GENES, GENOMES AND MOLECULAR BIOLOGY IN NUTRITION RESEARCH: A STORY OF OPPORTUNITIES AND CHALLENGES

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ABSTRACT: The wealth of freely available genetic information derived from genome mapping projects and the development of functional genomic and other powerful molecular biological tools have lead to profound changes in the scope of life science research and the way it is performed. As in many other disciplines, scientists in the fields of food science and nutrition are now beginning to fully realise the enormous potential these new resources and are seeking to integrate them into their research. However, there are still a number of issues specific to nutrition research that need to be addressed to ensure that this opportunity is exploited to the full.

KEY WORDS: Functional genomics; Genomic; Genotype; Molecular nutrition; Nutrition; Polymorphism

We are entering an exciting new phase for life science research. Precisely fifty years on from the first description of the structure of DNA by Watson and Crick (Watson and Crick, 1953), the International Human Genome Consortium have announced the completion of their primary goal with the release of the high-quality sequence of the entire human genome. Genome sequences of many other simple and a number of complex organisms are being processed at an astounding rate. This progress is paralleled by other spectacular technical advances in molecular biology that enable specific genes to be added, subtracted, over-expressed or silenced, essentially at will, in an ever-expanding range of organisms and model systems. Animals have been cloned successfully and the development of high-throughput functional genomic technologies, such as microarrays, proteomics and metabolomics, now enables scientists to profile global patterns of gene expression and metabolites and determine how these profiles change in response to specific stimuli.

In the light of all this, it might seem that there are few if any barriers to hinder or block systematic elucidation of how biological systems work at the molecular level. The truth is that many challenges remain. Not least among these are the warehousing, effective integration and extraction of the information present in the vast datasets that have been, and will be, generated. Nevertheless, we should quite rightly be very excited and enthused by the new scope for still more rapid and significant scientific advances.

Food science and nutrition research stand to benefit immensely from such developments. This is particularly true because the new approaches should be able to provide answers that we were simply unobtainable before now. We have known for many years from epidemiological studies that diet is a major factor in determining health and disease outcomes but to date we are still largely uncertain precisely which components of food are responsible for promoting health, how they work, or how much and in what physical form they should be consumed to elicit optimal effects. It is true that minimum requirements for essential dietary components have long been defined and there is also some understanding of toxicities associated with dietary excess of a number of food components. But there is also a wealth of tantalising experimental evidence suggesting that many other micronutrients, which traditionally have been considered as "non-essential", have properties that could be as, or even more, important in health promotion. It is the final definitive proof that any one of these compounds really does promote human health in the free living population, and does so to a meaningful extent via mechanisms that we understand, that has proved frustratingly elusive.

In some cases where health benefits have at first seemed clear-cut or have attained a widespread level of public and scientific acceptance, the resulting health claims/assumptions subsequently have required moderation as a result of the production of further conflicting data, for example in the case of dietary fibre and its proposed protective effects for colon cancer (Fuchs et al, 1999), or even findings of unexpected potential adverse effects, as in the case of trans-isomers of polyunsaturated fatty acids (Mensink and Katan, 1990; Wood et al, 1993). While this kind of thing is to some extent inherent in the nature of scientific discovery, the risk is that too much controversy leads to a degree of confusion and distrust amongst the public and possibly a wider perception, rightly or wrongly, that advice is being given on the basis of insufficient evidence, possibly due to vested interests, and perhaps even
that there continues to be slow progress in nutrition research compared to many other life sciences. These outcomes would be bad news for the nutrition research community, food industry and government.

In reality, these types of problem actually reflect the complexity of the scientific challenges that have to be addressed in nutrition research. To take an example, in pharmacology and toxicology active agents generally will elicit profound biological effects whereas the health-promoting components of the diet are more likely to produce relatively subtle biological effects that become important with chronic exposures over as much as a human life-span. Such effects may be detected in highly controlled experiments performed in vitro, but ultimately the very best model for human nutrition is the human and these are notoriously difficult “models” to work with. They are genetically diverse, exposed to many environmental variables that make experimental control a constant problem and can be relied on to behave unreliably and unpredictably. On this background, detecting moderate biological effects provoked by realistic dietary manipulation is always going to be a challenge, particularly in the relatively short term and/or small scale studies that financial constraints usually permit. There can be little doubt that this has doomed many human dietary studies to apparent failure and produced a significant volume of inconclusive data.

On top of all this, the diets we eat are also highly complex. Foods contain many thousands of components present in a wide range of concentrations. These are presented to the digestive tract in many different combinations and forms. This, in turn, affects patterns and rates of absorption and metabolism.

Given all this complexity and variability perhaps one might consider that it is remarkable that any meaningful progress has been made at all. Indeed, on a few occasions I have heard it argued by scientists from some other specialties that the challenges of human nutrition research are too great to make it worthwhile. I have always considered this a surprisingly defeatist attitude given that the history of science is rife with examples of what was considered by many to be impossible, ultimately being achieved (the sequencing of the human genome being a prime example). In fact, with the development of new technologies such as functional genomics, we genuinely have the tools to cope with such highly complex systems and so that this argument should lose any validity that it may have held.

