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Nutrigenomics: Looking to DNA for nutrition advice

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With the success of 'Human Genome Project' and the powerful tools of molecular biology, we have entered the era of genetic nutrition. The publication of the human 'blue print' has triggered an explosion in pharmaceutical research to utilize this knowledge in prescription of drugs to be tailored according to the genetic make up of susceptible individuals or in other words personalized medicine. Propelled by the recent unraveling of human genome; nutritional sciences are discovering the application of the so-called "omics" sciences. This has the potential of identifying and validating targets to improve personalized nutritional health and thus serves to define the added value for the next generation of foods and the crops. The first new term to emerge in this area was "Nutrigenomics." Today, the term nutrigenomics generally refers to the study of how dietary components interact with the genome and modify subsequent gene expression[1]. It is envisaged that nutrigenomics will lead to evidence-based dietary interventions for prevention of diet related common diseases.

Keywords: nutrigenetics, nutrigenomics, single nucleotide polymorphism, transcriptomics, proteomics, metabolomics, transgenics

Introduction

In 1996, Ghai and co-workers filed a seminal patent, which highlighted the potential for development of foods or supplements that could alter the expression of genes associated with human diseases[1]. They demonstrated that certain flavonoids in citrus peel enhanced expression of a gene involved in the human body's natural defense against cancer. This was the beginning of the study of the relationship of food, as nutrition with our genes. The new era of molecular nutrition can unfold in dichotomous directions—'Nutrigenomics' and 'Nutrigenetics'.

Nutrigenomics refers to the application of genomics in nutrition research, enabling associations to be made between the specific nutrients and genetic factors, e.g. the way in which food ingredients influence gene expression[2].

Nutrigenetics, on the other hand, refers to the study of how individual genetic disposition, manifesting as single nucleotide polymorphisms, copy number polymorphisms and epigenetic phenomenon affect susceptibility to nutrient intake. Nutrigenomics focuses on the effect of nutrient or food bioactives on the regulation of gene expression. Nutrigenomics has, however, also embraced the study of how nutrients influence the consequence of gene expression, i.e. synthesis of mRNA (transcriptomics), protein synthesis (proteomics) and metabolite production (metabolomics). The three can be combined into a Nutritional Systems Biology approach[4]. Nutrigenomics is a discovery science driven by paradigms of molecular biology, enabled by the microarray technology and integrated on an informatics platform[5,6]. In contrast, nutrigenetics is an applied science driven by the paradigms of nutritional pharmacology in the context of genetic polymorphism and clinical experience. In practice, the convergence of the two sets of knowledge that comprise genomics and genetics will be needed to fully realize the promise/potential of nutritional genomics.

The basic idea is that there are genes that affect the risk of getting illnesses like heart disease, cancer, osteoporosis and diabetes; and the impact of those genes can be modified by what you eat. Everybody carries one version or another of each of those genes. So why not find out what gene versions you have and base dietary advice on that. People already make dietary choices based on their genetics such as switching to soymilk for lactose intolerance, using

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cholesterol-lowering spreads, etc. As the science of nutrigenomics is evolving, it will reveal not only which foods can have direct impact on our genes, but also how and why. The ultimate goal is to be able to prevent, and potentially even treat diseases through targeted nutrition.

Nutrition and Human Genetic Diversity

The sequencing of human genome has laid the foundation for one of the most significant scientific contributions to mankind that although all the human individuals are genetically similar yet each retains a unique genetic identity. The genetic make-up gives varying instructions for each individual. Nutrigenomics must address how individual genomes respond to complex nutrient and chemical mixtures that comprise food. We understand that certain genotypes are more severely affected by specific dietary factors than others. One thing is clear that no genotype is free from the deleterious effects of inadequate diet[7].

