Functional foods: at the frontier between food and pharma

Editorial overview

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By training a microbiologist, Beat's research expertise is mainly in molecular biology and genetics of lactic acid bacteria. After having introduced genomic-based concepts for nutrition to Nestlé Research, he is now managing the project portfolio planning and intellectual property coordination for the Nestlé Research Center.

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Ian's main area of research is the relationship between dietary components and cancer risk, in particular the influence of probiotics and prebiotics on colorectal cancer and the role of phytoestrogens in the prevention of breast and prostate cancers.

It was the advances in understanding the relationship between nutrition and health, often at the molecular level, that led to the concept of 'functional foods' (also referred to as 'nutraceuticals' or 'pharmaceutical foods') as a practical and new approach to achieve optimal health and possibly reduce the risk of disease. An EU sponsored Concerted Action (Functional Food Science in Europe) coordinated by the International Life Sciences Institute Europe published recently a consensus paper defining that 'a food can be regarded as functional if it is satisfactorily demonstrated to affect beneficially one or more target functions in the body, beyond adequate nutritional effects, in a way that is relevant to either improved state of health and well-being and/or reduction of risk of disease' [1,2]. Today, the markets and product ranges of functional foods grow mainly in the first world countries. On the one hand, these products challenge the knowledge and understanding of consumers about nutrition and resulting implications to health; on the other hand, they challenge the legislative and regulatory systems on what benefits related to health and/or disease risk can be claimed and communicated in connection with food products [3]. In other words, where are the boundaries between a functional food and a pharmaceutical product? Furthermore, the fact that both the food and pharmaceutical industries are actively pursuing new developments in functional foods does not render this distinction more transparent.

Without doubt, optimal nutrition is a key factor in influencing physiological as well as psychological functions of an individual. Better knowledge and a broader communication should lead to better and healthier nutrition to the benefit of the consumer. This will contribute to improved individual health and a more cost-effective health management of entire populations. This issue of *Current Opinion in Biotechnology* is devoted to novel aspects of functional foods, including probiotics and prebiotics, nutraceuticals and phytochemicals. Furthermore, it covers aspects of validation of functional foods in man in the advent of improved technological possibilities in using holistic molecular approaches based on genomics and metabolomics research.

Probiotics probably represent the archetypal functional food. The purported health benefits, albeit vague, cover a wide range of areas including improvements in digestion, lactose intolerance, diarrhoea and immune defence [4]. Support for the health benefits was largely anecdotal and acquired over many centuries, but over the past 15 years or so scientific support has been forthcoming and several well-established clinical benefits are now apparent.

The first review in this issue by Marteau, Seksik and Jian (pp 486–489) describes two exciting new developments in the probiotics area — the control of inflammatory disease and reducing the risk of allergy. Inflammatory diseases of the intestine, such as Crohn's disease and ulcerative colitis, are chronic, painful conditions often recalcitrant to conventional drug treatments. Marteau and colleagues make the important point that clinical trials of a probiotic treatment with an *Escherichia coli* strain were shown to be as effective as the standard conventional treatment (mesalazine) in preventing the recurrence of ulcerative colitis. Several randomized trials have also shown that the incidence of atopic allergy can be reduced by probiotic treatment. Given the alarming increase in atopic disease in many western countries this could be an important, yet simple, dietary countermeasure.

As well as probiotics there is increasing interest in so-called prebiotics — dietary ingredients that stimulate the growth or activity of beneficial bacteria in the gut. The non-digestible oligosaccharides are the best known prebiotics and a wide range of such compounds, including fructo-, galacto- and xylo-oligosaccharides, are currently on the market. However, few have been rationally developed with specific functions or target microorganisms in mind and this is the topic of the paper by Rastall and Maitin (pp 490–496). The authors describe the new manufacturing biotechnologies, for example, the controlled hydrolysis of polysaccharides (plant, algal or bacterial) and enzymatic synthesis from monosaccharides or other oligosaccharides. They also discuss the increased understanding of the metabolism of oligosaccharides by probiotics and colonic microflora, which is enabling the development of prebiotics with specific functional properties and their associated health outcomes. Desirable functional properties include slower fermentation leading to increased persistence in the colon, so that beneficial effects and metabolic end-products are achieved in the distal region where many chronic gut disorders (ulcerative colitis and cancer) are primarily located. An exciting new development is the design of prebiotics targeted at specific probiotics of proven utility. The authors describe a novel approach in which β-galactosidases isolated from probiotic strains are used to synthesise galacto-oligosaccharide mixtures from lactose. Preliminary data indicate that these oligosaccharides support enhanced growth of the original probiotic. Such an approach could be of great value in the emerging field of 'synbiotics' (i.e. combinations of probiotics and prebiotics with enhanced health benefits).

