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Review

Harmonization of Eastern and Western Health Knowledge; Nutrigenetics and *Sasang* Typology

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The completion of human genome project and the powerful tools of molecular biology together with bioinformatics technology give possibility to open the dialog between modern medicine and traditional remedies including Eastern medicine. Many of functional foods are originated from the traditional herbal medicine, and the scientific substantiation of the effectiveness of these products is required for the regulatory standards as well as for consumer protection. Needs for the reliable and efficient methods of scientific substantiation are increasing, and nutrigenomics may provide a short-cut way to scientific evaluation of many functional food ingredients and herbal medicine which have been used in the traditional societies for thousand years. Studies to apply nutrigenomic methodologies to the objective classification of Sasang body constitution types of Korean are reviewed. It is suggested that the empirical health food knowledge accumulated in the Eastern medicine may be explained scientifically by using the nutrigenomic methods, and it will contribute to open the custom-made nutrigenetic food age in the near future.

Keywords: Functional food, nutrigenomics, Sasang body constitution typology

Introduction

Human perception on food has changed through history, from the survival food of the 19th century and before to the convenience food of the 20th century. We all realize that functional food and personally prescribed nutraceuticals will be the food for the 21st century consumer of the affluent societies (Lee, 2006). Nutrigenomics will play key role in prescribing the personalized health food for individuals. The degenerative diseases, cardiovascular disease, cancer, diabetes and obesity coming from imbalanced nutrition mainly by overeating and reduced physical activity, became the major causes of death today (Lee *et al.,* 2005), and people want to correct their imbalanced nutrition by taking functional food and dietary supplements which are made for special target group.

One of the difficulties in the evaluation of the effectiveness of a functional food or functional component is that it is true for some people but not for others. The personal specificity in the response to chemical components is often encountered in nutritional and pharmaceutical researches. Recent progress in human genome research and the powerful tools of molecular biology make us enable to explain the personal specificity by genetic basis. Although the knowledge of nutrigenetics is in the stage of impetus, it will open the age of nutrigenetic food, which supplies tailor-made personal food fulfilling individual requirement for best fitness.

The traditional societies in Asia as well as in Europe have used natural remedies and herbal medicine, and they are now considered as complementary and alternative medicine (CAM) supporting the Western scientific medicine. The Eastern medicine, generally known as traditional Chinese medicine (TCM), has long history of practical use, although the scientific substantiations of the effectiveness are not fully established. It emphasizes the organic harmony of whole body based on the Chinese old philosophy Yin/Yang and Five-phases theory (Maoshing, 1995). Korean Eastern medicine emphasizes the type of body constitution in diagnosis and treatment of diseases, which is represented by Sasang body constitution typology.

Recent scientific developments make us to start to raise the curtain between Eastern and Western health knowledge. The way to nutrigenetic food age will be shorten by combining the analytical approach of Western science to the holistic approach of Eastern traditional medicine.

Scientific Substantiation of Effectiveness

The most important issue of functional food market today is the substantiation of the effectiveness that producers claim. In the Western society, food and medicine are strictly divided by regulation, and food can not claim any medicinal effect. In case of functional food, health benefit claims are permitted only when the sufficient scientific substantiation is provided (Ashwell, 2002; Hasler, 2002). For the scientific substantiation, we should know the chemical composition of a food and identify the effective components to determine the effectiveness by *in vitro* and *in vivo,* and then ultimately by human trial (Kim, 2004). However, the present scientific approach has important drawbacks.

Firstly, many of health and medicinal effects of natural

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products come from not a single component but the integrated action of multiple components. Not a single component can provide absolute benefit to the body, which is made of various organs and tissues having different functions and chemical reactivity. This fact is recently evidenced by the nutrigenomic researches (Ordovas and Mooser, 2004; Weggenmans *et al.,* 2001). The present nutritional science simplifies the matter too much. Emphasizing only a known beneficial effect by concentrating the responsible component in the diet may possibly create numerous unknown adverse effects. The emphasis of useful nutrients in the Western nutrition science last century resulted in the consumption of highly refined and concentrated foods by removing fiber and filthy substances, and we all know that it is the main cause of obesity, constipation, some cancers and heart diseases (Lee *et al.,* 2002).

