FUNCTIONAL FOODS AND THE IMUNE SYSTEM

In the last decade, preventive medicine has undergone a great advance, especially in developed countries. Research has demonstrated that nutrition plays a crucial role in the prevention of chronic diseases, as most of them can be related to diet. Functional food enters the concept of considering food not only necessary for living but also as a source of mental and physical well-being, contributing to the prevention and reduction of risk factors for several diseases or enhancing certain physiological functions. In reference to the immune system, many studies have pointed out that not only pre- and probiotics, but also single micronutrients incorporated into functional foods contribute to an enhancement of immunocompetence. In fact, one of the authorized claims consists of pointing out the immunomodulator properties of functional foods. In this article, the effect of some functional foods and ingredients such as probiotics, selenium and dietary antioxidants (vitamins A, E and C) on the immune function are reviewed. However, the optimum intake level and recommended amounts of functional foods have not yet been established. Thus, in order to remove the controversy surrounding functional food, further research studies are necessary, both in experimental animals and in humans. Finally: efforts should be directed towards the ultimate goal, that is, a 'functional diet'.

INTRODUCTION

The term 'functional food' was born in Japan. The Japanese were the first to observe that food could have a role beyond gastronomic pleasure and energy and nutrient supply to the human organism. Following this pioneering, Japan is the country where most functional foods are on the market and the first country to legislate these products in the FOSHU (Foods of Specified Health Use) legislation. Only the products which meet certain requirements (Table 1) can have the FOSHU stamp. Europe and the American countries incorporated later the concept of an added value of food.

TABLE 1 - THE JAPANESE 'FOSHU' CRITERIA FOR FUNCTIONAL FOOD

1. They are food (not capsules, pills or powder) on the basis of naturally occurring food components.
2. They can and should be consumed as part of a normal daily diet.
3. They have a defined function on the human organism:
- to improve immune function
- to prevent specific diseases
- to support recovery from specific diseases
- to control physical and psychic complaints
- to slow down the ageing process

There is no consensus between Europe and the USA regarding a concrete definition, leading to a series of different terms: nutraceutical, designer food, pharmafood, etc., which has contributed to increasing the confusion among professionals and consumers. Whereas the USA prefer the term nutraceutical, European experts decided in the FUFOSE (Functional Food Science in Europe) project, under the auspices of the European Union and ILSI Europe.

TABLE 2 - FUNCTIONAL FOOD IN EUROPE; THE FUFOSE DEFINITION (INTERNATIONAL LIFE SCIENCES INSTITUTE EUROPE, 1999)

Functional foods are:
- conventional or everyday food consumed as part of the normal diet.
- composed of naturally occurring components, sometimes in increase concentration or present in foods that would not normally supply them
- scientifically demonstrated to promote positive effects on target functions beyond basic nutrition
- thought to provide enhancement of the state of well-being and health in order to improve the quality of life and/or reduce the risk of disease
- advertised by authorized claims

It is important to highlight that functional food must be a food, not a drug. Beneficial effects should be obtained by consuming normal amounts of a functional food within the 'normal' diet. As it has been recently stated, the ultimate goal of the scientific community and food industry should be to develop functional foods for improving life quality (Danone Vitapole, 2000).

Therefore, as Western civilization is facing up to a progressive increase in immune-mediated and gut-related health problems, such as autoimmune and inflammatory diseases, it seems adequate to analyze the effects of functional foods on the immune system.

WHAT ARE FUNCTIONAL FOODS?

Basically, functional foods are used to enhance certain physiological functions, in order to prevent or even to cure diseases (Roberfroid, 2000). Although natural foods, such as strawberries or onions, have been defended as included as functional foods, only those foods which are submitted to certain methodology are considered functional foods. Thus, several methods to obtain functional foods include the addition or removal of a component, modification of the food processing, genetic engineering, etc, which is allowing the food industry to develop new products with additional value for the market. So far, the most important components that can be added to food are:

• Probiotics - living micro-organisms which when ingested in certain amounts, have a positive impact on host health, which goes beyond conventional nutritional effects (Isolauri, 2001). The bacteria most often used as probiotics are Lactobacilli and Bifidobacteria. They can be given with fermented foods such as yoghurt, fermented vegetables or meats and they may briefly establish in the gut.

• Prebiotics - ingredients or compounds that have a beneficial effect on the microflora in the host itself, such as fiber, fructooligosaccharides, inulin, lactulose, sugar alcohols. They are short-chain carbohydrates that may be fermented in the large bowel and stimulate the growth

of potentially beneficial bifidobacteria (Englyst & Hudson, 2000).

• Synbiotics - a mixture of prebiotics and probiotics.

• Nutrients - minerals, vitamins, fatty acids or dietary fiber, for example, that are specific and have a very targeted action.

