed more in the group ingesting probiotics.

Probiotics administered concurrently with a renutrition diet favours the anatomical recovery of the digestive tract, atrophied during a period of malnutrition. Improvements to these histological parameters suggest that probiotics could help to restore the barrier effect. However this point remains to be shown.

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This scientific letter "Yoghurts & fermented milks" is also available on the following website:  
[www.maison-du-lait.com](http://www.maison-du-lait.com)

## Live bacteria more effective for the immune system

Gabriela Perdigon's team has shown that live bacteria are more effective in stimulating the intestinal immune system than inactivated bacteria. This team has attempted to show how probiotics enter in contact with epithelial cells and intestinal immune cells. It seems that only the

probiotic antigens, and not the whole bacteria, penetrate the epithelial cells and enter into contact with the immune cells. These antigens only stay in the intestine for short period, which, according to the authors, is a safety criterion for the use of probiotics in humans.

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## Lactobacillus GG inhibits extra-intestinal inflammation

Arthritic rats are a model for studying the effects of probiotics on extra-intestinal inflammation. Results show that different fermented milks containing lactobacilli, and in particular *Lactobacillus* GG, have a remarkable preventative and curative effect on arthritis induced in

rats using alpha-tropomyosin or Freund's adjuvant. This result is a first step towards the use of probiotics in patients suffering from arthritis. It indicates that the anti-inflammatory effects of probiotics are not restricted solely to the intestine.

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## Lactobacilli strengthen the intestinal barrier

A study conducted double blind and placebo-controlled shows that, in children suffering from atopic dermatitis, the barrier role played by the intestinal mucosa is less effective if paracellular permeability

is increased. This study shows the efficacy of *Lactobacillus rhamnosus* 119070-2 and *Lactobacillus reuteri* DSM 1246 probiotics in stabilising these barrier functions by reducing intestinal permeability.

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## Lactobacillus GG and maturation of the immune system of new-born babies

A link has been highlighted between babies that are allergic to cows' milk and that are at the same time IFN $\gamma$  deficient. In the knowledge that the immune response of allergy-sufferers is deviated from a Th1 type profile to a Th2 type profile, it is anticipated that the stimulation of Th1 immunity will be beneficial. A randomised, dou-

ble-blind study showed that consumption of *Lactobacillus* GG by these infants has caused an increase in IFN $\gamma$  production by circulating lymphocytes. According to these authors, *Lactobacillus* GG could be considered beneficial for the maturation of the immune systems of babies that are allergic to cows' milk.

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## Immunomodulating role of peptides produced during fermentation

Biologically active peptides from milk fermented with probiotics could be considered as immunomodulating agents able to protect the host from enteric infections. A peptidic fraction isolated from milk fermented with *Lactobacillus helveticus* was tested on mice infected with *E. coli* O157:H7. This peptidic fraction was able to induce an increase in

the bloodstream of IgA-producing B lymphocytes in the lamina propria and specific IgA antibodies of the pathogenic agent. This result suggests that the immunomodulatory role attributed to probiotics could bring into play biologically active peptides produced during milk fermentation with these probiotics.

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