Genes express themselves through proteins. Enzymes are special proteins designed to get things started. Our genome instructs ribosomes to produce many enzymes that destroy toxins. Some foods such as cauliflower, broccoli and brussels sprout contain chemicals that actually prod our genes to direct biosynthesis of these enzymes. The response to this prodding may be hindered by the genetic make-up. For example, fava beans contain a toxin usually degraded by a chemical produced in the body. Without this chemical, the toxin leads to destruction of red blood cells (RBC). For those whose genes do not direct the production of enough of this chemical, eating fava beans results in loss of RBC and serious health problems. In some individuals, genes give unclear instructions for making an enzyme that metabolizes the amino acid, phenylalanine. As a result, this amino acid builds up, thereby causing brain damage. A diet restricting this amino acid will help stop the damage if detected in early infancy.

Transfer of nutrients from gut to cells requires carrier and receptor proteins. Some individuals have genes that direct overproduction of iron carrying proteins. The resulting iron overload is extremely toxic and may lead to death. Similarly *GLUT4* is a protein that transports glucose across skeletal muscles and fat cell membranes. Individuals with Type-2 diabetes lack the ability to grasp the message instructing the ribosomes in skeletal muscles and fat cells to produce *GLUT4*. As a result, glucose stays in the blood causing a number of problems[8].

Currently, several nutrition related issues benefit from genetic research. A number of conditions like phenylkentonuria (PKU), caffeine intake and bone loss in post-menopausal women[9], folic acid and heart disease, obesity, anorexia nervosa, vitamin C supplementation to reduce cancer risk and low fat diet for high blood cholesterol levels, show the influence of genetic variation on nutrition advice.

It is clear now that there is heterogeneity in response to dietary regiments. Nutritional genomic research will determine the genetic basis for that heterogeneity, clarify the molecular basis by which specific genotypes respond to dietary components and other environmental signals, generate analytical tools for determining the genotype of a person and provide targeted therapeutic interventions for disease amelioration and prevention.

Diet and Gene Expression

Although our understanding of nutrigenomics is still very rudimentary but it is clear that the genomic response of an individual is finely tuned to its diet. Not only humans but insects too employ a number of behavioral, biochemical and physiological mechanisms to respond to nutrient intake in terms of quality and quantity of food[10]. Such responses have been clearly observed at molecular level. Zudaire *et al* have found that when the protein carbohydrate ratio is altered from the optimum, there is a decrease in the expression of the proliferating cell nuclear antigen gene in the gut of *Locusta migratoria*[11]. Similarly, starvation and a high sugar diet leads to induction of specific sets of genes in *Drosophila melanogaster* larvae[12]. The herbivorous insect, Colorado potato beetle, is able to adapt to changes in defence proteins that plants synthesize in response to various environmental stresses[13].

Yocum and co-workers fed *Perillus bioculatus* nymphs on suboptimal artificial diet and examined them for differential expression of the two genes (i) the tyrosine-3 monooxygenase and (ii) the gene for chitin binding protein, *Gasp*. They found a positive correlation between the levels of expression of the isolated genes and the number of generations the insects had been reared on the artifical diet[14]. Nutrigenomics is a directed method to examine as to how the nutrition affects gene expression and offers not only a means to quantify insect's response to diet reformulation but also furnishes information on diet limitations. This can lead to the development of an optimized artificial diet, which in turn, may greatly reduce the cost of production of beneficial insects.

The dietary factors seem to have a profound effect on many aspects of the human health including ageing, inflammation, obesity, reproductive performance, cancer and other diseases at least partly, through interaction with the genome, which results in altered gene expression. Caloric restriction (CR) seems to be an important modulation of ageing. The results of global assessments of gene expression during ageing in mice and the impact of CR were first published by Lee *et al,* who used genome wide microarry expression analysis to establish this[15].

Ageing results in differential patterns of gene expression characteristic of increased stress response with reduced expression of biosynthetic and metabolic genes. CR reversed most of these alterations partially or completely in various tissues[15,16]. Except for CR, there is no proof of the role played by particular food constituents in influencing longevity[17].