OBJECTIVES OF FUNCTIONAL FOODS

The consensus statement of the FUFOSE project (International Life Sciences Institute Europe, 1999) establishes that basic research in biological sciences is relevant in order to establish the mechanisms which modulate the function of interest in the maintenance of health and in the reduction of disease. This can also be sustained by means of a significant, epidemiologically proven association between a marker of the amount ingested of a specific component and the specific beneficial effect which is attributed to it. One of the most clear objectives of the study of functional foods is to identify and validate biological markers in order to understand the interaction mechanisms between the food component and a body function.

HEALTH EFFECTS OF FUNCTIONAL FOODS

A number of health-related effects has been documented for functional foods and they are listed in Tables 3 and 4.

Regular consumption of functional foods should reduce the risk for seve-

TABLE 3 - SOME NUTRIENTS AND FOOD COMPONENTS WITH FUNCTIONAL PROPERTIES

	Properties	Related diseases
Dietary fibre	Regulation of bacterial balance Improvement of intestinal transit Dilution of carcinogenic agents Increase of bile salt excretion Reduction of plasma cholesterol Regulation of blood glucose levels	Colorectal cancer Constipation=diverticulosis Hypercholesterolaemia Diabetes Obesity
Antioxidants vitamins A, E and C xantophylls flavonoids	Elimination of free radicals (protection against cellular oxidative damage) Inhibition of lipid peroxidation	Cardiovascular diseases Cancer
Lactic bacteria	Improvement of lactose digestibility Increase in calcium absorption Stimulation of the immune system	Lactose intolerance Constipation=diarrhoea Gastro-enteritis Cancer
o-3 fatty acids	Reduction of triglycerides and LDL-cholesterol levels Reduction of platelet aggregation Stimulation of the immune system	Cardiovascular disease
Micronutrients: Se, Fe, Cu, Zn, Mn, Ca, Fe, Folate	Enzyme cofactors Stimulation of the immune system	Cardiovascular diseases Cancer Osteoporosis Anaemia Neural tube defects
Amino acids tryptophan tiramine glutamine arginine cysteine	Hypnotic and sedating effect Memory improvement Recuperation of mental fatigue Stimulation of immune system Slowdown of the ageing process	Sleep regulation Stress
Caffeine	Stimulation of the central nervous system	

TABLE 4 - HEALTH-RELATED EFFECTS OF PROBIOTICS
Alleviation of symptoms of lactose intolerance
Immune enhancement (immunomodulation): alleviation of intestinal inflammation normalisation of gut mucosal dysfunction down-regulation of hypersensitivity reactions
Shortening the duration of rotavirus diarrhoea
Decreasing faecal mutagenicity
Decreasing faecal bacterial enzyme activity
Prevention of recurrence of superficial bladder cancer

ral chronic diseases, such as cardiovascular disease, cancer, diabetes, hypertension and osteoporosis. The aim of the present article is not to go deeper into these aspects, but to review some concepts that have been discussed in the literature, which are very controversial (Hornstra et al, 1998; López-Varela et al, 2000).

FUNCTIONAL FOODS AND THE IMMUNE SYSTEM PROBIOTICS

Probiotics have several immune-enhancing effects (Table 4) that have been documented in different studies by different research groups (Marcos et al, 1996; Isolauri, 2001). An enhancement of the circulating IgA secreting cell response has been observed in infants supplemented with Lactobacillus casei, and correlated with a shortened duration of diarrhea in the study group when compared with a placebo group (Kaila et al, 1992). An improvement of the non-specific immune phagocytic activity of granulocytes has been shown in the blood of human volunteers after consumption of *Lactobacillus acidophilus* and *Bifidobacterium bifidum* (Schiffrin et al, 1995; Marteau et al, 2001). Since phagocytic activity involved with natural immunity and phagocytes is implicated in antibody immune response as antigen-presenting cells, it is possible that stimulation of intestinal IgA antibody responses induced by lactic-acid bacteria may be explained partly by an effect on phagocyte cell functions. Ingestion of yoghurt has been reported to stimulate cytokine production, including interferon g (IFN-g) in human blood mononuclear cells (Solis-Pereyra & Lemonnier, 1996). It has also been reported that the consumption of yoghurt stimulates cytokine production by monocytes (Roberfroid, 2000).

MICRONUTRIENTS

Many studies have pointed out that micronutrients such as selenium, vitamins A, C and E can influence several components of the immune system (Erickson et al, 2000). Many of these micronutrients are included in functional foods actually on the market (breakfast cereals, juices, dairy products, etc) because of their important role in the prevention of disease and promotion of health (Table 3).