Hugenholtz and Smid (pp 497–507) take the concept of bacterial production of prebiotics a stage further in their review by discussing the production of a wide range of nutraceuticals by food-grade microorganisms, notably *Lactococcus lactis*. *L. lactis* is the best studied of the lactic acid bacteria and is of enormous industrial importance being used for a wide variety of food fermentations. This microorganism has been a prime target for metabolic engineering strategies aimed at modulating the expression of desirable and undesirable genes. This capacity of *L. lactis* to act as a cell factory is leading to its exploitation as a source of nutraceuticals for the food industry and its use to enhance 'naturally' the levels of beneficial nutrients in dairy products. This review focuses on two areas — the synthesis of low-calorie sugars, such as mannitol, sorbitol tagatose and trehalose, and the production of vitamins. In the latter group, one of the most exciting areas is in the production of folate. Folate is increasingly being recognised as a vitamin with enormous potential nutraceutical benefits. Its role in the prevention of neural tube defects in neonates is proven and evidence is accumulating for beneficial effects on coronary heart disease and colon cancer. To achieve these benefits, relatively large amounts (~400 μg/day) need to be consumed and this intake is difficult to achieve without supplementation. Current work on *L. lactis* is focussing on the overexpression of genes involved in folate biosynthesis and in enzymes that increase the bioavailability of folate. This could lead eventually to the development of starter bacteria that could be used for the production of dairy products with elevated levels of highly bioavailable folate. Analogous research programmes are aimed at developing strains of lactic acid bacteria that enhance the natural levels of B_{12} and riboflavin in dairy foods, as well as providing a means of industrial scale vitamin production.

Since ancient times, plants have been known as a source of diverse biologically active chemicals (phytochemicals) essential for maintaining health and useful for treating and preventing disease. It is not surprising, therefore, that phytochemicals are being exploited as functional food ingredients and nutraceuticals. The levels of these beneficial chemicals in plants are extremely variable, and efforts are underway to improve the phytochemical composition of certain food crops. Conventional breeding is limited in this regard and transgenic approaches will be necessary in many cases to increase significantly the phytochemical content. This is the subject of the review by Grusak (pp 508–511) who discusses the principles, strategies and constraints in the use of genomics to manipulate phytochemical levels in crop plants. One of the major problems is the lack of knowledge of the function of the many thousands of gene products made by plants — thus, gene discovery and functional genomics are critical issues in the development of transgenic plant improvement strategies. The complexity of the biochemical pathways of secondary plant metabolites means that it will be necessary not only to identify multiple genes (DNA microarrays will be useful here), but also to transfer those genes to the target crop — a very difficult process. Nevertheless, there have been early successes, notably the production of 'golden rice' containing β-carotene and a strain of rice with enhanced iron bioavailability. It must be noted, however, that the nutritional efficacy of these strains has not been established. The author emphasises the urgency of developing transgenic crops, as the process is a slow and complex one, especially in comparison with the rapid growth in the human population.

One of the underlying themes of the review by Grusak is the importance of a profound understanding of the biochemistry and physiology of both the phytochemical and the target plant in question. This is a theme that is reflected in the contributions of Watkins and German (pp 512–516) and van Ommen and Stierum (pp 517–521). These authors concentrate on the use of the new genomic and post-genomic technologies to provide a sound understanding of the human genes and their functions in relation to disease, and in particular the extent to which nutrition and food components can influence health promotion and disease prevention.

Watkins and German (pp 512–516) note that of the global or 'omic' approaches (e.g. genomics, transcriptomics, proteomics and metabolomics), metabolomics, which measures the concentration of different metabolites in tissues and body fluids, is the most closely linked to the variations in phenotype that are relevant to growth development and overall health. Thus, it is likely that metabolomics will, at least in the short term, be the most useful resource for investigating diet and health relationships in humans. The subject is not without its limitations one of which is the accurate sampling of biological materials, which has an impact on the accuracy of the quantitation of metabolites. The authors point out the importance of building an integrated knowledge base of all metabolites and their responsiveness to nutritional changes and disease. It is clear that these new technologies are going to require sustained and collaborative international work.

Van Ommen and Stierum (pp 517–521) introduce the concept of systems biology, which attempts to provide an overview or holistic picture of a disease process by integrating information at different levels of genomic expression (e.g. mRNA, protein, metabolite). This type of approach is eminently suitable for investigating the relationship between nutrition and health, as nutrients usually have multiple biochemical targets (not all known); furthermore, dietary constituents are part of a complex mixture. It is envisaged that systems biology will facilitate the assessment of the activity of functional foods in humans and animal models, not least because it has the potential to measure small, multiple perturbations or patterns of response (such as those often induced by nutritional change) and to factor in variables such as genetic polymorphisms. There are immense challenges to overcome in this area, notably in developing the bioinformatic systems to handle the huge quantity of data generated. This exciting approach is, as yet, in its infancy, but the authors provide several examples of how it is currently being applied in the area of functional dietary components to give a taste of its potential.

References

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