The science of nutrigenomics has begun to use specific gene expression patterns to evaluate the effects of nutrition on key metabolic processes relating to reproductive performance. While the effects of nutrition on fertility are poorly understood, there are reports of some fertility associated gene expression patterns that are changed by supplementation of various dietary forms of selenium e.g. selenomethonine, sodium selanite and selenium yeast. In mice, using a basic 23,000-element murine microarray, the researchers found a dramatic change in gene expression of 2500 genes being influenced by selenium supplementation and at least 100 of these seem to be associated with reproductive function directly or indirectly[18]. It has been observed that a set of oxidative stress-associated genes and the genes involved in the thioredoxin electron carrier system also get readily influenced by selenium supplementation.

There is an emerging body of data supporting the remarkable effects nutrients can have on gene expression. It is now well known that nutritionally significant dietary metals such as zinc do affect the gene expression levels. Zinc interacts with DNA-binding proteins forming the motifs known as zinc-fingers. The zinc fingers assume appropriate conformation and bind to DNA and thereby act as molecular switches affecting gene expression by blocking the transcription[19].

In addition to metals, some macroscopic nutrients like soluble and insoluble dietary fibres have been shown to affect gene expression e.g., colonic gene expression gets affected by the fibre[20].

Screening Novel Potential Biomarkers—Predicting the Risk of Disease

Biomarkers are the genetic variants that predict the risk of disease and improve diagnosis and risk assessment. For the testing of efficacy of bioactive functional food ingredients, an urgent need exists for biomarkers. Genetic polymorphism may be partially responsible for variations in individual's response to bioactive food components. Single nucleotide polymorphisms (SNPs) are becoming increasingly recognized to have an important influence on disease risk[21], for example, inherited polymorphism in BRCA1 and breast cancer susceptibility[22]. Some common SNPs in genes involved in nutrient metabolism, metabolic activation and/or detoxification could establish the magnitude or whether there is a positive or negative response to food components[23]. Women, who consume less fruits and vegetables than required were reported,to be at the greatest risk of developing breast cancer because of a polymorphism that causes a valine to alanine (Val to Ala) change in the ninth position in the signal sequence for the enzyme manganese dependent superoxide dismutase[24]. Consumption of well-done meat was correlated with increased breast and colon cancer susceptibility among individuals with a rapid/intermediate N-acetyl transferase genotype but not among individuals with slow acetylator genotype[25,26].

Several epidemiological studies have shown correlations between mildly elevated homocysteine levels and cardiovascular disease risk. Methylene tetrahydrofolate reductase (MTHFR) catalyzes a reaction, which produces 5-methylenetetrahydro-folate, a cofactor donating a methyl group to a reaction converting homocysteine to methionine. The SNPs (C677T and A1298C) are associated with reduction in MTHFR activity. This might lead to increase in the plasma concentrations of homocysteine and thereby to venous thromboembolic disease, ischemic arterial disease and neural tube defects[27,28]. Treatment with folic acid supplementation helps to overcome the effects of these polymorphisms in MTHFR gene[29,30].

Cardiovascular diseases (CVDs) are a group of multifactorial conditions associated with atherosclerosis, hypertension and thrombosis. Of these, atherosclerosis is the key element in the pathogenesis of CVD. Risk of atherosclerosis can be detected at a preclinical stage by quantitative assessment of blood lipid levels. Genetic polymorphism in key genes that have a bearing on blood lipid levels has been

addressed in several recent reviews[31-33]. Nutritional counseling to reduce the dietary fat would be beneficial to overcome the negative health effects of certain polymorphisms.

Similarly, a number of polymorphic genes have been implicated to cancer development e.g. variants of melonocortin 1 receptor gene (MCIR) have been found to be associated with several types of skin and prostrate cancers[34]. There are claims of dietary supplements that may protect against diseases like cancer. New foods are being developed as functional foods. Introduction of the concept of 'kinetics of biomarkers' would be an important step in the validation of such claims[35].

Obesity has become a major public health problem. Mutations in genes like leptin and leptin receptor genes have emerged as leading candidates towards predicting obesity. In addition, mutations in melanocortin 4 receptor and melanocortin 5 receptor gene and in the non-coding regions of the gene for neuropeptide Y (NPYY5R) receptor have also been shown to be strongly correlated with the risk of obesity[36]. Once the mutations are detected in the family, the physician might be in a position to offer diet restriction/intervention at an early stage of life.