Secondly, the response to the intake of nutrient and chemical components in food varies with people. The statistical method to overcome this problem is apt to select and generalize a response which is most probable in the cost of variable individual responses. In many cases, the large variation in test results makes the researcher impossible to draw any conclusion on the health effectiveness of a food. We should have in mind that the health benefit of a food or food component is personalized response that is hard to generalize, same as food allergy. It is closely related to the individual genetic trait and the environmental factors.

Application of Nutrigenomics

Recently, the molecular biologists start to recognize that the variation in genetic make-up of individuals may cause the variation in response to nutrient intake (Milner, 2004). It is often observed that, with similar food consumption pattern in a family, one suffers from obesity but the other is normal. Food allergy and celiac disease, for example, are another evidence of genetic variation on food components (Murray, 2005).

Genetic components responsible for differences in dietary response have been proposed for many years by the molecular biologists, and the researches to examine these nutrient-gene interactions has begun recently (Ordovas and Mooser, 2004; Kaput, 2004). The individual genetic variation is possibly explained by single nucleotide polymorphism (SNP). The total number of SNP expected to be found in human races of the world is 3×10^6, which are less than 1% of human genome length (3.2×10^9 bp) and are mostly localized in the non-coding region of human genome.

Many polymorphisms influence an individual's risk of diseases as well as the response to foods and their components (Kim, 2006). Increased knowledge about the interdependence of a response to food components on an individual's genetic background (nutrigenetic effects), the cumulative effects of food components on genetic expression profiles (nutritional transcriptomics and nutritional epigenomics effects), the occurrence and activity of proteins (nutritional proteomic effects), and/or the dose and temporal changes in cellular small molecular weight compounds (metabolomics effects) will assist in identifying those who respond and do not respond to dietary intervention.

Methods for the detection of SNP by scanning and screening are now established, and the genetically regulated heterogeneity in food and drug responses of individuals is under investigation in many research groups. Many efficient high-throughput SNP genotyping technologies have developed, and as many as 500,000 SNPs can be detected at a time (Lee, 2006).

The effect of a dietary component on a specific phenotype (e.g. plasma lipid concentration, obesity, or glycemia) can be explained by one or more genetic polymorphism (Ordovas and Mooser, 2004). The most rapid development of gene-diet interaction researches has been achieved in the area of cardiovascular disease risk, which can be easily quantified (i.e. plasma cholesterol concentration). However, the preliminary results regarding gene-diet interactions in cardiovascular diseases are for the most part inconclusive because of the limitations of current experimental design (Weggenmans *et al.,* 2001). In addition, most cases of obesity, cardiovascular disease, diabetes, cancer and other chronic diseases are resulted by the complex interactions between several genes and environmental factors (Kaput and Rodriguez, 2004). The integrated research of various disciplines designed to work on large population studies is required in order to relate the genotype to the resulting phenotype through systems biology.

Traditional Approaches

The traditional societies like China and Korea have long history of using food as medicine (Kim *et al.,* 1995; Lee *et al.,* 1998). Traditional Chinese medicine, for example in Shennong's Materia Medica, divides medicines into three classes as follows (Lee and Kwon, 2003).

120 upper medicines, which is non-toxic used for long term as food.

120 middle medicines, which have low level of toxicity used for chronic diseases

125 lower medicines, which have high level of toxicity used for acute illness

Food is considered the most important medicine to be used for the maintenance of health and prevention of illness and also at the first stage of treatment of an illness. The middle or lower class medicines are used only when the medicinal food (upper medicine) cannot cure the disease. The lists of medicines are found in many traditional Chinese literatures (Dang *et al.,* 1999). They have been developed by thousand years of experience, mainly acquired by human trials, and explained the effectiveness on the basis of yin/yang and Five Phases theories (Lee, 2004).