These techniques will streamline the process of defining the mechanisms of action of individual and complex mixtures of food components and their metabolites. They have the potential to generate and validate many new and better biomarkers. These could include complex biomarkers in which, for example, the pattern of expression of a defined set of genes is used to provide greater confidence and enhanced sensitivity over the analysis of such genes individually.

In addition, the all-encompassing nature of the data produced with functional genomic techniques makes them ideally suited to the identification of unexpected and unintended effects. This should be exploited to reduce the number scares of the types described above in which unexpected adverse effects are found to be caused by food components that had been considered to be exclusively health-promoting in nature. Indeed, functional genomic approaches are ideally suited to form a central component of new frameworks for risk/benefit analyses that can be used to define safe and efficacious dietary intakes of different dietary compounds. With rafts of new legislation on the way that are supposed to protect the consumer, such frameworks are likely to become essential components in the production and validation of new functional foods and associated health claims.

Success here should help to reduce some public concerns about the use and value of nutritional genomic and molecular biological tools in food science. However, at the moment public concern about new molecular approaches is relatively widespread and we should take careful note of the public backlash that has occurred against genetically modified foods. If we do not take note, we risk a similar backlash against the application of nutritional genomic to develop new products. It is vital that a clear distinction is made between approaches that do and do not use genetic modification. For most nutritional genomic approaches, genetic modification is not required. Rather these tools are used to examine biological effects in model systems that are generally designed to be as close to “normal” as possible. In the current climate, the majority of new functional foods are likely to be prepared by modification of formulations rather than through genetic modification and it is this process of formulation that will be informed by the new technologies. Consequently, nutritional genomics should not be seen as a matter of “messing with nature” but a way of scrutinising nature and taking advantage of what is found. It is vital that these facts are conveyed to the public effectively.

The other major area of concern is human genetic analysis. Together with the consensus genomic sequence databases, vast amounts of information about sites of genetic polymorphisms are being made available to the scientific community (International SNP MAP Working Group, 2001) and high-throughput techniques for analysing DNA samples for such polymorphisms are being developed. Again this is a cause for considerable scientific excitement as it is starting to make it possible to account for the genetic component of inter-individual variation. In nutrition, this progress is frequently held up as opening the door to what some might consider a utopian world in which dietary advice is targeted to the individual based on their genetic makeup. Indeed, there already are a number of examples in which clear links are being made between specific common genotypes and differences in optimal dietary requirements (Sarkkinen et al., 1998; Smith, 2000; Ueland et al., 2001). But regardless of the practical and logistical problems that remain to be solved if this goal is actually to be achieved, many can imagine a far more sinister side to the story. There is a fear that such testing, whether it be for medical, nutritional or other lifestyle purposes, could contribute to the development of some kind of “big brother” state in which
a genetic underclass develops. While this nightmarish scenario may be rather fanciful, it is far easier to envisage a situation in which individuals find difficulty in obtaining life assurance or are faced with elevated premiums because of the results of genetic tests that they could have undertaken voluntarily. Indeed this legal fight is already underway. Additionally, there are many other moral, ethical and legal issues concerning genetic testing still require considerable reflection and raise legitimate public concerns.

The onus is upon the scientists and ethicists to address such fears sooner rather than later and it would be unwise for us to assume that this can be done simply by programmes of education. It would be far better for the scientific and industrial communities together with the legislators to take the slightly unusual step of establishing mechanisms for dialogue with the concerned public at this early stage so that we can be sure exactly what their primary concerns are, address them effectively and start to build greater trust.

There appears to be widespread acceptance amongst the nutrition and food science research community that the new molecular approaches do present enormous potential for substantial scientific advance but further clear evidence is still required that this potential genuinely can be realised and realised now. This proof of principal is likely to start with the demonstration that the new approaches are consistently sensitive and reliable enough to detect the subtle but important biological changes produced by bioactive components of the diet when applied in physiologically representative manner to physiologically representative systems. This surely is imminent as an increasing number of research groups around the world are taking up the challenge. Indeed, some might even argue that there is sufficient evidence already.

Beyond this stage, I would contend that something of a transformation of the way we perform nutritional studies will be required. Although the new techniques can be applied to continue with the currently favoured approach of maintaining a close focus upon only one or a few specific processes, a much more powerful approach is to use them to adopt a broader, systems biology, viewpoint. This makes use of all the available experimental technologies together with the developing mathematical, computational and statistical methodologies. Although this is a daunting prospect, it is one way (possibly the only way) to obtain a complete overview of the manner in which the human interacts with the food he/she consumes. I sincerely hope that the timely launch of this journal will help in promoting the new approaches in nutrition research and expedite the full realisation of this opportunity.

REFERENCES


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