Evidence is accumulating that variability is induced by SNPs in the genes associated with the inflammatory process as well[37]. This variability influences the responsiveness of individuals to changes in nutrient intake, for example, SNP may be responsible for modulating the ability of fish oil to reduce the production of proinflammatory cytokine tumour necrosis factor (TNF)[38].

To understand our personal uniqueness with regard to nutrigenomics, SNPs have opened the door to manage and optimize our health through tailored nutrition. Of course, this is a lofty and distant goal but the fact is that we have already started the journey towards it[3].

In addition to SNPs, copy number polymorphisms[39] (CNPs) and epigenetic phenomenon[40] too have shown to affect the susceptibility to diet. Epigenetic phenomenon like DNA methylation, histone acetylation and RNA interference add to the complexity of gene regulation. Methylation is the best characterized epigenetic process. Around 3-5% of the cytosine residues are methylated in mammalian cells. These methylated cytosine residues appear as 5-methyl cytosine (5MeC); 70-80% of these residues are clustered in CpG islands. If these CpG islands are present in the promoter of the genes, this suppresses their expression (gene silencing). The presence of 5MeC may interfere with the binding of transcription factors or other proteins and hence block the transcription. It has been reported that increased methylation in the CpG island in the promoter region of oestrogen receptor (ESRI) gene occurred during ageing and tumour development, and was associated with the loss of expression of the protein[41].

In addition to this, DNA methylation prevents the genome from selfish DNA elements like transposons, endogenous retroviral long terminal repeats and other dispersed repeat sequences. Loss of methylation from these leads to genomic instability and activation of tumour inducing genes[42]. There are a number of reports suggesting altered intake of several nutrients like folate[43], selenium[44], polyphenolics[45] and food contaminants like arsenic[44] can affect DNA methylation patterns. However, we have to go a long way to understand the molecular mechanisms by which dietary components affect DNA methylation patterns.

Histones are a dynamic component of chromatin. Individual histone molecules get modified as a result of modifications occurring in their individual amino acids especially at their tails. These include adding acetyl groups (CH_3CO) to lysines, phosphate groups to serines and methyl groups to lysines. These specific modifications can either stimulate or inhibit gene expression by allowing or denying access to proteins involved in transcription. Diet-derived factors can also influence the histone modifications. For example, addition of 4-phenyl butyrate to the diet of *Dorsophila,* leads to increased acetylation of histones H3 and H4 and thereby altered pattern of gene expression[46]. Similarly, diallyl sulphide found in garlic leads to increase in histone acetylation, which in turn re-expresses the previously epigenetically silenced genes and also alters the cell growth kinetics[47].

Transcriptomics, Proteomics and Metabolomics

The inadequate success of single biomarkers in predicting chronic diseases attests to the need for other approaches like transcriptomics, proteomics and metabolomics or in other words thinking beyond the interaction of genes and nutrients. Moving from the single biomarkers to the other approaches is necessary because lowering the unilateral risk of one disease in an individual simply increases the risk of another disease in the same individual. Single nutrients may

have multiple and unknown biochemical targets and physiological actions, which may not be easily addressed with chemical biomarkers[48].

An important challenge in the development of functional foods for the prevention of complex (multifactorial) diseases is to obtain a better and improved overview (holistic) picture of the early processes. Here, the concept of *systems biology* steps in. It is related to the integration of all the information at different levels of genomic expression i.e. mRNA, proteins and metabolite (Fig. 1), which depicts the effects of bioactive food components on systems biology.

Currently, transcriptomics is relatively a mature technology, in comparison to proteomics and metabolomics. We can get an overview of expression of almost all the genes in a single microarray experiment but it has not been possible to measure the whole proteome or metabolome till date[49]. The expression of genes can be evaluated at an unprecedented scale, using cDNA microarrays. These techniques are based on quantitative assay of the relative concentrations of specific mRNAs in tissue samples, which in turn reflects the level of gene regulation. This information can be used to examine the factors (including nutrients) that influence the key gene expression patterns[18].