Considering food to be medicine, practitioners of traditional medicine studied each food ingredient for its yin/yang property, and its applicability in diet therapy. Their knowledge has been compiled in numerous classical medicinal books in both China and Korea for thousands of years, and has been practiced in everyday life at the household level as a dietary custom (Lee *et al.,* 1995; Cowmeadow, 1993; Hur, 2002).

Healthy food in traditional Chinese medicine implies balancing and harmonizing yin and yang and Five Phases in a diet. A healthy diet must contain food materials having cold/cool (yin) and warm/hot (yang) properties and five tastes evenly (Lee, 1998; Kim, 1995). Therapeutic food means enforcing certain Chi (or energy) for the imbalanced condition (illness) of a body, and enriching certain taste to enhance or suppress an organ function. The effectiveness of functional food has been explained systematically by this principle in the traditional Chinese medicine.

The disease susceptibility and medicine response of individuals are also explained by the differences in Chi and properties of personality trait. The body constitution consideration in the Traditional Chinese Medicine is focused on the medicinal practice based on yin/yang and Five Phases theories. On the other hand, Korean Sasang constitution typology is based on the combination of Neo-Confucianism and the medical tradition of Korea, and describes nature as quaternary (Chae *et al.,* 2003). Traditional Chinese medicine places importance on the harmony between humanity and nature, whereas Sasang typology emphasizes the harmony in social life and developing one's character.

Sasang Constitution Typology

The personal variable responses to food and medicinal treatment have long been recognized in Eastern traditional medicine and explained by the body constitution typology. At the end of the 19th century a Korean traditional Eastern Medicine practitioner, Je-Ma Lee, proposed Sasang Medicine in his book, Dongeuisusebowon (Lee and Choi, 1996). Sasang is a unique theory of categorizing people into four body types, TaeYang, TaeEum. SoYang, SoEum. According to their temperaments, body shapes and other general character features. Figure 1 shows a schematic diagram of Sasang types from a biopsycologic perspective (Chae *et al.,* 2003). The Yang types (TaeYang and SoYang) are extroverted and the Eum (yin) types (TaeEum and SoEum) are introverted. TaeYang type is very rare in Korea. The body shape of TaeEum type is larger than that of SoEum and SoYang types. The personality trait and physical characteristics are symbolically expressed by the organ size; TaeYang - large lung and small liver, SoYang - large spleen and small kidney, TaeEum - large liver and small lung, SoEum - large kidney and small spleen (Lee and Choi, 1996). Sasang typology emphasize the importance of individual body type in the diagnosis and treatment of diseases, and suggest prescribing different medicinal treatments and food intake for different body constitution types.

Many attempts to establish a reproducible and objective method of assessing Sasang constitution types have been reported after Je-Ma Lee (Song, 1998; Choi *et al.,* 2000; Park *et al.,* 2000).

A questionnaire developed by KyungHee University (QSCC II) was most widely studied for the assessment of Sasang types, and distinctive personality traits associated with Sasang types could be demonstrated by using psychometric and anthropometric instruments (Chae *et al.,* 2003). Numerous food therapy schemes suggesting beneficial and harmful food items for different Sasang types have been reported and used by TCM doctors and dietitians in Korea (Kim *et al.,* 1995; Lee *et al.,* 1998; Hur, 2002). Table 1 shows an example of Sasang food list beneficial for different body constitution types.