Selenium. Selenium (Se) has additional important health effects, particularly in relation to immune response, viral disease and cancer prevention (Rayman, 2000). Numerous studies suggest that deficiency of Se is accompanied by a loss of immunocompetence. In fact, both cell-mediated immunity and B-cell function can be impaired (Spalholz et al, 1990). This failure in the immune system is probably not unconnected with the fact that Se is normally found in significant amounts in immune tissues such as liver, spleen and lymph nodes. On the other hand, supplementation with Se, even in 'selenium-replete' individuals, has marked immunostimulant effects, including an enhancement of proliferation of activated T cells (cytotoxic lymphocytes) and an improvement of NK-cell activity (Kiremidjian-Schumacher & Roy, 1998). Selenium also appears to abrogate the agerelated deficiency of lymphocytes from the aged host to respond to stimulation by proliferation and differentiation into cytotoxic effector cells.

Dietary antioxidants. The immune system is highly reliant on accurate cell - cell communication for optimal function, and any damage to the signaling systems involved will result in an impaired immune responsiveness. Oxidantmediated tissue injury is a particular hazard to the immune system, since phagocyte cells produce reactive oxygen species as part of the body's defense against infection. Adequate amounts of neutralizing antioxidants are required, therefore, to prevent damage to the immune cells themselves. Many antioxidants can be obtained directly from the diet. Numerous epidemiological studies have found strong associations between diets rich in antioxidant nutrients and a reduced incidence of cancer, and it has been suggested that a boost to the body's immune system by antioxidants might, at least in part, account for this (Hughes, 1999).

Vitamin A. Vitamin A deficiency can affect the function of different cells of the immune system. Different studies have reported defects in phagocytic activity (defect in chemotaxis, adhesion and the ability to generate reactive oxygen metabolites in neutrophils) and impairment of T and B cell function. In addition, vitamin A-deficiency reduced natural killer activity, lower production of interferon, less effective fixed fat macrophage activity, and lower lymphocyte response to stimulation by mitogens (Ross, 1992) have also been reported. In general, improvement of immune function and increased resistance to infection is observed in vitamin A-deficient hosts after supplementation (Meydani et al, 2001).

Vitamin E. Vitamin E is a potent antioxidant and has an ability to modulate host immune functions. In addition, vitamin E is an important nutrient for maintaining the immune system, especially in the elderly (Moriguchi & Muraga, 2000). In vitamin E deficiency most of the immune parameters show a downward trend, which is associated with increased infectious diseases and tumors. In contrast, vitamin E supplementation

has various beneficial effects on the host immune system. The decrease in cellular immunity with ageing or during the development of degenerative diseases is markedly improved by the intake of a high vitamin E diet. In addition, vitamin E plays a role in the differentiation of immature T cells in the thymus.

Vitamin C. Recent scientific data indicate that important functions of the body, such as several indexes of immune response, including responses on delayed-type-hypersensitivity skin tests, antibody production, lymphocyte proliferation, and numbers of the specific subgroups of white blood cells (Grimble, 1997), pulmonary function and iron absorption are related to vitamin C intakes. In addition, epidemiological studies support the hypothesis that vitamin C plays a critical and beneficial role in the prevention of coronary heart disease (CHD), cancer and cataract. It has been reported that an intake of at least 150 - 200mg per day of vitamin C is capable of enhancing these functions (Weber et al, 1996).

Otherwise, ascorbic acid (a powerful antioxidant) has been shown to exert anti-inflammatory effects in human and animal studies. Dietary supplementation with ascorbic acid enhances a number of aspects of lymphocyte function, and this effect is most apparent in the elderly.

On the other hand, the role of oral vitamin C in the prevention and treatment of colds is controversial, and there appears to be a modest benefit in reducing duration of cold symptoms from ingestion of relatively high doses of vitamin C. The dose - therapeutic benefit relationship needs further exploration (Douglas et al, 2000).

FINAL STATEMENT: A FUNCTIONAL DIET

Development of functional foods in Europe is a crucial aspect and at the same time a scientific challenge that must progress based on reliable scientific evidence which studies the possible modulation that food components exert over the physiological functions that have been outlined throughout this article. However, functional foods are not universal; it is necessary to consider local aspects when talking about food consumption. As it is assumed for 'normal' food, functional foods must be integrated into cultural and habitual dietary patterns. Nevertheless, we must be careful, because the over-intake of functional foods could lead to a new nutritional imbalance. The most convenient message should be oriented towards a functional diet, high in functional food components, with functional foods as an additional health benefit. It is important to establish the dynamic interactions between components of the total diet and of the functional foods. Therefore, and in order to find out the actual effects, to check the precise bioavailability of those nutrients included in functional foods and to establish who can get benefits from functional food consumption and how, it is necessary to identify biological markers, as well as genetic and environmental factors.