Bioactive ingredients directly from food pass through our cells into the nucleus where they interact with DNA to affect transcription of RNA and ultimately translation of proteins. Although the mechanisms by which dietary components influence gene expression are poorly understood but it appears that transcription factors (TFs) are the main targets or nutrient sensors. In this context, the nuclear receptor superfamily of transcription factors with 48 members in humans, is gaining much attention. Many nutrients and their metabolites bind to numerous receptors in this superfamily. For example, peroxisome proliferator activator receptor-α (PPAR α) binds fatty acids or liver X receptor ά binds cholesterol metabolites. PPAR α is present in liver and there are 3000 to 4000 target genes where this transcription factor is involved. During ligand binding, the nuclear receptors undergo a conformational change. These nuclear receptors go and bind to the specific nucleotide sequence in the promoter region. The conformational change (brought about by the nutrients) in nuclear receptors leads to a change in the level of DNA transcription of specific genes[49]. The

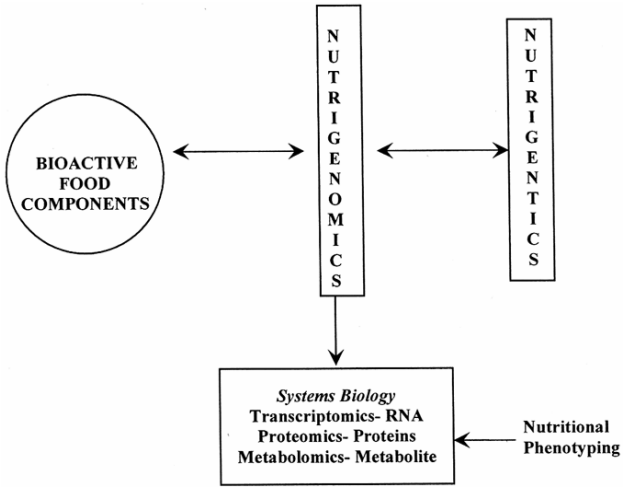

Fig. 1—Effect of bioactive food components on *Systems Biology*.

transcription gets promoted or inhibited as required for the appropriate response to the environment[48]. For example, during fasting free fatty acids are released from the adipose tissue. These fatty acids then travel to liver and undergo partial or complete oxidation. In addition to this, these fatty acids also bind to PPAR α, which in turn increases the expression of a number of genes, by binding to specific sequences in the promoter regions. Fasting null mice (lacking functional PPAR α) suffer from a number of defects like hypoketonemia, hypothermia, elevated levels of plasma free fatty acids and hypoglycemia[50,51].

Proteomics refers to all the studies related to structure of proteins, expression levels, biochemical activity, protein-protein interaction and cellular localization. The protein content of an organism varies from cell-to-cell and it depends on the type of function carried out by a particular cell. Proteins can be analysed before and after diet intervention therapies.

Plasma proteomics would be of great importance to nutrigenomic research. Progress in this area is likely to generate a wealth of information about important proteins like cytokines or hormone levels from a small plasma sample. Major plasma proteins need to be separated for further analysis. Determining nutrition status, by proteome derived biomarkers, may be possible before too long[49].

In fact, a gene product often requires post-translational modifications after it is produced for functioning properly. The control levels in the genomic pathways are truly multilevel[21]. Brudnak has called nutritional supplements capable of altering the integrity, expression or fidelity of genes, collectively

as genomoceuticals, for their ability to act on the genome in a manner related to pharmaceuticals acting on biochemical pathways. In this paper, it has also been discussed as to how glucosamine can up-regulate the obese gene (*ob*) by acting on a nutrient-sensing pathway[52].