Although the assessment of constitution type of individuals is not conclusive, many people in Korea follow Sasang theory in selection of their food and herbal treatment, especially when their health condition is not satisfactory. A recent survey conducted in my laboratory revealed that 90% of the respondents (total 839 Korean men (55%) and women (45%) of 20 to 60 years old) knew about Sasang typology and 88.4% believed that man should consume the desirable diet for his/her body type

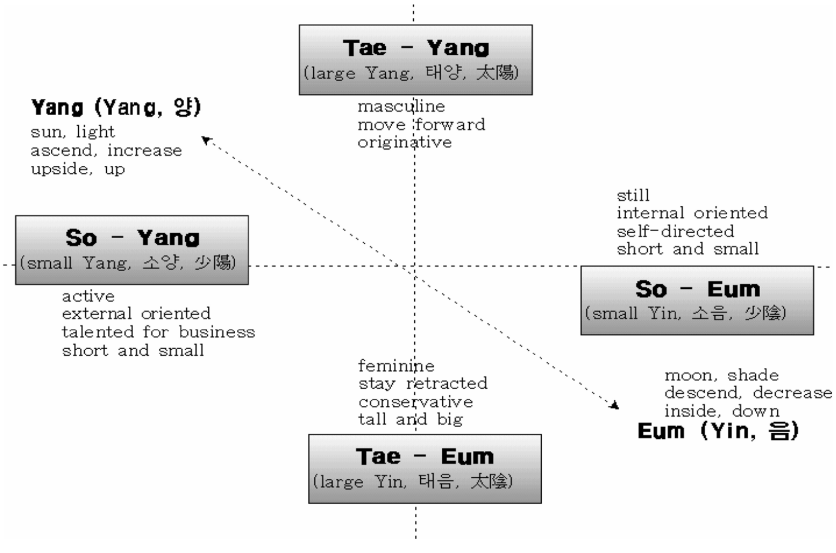

Fig. 1. A schematic diagram of Sasang types from a biopsycologic perspective (Chae *et al.,* 2003).

Table 1. An example of Sasang food list (Kim *et al.,* 1995).

	Tae Yang	**So Yang**	**Tae Eum**	**So Eum**
Cereals	Buckwheat	Barley, red beans, mung beans, barnyard millet, sesame	Soybeans, Job's tears, sugar, wheat, wheat-flour, great millet, perilla, sweet potato, common millet, peanut	Sticky rice, hulled millet, glutinous millet, potato
Fruits	Kiwifruit, grape, persimmon, cherry Chinese quince	Water melon, oriental melon, strawberry, banana, pine apple	Chestnut, pear, walnut, gingko nut, pine-nut, apricot, mum, plum	Apple, mandarine orange, peach, jujube
Vegetables	Water shield, pine needles	Cucumber, Chinese cabbage pumkin, lettuce, eggplant, sowthistle, edible burdock bamboo shoot, , asian plantain	Raddish, bellflower root, Indian lotus, taro, hemp, bracken, lanceolate root shiitake mushroom, ear mushroom, mastutakemushroom, *Umbilicariaesculenta*	Water dropwart welsh onion, garlic, black pepper, ginger, spinach, carrot, red pepper, crown daisy, onion, mustard
Fishes	Oyster, abalone. conch, shrimp, crucian carp, crab, sea slug, mussel	Flatfish, puffer, turtle, crawfish, carp, snapping, snakehead fish	Freshwater-snail, codfish, yellow corvina, small octopus brown croaker, herring, squid, , brown seaweed, laver, kelp	Alaska Pollack, loach, eel, snake, catfish
Meats		Pork, eggs, duck	Beef, milk	Chicken, lamb dog meat, pheasant, goat, sparrow meat

for the prevention and cure of diseases. 45.5% of the people believed that they knew their own body type, which were mainly determined by Eastern medicine physicians (23%) and by the questionnaire (12%).

Dr. Bong-Su Hur, a therapeutic food doctor in Korea, applies yin/yang theory in selection of food for his patients. He believes that yin (Eum) type people should have food of yang property, and vice versa, in order to harmonize yin and yang in the body. Combining this principle to the Sasang constitution, he listed food items desirable for the four body constitution types (Hur, 2005). He also suggested that celiac disease, the gluten intolerance, is an evidence of body constitution and food relationship in Sasang theory; celiac disease occurs mainly in yin type people.