* S. López-Varela - Instituto de Nutrición y Bromatología. Consejo Superior de Investigaciones Científicas (CSIC), Madrid, Spain.
* M González-Gross - Instituto de Nutrición y Bromatología. Consejo Superior de Investigaciones Científicas (CSIC), Madrid, Spain, and Institut fuer Ernaehrungswissenschaft, Rheinische Friedrich-Wilhelms Universitaet, Bonn, Germany.
* A. Marcos - Instituto de Nutrición y Bromatología. Consejo Superior de Investigaciones Científicas (CSIC), Madrid, Spain.

References

Danone Vitapole (2000): Functional Dairy Products. London: John Libbey Eurotext.
Douglas RM, Chalker EB & Treacy B (2000): Vitamin C for preventing and treating the common cold. Cochrane Database Syst. Rev. 2, CD000980.
Englyst HN & Hudson GY (2000): Carbohydrates. In Human Nutrition and Dietetics, eds. JS Garrow, WPT James & A Ralph, pp 61 – 66. London: Churchill Livingstone.
Erickson KL, Medina EA & Hubbard NE (2000): Micronutrients and innate immunity. J. Infect. Dis. 182, S5– S10.
Grimble RF (1997): Effect of antioxidative vitamins on immune function with clinical applications. Int. J. Vitamin Nutr. Res. 67, 312 – 320.
Hornstra G, Barth CA, Galli C, Mensink RP, Mutanen M, Riemersa RA, Roberfroid M, Salminen K, Vansant G & Verschuren PM (1998): Functional food science and the cardiovascular system. Br. J. Nutr. 80, S113 – S146.
Hughes DA (1999): Effects of dietary antioxidants on the immune function of middle-aged adults. Proc. Nutr. Soc. 58, 79– 84.
International Life Sciences Institute Europe (1999): FUFOSE: scientific concepts of functional foods in Europe. Br. J. Nutr. 81, 1S–27S.
Isolauri E (2001): Probiotics in human disease. Am. J. Clin. Nutr. 73, 1142S – 1146S.
Kaila M, Isolauri E, Soppi E, Virtanen V, Laine S & Arvilommi H (1992): Enhancement of the circulating antibody secreting cell response in human diarrhea by a human Lactobacillus strain.
Pediat. Res. 32, 141 – 144.
Kiremidjian-Schumacher L & Roy M (1998): Selenium and immune function. Z. Ernahrungswiss. 37, 50– 56.
López-Varela S, Nova E, Montero A, Gómez-Martínez S, Samartín S, de la Rosa B & Marcos A (2000): Alimentos funcionales. In Guías Alimentarias para la Población Española, ed. SENC, pp 303 – 312. Madrid: IM&C.
Marcos A, Toro O, Varela P, Nova E, López-Vidriero I, Requejo A & Morandé G (1996): Nutritional therapy in anorexia nervosa.
Immunomodulator effect of yoghurt. J. Adolescent Health 18, 157 – 162.
Marteau PR, de Vrese M, Cellier CJ & Schrezenmeir J (2001): Protection from gastrointestinal diseases with the use of probiotics. Am. J. Clin. Nutr. 73, 430S – 436S.
Meydani SN, Fawzi WW & Sun NH (2001): The effect of vitamin deficiencies (E and A) and supplementation on infection and immune response. In Nutrition, Immunity and Infection Disease in Infants and Children, ed. K Tontisirin & R Suskind, 45th Nestle Nutrition Workshop, Vol. 45, pp 213 – 241. Nestle Nutrition Services.
Moriguchi S & Muraga E (2000): Vitamin E and immunity. Vitam. Horm. 59, 305 – 336.
Rayman MP (2000): The importance of selenium to human health. Lancet 356, 233 – 241.
Roberfroid MB (2000): Prebiotics and probiotics: are they functional foods? Am. J. Clin. Nutr. 71, S1682 – S1687.
Ross A (1992): Vitamin A status: relationship to immunity and the antibody response. Proc. Soc. Exp. Biol. Med. 200, 303 – 320.
Schiffrin E, Rochat F, Link-Amster H, Aeschlimann J & Donnet-Huges A (1995): Immunomodulation of blood cells following the ingestion of lactic acid bacteria. J. Dairy Sci. 78, 491 – 497.
Solis-Pereyra B & Lemonnier D (1996): Introduction of human cytokines by bacteria used in dairy foods. Nutr. Res. 13, 1127 –1140.
Spalholz JE, Boylan LM & Larsen HS (1990): Advances in understanding selenium's role in the immune system. Ann. NY Acad. Sci. 587, 129 – 139.
Weber P, Bendich A. & Schalch W. (1996): Vitamin C and human health - a review of recent data relevant to human requirements. Int. J. Vitamin Res. 66, 19-30.