Relatively few studies relating diet to proteomics are available. Recent work by Roos *et al* has, however, shown the potential of proteomics to reveal unknown associations between particular protein and metabolic disorders[53]. In contrast, there is a global surge in optimism for a role of metabolomics in human nutrition[54]. Metabolomics is emerging as an exciting post-genomics science with applications that span the scope of biotechnology and medicine. It provides nutrition with an invaluable tool for determining the distribution of metabolite concentrations in humans, the relationship of these metabolite concentrations to disease and the extent to which nutrition can modulate metabolite concentrations. So why not change the single biomarker concept into one in which the entire range of plasma metabolites (plasma metaboloma) is measured simultaneously. This is going to be bolder step and the databases of metabolome information will be used to provide a significant reflection of the entire biochemical status of an individual at a given point of time[55].

For the broad screening of metabolites, mass spectroscopy and nuclear magnetic resonance spectroscopy seem to be appropriate and robust technologies[54]. The great expectation of metabolomics is that it might offer the prospects of the ultimate biomarker of overall dietary pattern. Preliminary results show that dietary patterns could have a powerful effect on the metabolic profiles[56]. Therefore, the emerging field of nutrigenomics requires a multi-disciplinary and international collaborative approach. A global initiative on nutritional metabolomics has been already initiated by the NUGO, the European Nutrigenomics Society (www.nugo.org).

Improving Plants for Nutritional and Health Benefits

Biotechnology was used in the first generation of the so-called GM crops to provide growers with complimentary and sometimes alternative crop management solutions to herbicides, pesticides, etc. Selected genes from other plants or non-plant sources are transferred to the desired plants. The new or altered protein expression resulting from these modifications confer on the plant a desired physiological trait. Second generation modifications would be aimed at identification of plant genes of nutritional importance and then transferring them to desired crops[57]. Already some foods have been modified using biotechnology to provide better nutrition. Golden rice is one example, with its high carotene levels that will help in preventing blindness in children.

Micronutrients malnutrition that exists in various population groups throughout the world could be reduced by a more nutritious food supply, especially if efforts are focused on staple crops such as rice, maize, wheat, beans and cassava[58]. Identifying the genes needed to increase the levels of essential micronutrients in staple crops is an immediate goal that would have significant impact on human nutrition worldwide. For essential minerals and vitamins that are limiting in the world diets, improvement strategies should be pursued keeping in mind the upper safe limits for each nutrient.

The nutritional genomics approach has been applied to vitamin E biosynthetic pathway in plants. The researchers isolated the first step of the pathway from *Arabidopsis* with fungal and human orthologs as database queries. This *Arabidopsis* sequence provided a genomic stepping-stone to identify an ortholog in 10-gene operon in photosynthetic bacterium, *Synechocystis PCC6803.* Gene disruption experiments showed that this operon also encoded the final step in vitamin E synthesis, γ-tocopherol methyltransferase (γ-TMT). The *Synechocystis* γ-TMT gene allowed isolation of an ortholog from the *Arabidopsis* database whose overexpression increased vitamin E levels nearly nine-fold in *Arabidopsis*[59]. Therefore, by using database, proteins and DNA homologies and insilico-computer searches it is possible to rapidly move experimentally between organisms while remaining focused on the single pathway or enzymatic reaction of interest from the target organisms.

Continued efforts in gene discovery, functional genomics, secondary metabolism and nutritional physiology must be pursued, as these investigations will provide the necessary molecular insights and whole plant understanding to help us formulate sensible high-impact improvement approaches. The use of model system to assess the efficacy of various transgenic strategies will remain an important proof of concept tool, but researchers must continue to look towards the transformation of agronomically important crops as soon as an effective strategy is identified[60].

Ethical Issues

As nutrigenomics is involved in public health and food, there are some ethical concerns. Firstly, people need to be educated on nutrigenomics. As there are functional foods that claim to have health promoting/enhancing effects on the individual, acting at the DNA-level, is not known if they are suitable for all, as each person differs genetically.

Secondly, there needs to be a basic understanding of not only which foods have direct impact on the genes but also how and why? Some companies like Sciona Inc. from Boulder, Colorado (USA) have already started giving personalized nutrition advice based on a person's genetic profile since 2001. Some scientists are skeptical about this as there is a lot more research to be carried out. At present, genetic science is still too immature to promise such sweepings. So there should be understandable concerns about quality control in this area.