Nutrigenetics and Sasang Constitution Typology

The health effects of food components are related to specific interactions on a molecular level SNP in gene regulation, translational control of RNA, enzyme regulation (proteomics) and metabolite modulation (metabolomics), which occur as genotype (Ommen, 2004). On the other hand, in the traditional Eastern medicine numerous phenotypic data on diet response to health have been accumulated, and systematically classified by the Sasang body constitution theory. Body constitution is a genomic trait of individuals, which is mainly determined by the SNPs. Therefore, it is possible to relate the molecular level genomic studies to the body constitution typology.

An attempt was made to develop marker genes for the classification of Sasang body constitutions (Park, 2006). 34 TCM school students in Korea, who were classified identically by QSCC and by three TCM doctors, were selected and their blood samples were assayed with microarray analysis, and the Sasang-specific genes were identified. About 145 genes were differentially expressed

Table 2. Genes expressed differentially in microarray with Sasang constitution types (Park, 2006).

Category	Locus ID	Mean of Tae-eum	Mean of So-eum	Mean of So-yang	F-value	P-value
Anti-oxidation	SOD2	0.532	0.44	0.526	5.387	0.029
ATP synthesis	ATP5D	0.396	0.58	0.388	4.006	0.057
	ATP5H	0.479	0.529	0.441	3.602	0.071
Cell cycle, Growth and Differentiation, Apoptosis	DAPK1	0.535	0.443	0.477	53.999	0
	S100A9	0.431	0.546	0.448	33.52	0
	BCL2A1	0.529	0.458	0.468	7.938	0.01
DNA or RNA binding protein	HNRPA2B1	0.541	0.433	0.459	49.855	0
	CHD3	0.516	0.44	0.482	21.464	0
Immune response	FCGR3A	0.538	0.437	0.494	204.969	0
	GZMA	0.493	0.477	0.542	30.029	0
	IGHG3	0.485	0.48	0.537	18.592	0.001
	GZMB	0.547	0.444	0.459	8.712	0.008
	PF4	0.54	0.433	0.494	68.165	0
Metabolism	B4GALT6	0.483	0.458	0.515	21.643	0
Transport	ABCB1	0.56	0.39	0.51	14.43	0
Protein degradation	PSMC4	0.476	0.46	0.518	23.459	0
	PSMC5	0.565	0.437	0.404	8.438	0.009
	UBC	0.557	0.473	0.378	4.359	0.048
Signal transduction	TM4SF4	0.521	0.459	0.473	7.332	0.013
	GNAI3	0.452	0.533	0.487	56.048	0

in microarray, and they were clustered into three groups, respectively, Tae-Eum, So-Yang and So-Eum. Genes expressed differentially depending on the Sasang constitution types were related to signal transduction, transport and immune response in their function (Table 2). Among them Cytochrome p450 2D6, 2C9, 1A2, SOD2 genes were related to Sasang types. SOD2 showed higher expression in Tae-Eum type than in So-Yang and So-Eum types. Three SNPs, -455C/A, -257T/C and -247A/G were found in 5′-UTR of SOD2 gene. The SNP distribution pattern of So-Eum type was different from those of other two types. A total of 6 haplotypes were obtained with the three SNPs. The distribution pattern of each haplotype varied with Sasang constitution types. Statistically SOD2 expression was significant ($P < 0.05$), depending on the haplotypes. However, the SNP analysis of single SOD2 genes was not sufficient enough to determine the Sasang constitution type, since diverse genes were involved in the phenotypic expression of the constitution. Although this study is not conclusive in classification of the constitution types, it provides the possibility of using microarray analysis and SNP analysis of specific genes for the objective determination of the body constitution types.

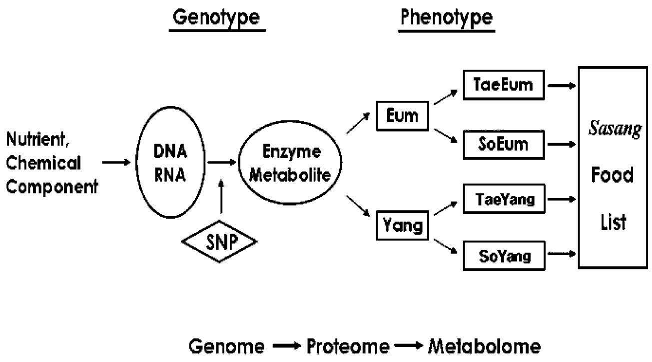

Fig. 2. The relationship between nutrigenetic studies and Sasang body constitution studies.

A Novel Integrated Approach

As body constitution is a genomic trait of individuals, it will be possible to determine Sasang body constitution types with the molecular level genomic studies, when sufficient data are accumulated. It is important to know the genes or SNPs responsible to the phenotypic body constitution types, specifically TaeYang, TaeEum, SoYang and SoEum. Once they are found, we will be able to classify Sasang constitution types objectively and reliably, and ready to utilize the old wisdom of diet therapy which has been developed for thousand years by human trial, as illustrated in Fig. 2. The metabolomics studies, which depict the phenotypic consequences of genetic coding, will also assist to relate the genotypic make-up to Sasang constitution types.

Figure 3 illustrates the relationship between nutrigenetic studies and Sasang typology, which have developed toward opposite directions in the East and the West. If we are able to find a channel to relate the Western analytical approach to the Eastern holistic approach, we will

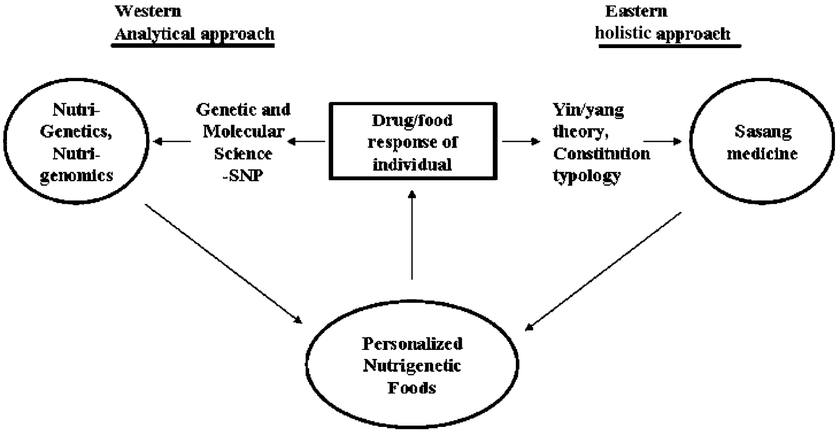

Fig. 3. Collaboration of Western analytical approach and Eastern integral approach in the field of functional food.

achieve a great advancement in the human nutrition and biomedical researches. It will allow us to utilize all the data accumulated in the Eastern medicine for predicting health effectiveness of foods. If we are able to identify the SNPs that are responsible to Sasang Typology, we can select food materials useful for a person having specific SNP from the Sasang food list. It will make possible Western analytical researchers to communicate with the Eastern medical doctors, and discuss the scientific substantiation of traditional functional foods in the East (Lee, 2003).

It will open the new era of nutrigenomics, and we will be able to substantiate scientifically the health benefit of functional foods more easily. It will reduce the variation in the experimental results, minimize the cost for scientific evidence of functional foods, and consequently prevent the adverse effect of functional food, which occurs often in some segments of population. The personalized or custom-made functional food which is effective for a specific group of body constitution will enhance the vitality of consumers and will treat their health problems. The new era of personalized nutrigenetic food will lend great opportunity to future food industries, and it will also contribute greatly to the betterment of the quality of human life.

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