Thirdly, the role of professional nutritionists needs to be carefully thought in terms of genetic testing and conveying information. There has to be guidelines established while undertaking population screening, as sometimes the disorders may not be as clear-cut as PKU[61]. In addition to this, the information from genetic tests may become increasingly attractive to outside parties who stand to gain from it. There is a concern that employers or insurers could use genetic information to the unfair disadvantage of some people. So, the question arises where to store information relevant to individuals and who should have access to it. How would the nutritionists get access to this information? Would there be access to large population database or the individuals carry a smart card containing their genetic profile? Large population databases need controls relating to who shall have access and on what terms[61].

Fourthly, it would not be long before each individual gets his/her own personalized nutrition, i.e. what a person should eat to promote health and what food products the individual has to avoid. Can this be looked upon as invasion of freedom of food choice?

Fifthly, even though the analysis of nutrient-gene interaction is carried out in cell cultures and other animal models, it has to be clinically tested on human subjects. With an ethnically diverse population, the testing has to be carried out on ethnic and culturally diverse groups. The question of testing on human subjects is sensitive with the risk of some researchers/institutes using humans as laboratory animals and also exploiting the socio-economically poor.

The availability of DNA is limited to blood for nutrition research. One cannot solely rely on the DNA available from this, as gene expression in each tissue is different. The only way to get DNA from liver, kidney, and gut is by carrying out biopsies. This method of collecting samples is very invasive.

Conclusions

The knowledge of nutrigenomics would spawn a revolutionary way of viewing the food just not for sustenance, but as a pharmaceutical capable of reversing disease and stalling the rigors of ageing.

The nutrigenomics approach resembles pharmagenomics, which looks at the relationship between SNPs in gene and patient's response to drugs to personalize medicine. The two are closely linked, without nutrigenomics, pharmacogenomics data cannot be interpreted correctly, because diet may affect the expression of genes involved in drug metabolism. Kaput *et al* suggest that pharmaceutical companies should include nutrigenomics in the design of new drugs because 'what you eat affects a drug's efficacy.' The combined knowledge from these two 'omics' could pave the way for most successful dietary recommendations[7].

Although Indian Ayurvedic medicine and traditional Chinese medicines have already documented effects of plants on human disease since generations, we are yet to analyze the effects of Ginko, St. John's wort and different types of dietary fat/carbohydrate on different individuals. Again, nutrigenomics would become the means for confirming the mechanism of action.

The real challenge for nutrigenomics research is to target the genes involved in the major human diseases like cancer, heart disease, arthritis and obesity. In fact, many of the genes involved in these polygenic, chronic diseases are yet to be identified. The bioactive ingredients of food may turn on some genes and simultaneously turn off other set of genes involved in a disease. The success of this science will require meaningful biomarkers and completion of clinical trials that monitor biomarkers. The broader and much more exciting aspect of this technology is the generation of metabolic content of a cell or organism at a given point of time. The knowledge of 'metabolimics' will ultimately guide us on wholesale renovations of agricultural products for nutritional importance.

There has to be global sharing of knowledge for the successful progress, as expertise from various fields is required. With the growing information about nutrigenomics generated by microarray technology, there is a need for databases to store this information securely. This database (<url>http://a-yo5.ch.a.u-tokyo.ac.jp/index.phtml<url>) is built on an open-source database system and is freely accessible.

Establishing links between genetic factors and dietary habits is more complex than establishing links between genetic factors and adverse reactions of drugs. In the past, national dietary surveys carried out studies to establish links between food and nutritional status by collecting blood and urine samples. However, these studies are controversial as samples were collected only from healthy individuals.

The ultimate aim of this emerging field of science is prevention rather than cure. This is not very different from the opinion of Hippocrates-father of medicine (460-360 BC) who said "Leave your drugs in the chemist's pot if you can heal the patient with food."

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