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# Omics and Integrated Omics for the Promotion of Food and Nutrition Science

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## Abstract

Transcriptomics, proteomics, and metabolomics are three major platforms of comprehensive omics analysis in the science of food and complementary medicine. Other omics disciplines, including those of epigenetics and microRNA, are matters of increasing concern. The increased use of the omics approach in food science owes much to the recent advancement of technology and bioinformatic methodologies. Moreover, many researchers now put the combination of multiple omics analysis (integrated omics) into practice to exhaustively understand the functionality of food components. However, data analysis of integrated omics requires huge amount of work and high skill of data handling. A database of nutritional omics data was constructed by the authors, which should help food scientists to analyze their own omics data more effectively. In addition, a novel tool for the easy visualization of omics data was developed by the authors' group. The tool enables one to overview the changes of multiple omics in the KEGG pathway. Research in traditional and complementary medicine will be further facilitated by promoting the integrated omics research of food functionality. Such integrated research will only be possible with the effective collaboration of scientists with different backgrounds.

**Key words:** Nutrigenomics, Transcriptomics, Proteomics, Metabolomics, Database

## Introduction

More than a decade has passed since concept of nutrigenomics was first proposed. Nutrigenomics, also referred to as nutritional genomics, nutritional omics or nutri-omics, can be simply defined as a discipline of food and nutrition research making use of comprehensive analyses (omics) of molecules or other physical phenomena (Muller and Kersten, 2003). Among the well-known omics are transcriptomics, proteomics, and metabolomics, which are the main topic of the present manuscript. Many other omics disciplines are also employed in food and nutrition research. Examples of various omics platforms are shown in table 1. It is a prevalent recognition among food scientist that omics-based approaches are highly effective when they are exploited properly. The rapid advancement of technologies such as high-throughput DNA sequencing, highly refined mass spectrometry, and improved products of DNA microarray chips has contributed much to the broadened application of omics in food science. Also, it is the rapid progress of computer technology, including techniques for the handling of massive amounts of biological data (bioinformatics), that has guided the area of nutri-omics in the right direction (Fu et al., 2010, Gehlenborg et al., 2010).

Considering the complexity of the human body and of the possible interactions between food and the body, it is conceivable that holistic analyses of food-

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**Table 1.** Examples of omics technologies in functional food research

| | Name | Target |
|---|---|---|
| Genomics | | |
| | Genomics | Genes (DNA sequence) |
| | Epigenomics | Modification of DNA and DNA-binding proteins |
| Transcriptomics[1] | | |
| | Transcriptomics | mRNA |
| | ncRNAomics | non-coding RNA (including microRNA) |
| Proteomics | | |
| | Proteomics | Proteins |
| | Phosphoproteomics | Protein phosphorylation |
| | Localizomics[2] | Protein localization |
| | Fluxomics[2] | Protein flux |
| | Interactomics[2] | Protein-protein interaction |
| | Structural Proteomics | Protein structure |
| Metabolomics | | |
| | Metabolomics | Metabolites |
| | Lipidomics | Lipids |
| | Aminomics | Amino acids |
| Others | | |
| | Glycomics | Sugar chains |
| | Cytomics | Cells |
| | Populomics | Human population |
| | Exposomics | Environmental exposure[3] |

Four major categories and their subcategories are shown.
[1] Transcriptomics can be regarded as a subcategory of genomics.
[2] Corresponding omics of metabolites can also be the targets. In addition, omics analysis of protein-metabolite interaction may be possible.
[3] Borrell, 2011

body interactions (i.e., nutri-omics) are a prerequisite to reaching a full understanding of the effect of dietary components. By inference, the combination of different omics platforms will surely provide a deeper insight into the influence of food components and the mechanism of their actions. Such a combination is referred to as integrated omics.

This review describes the current situation of omics approaches in food and nutrition science, with some reference to our attempts to promote the efficient progress of the nutri-omics discipline.

## The development of new tools for nutri-omics research

To accelerate the effective development of omics analyses in food science, we have constructed and have been maintaining a database of nutri-omics information (Nutrigenomics Database, http://www.nutrigenomics.jp, Saito et al., 2005). The database holds two major bodies of data. One is the publication data of nutrigenomics research, and the other is DNA microarray data. The purpose of the former is to organize the publication information that includes the omics analyses in food and nutrition science. More than 750 published papers have been scrutinized and tagged already. Papers can be searched using key words or free words. The full-text search enables users to retrieve information of the published papers on nutrigenomics by using any food components or genes of interest as inquiries. The words obesity, flavonoid, insulin, and PPAR, for example, results in hits of 36, 19, 59, and 35 papers, respectively, as of August 2011.

As a depository of nutritional omics data, the database benefits researchers in many ways. A researcher who has obtained transcriptome data can compare them with those of other experiments, and their similarity and difference can be analyzed. Another useful function of the database is that one can retrieve food factors or experimental interventions that alter the expression of the genes of interest. If a researcher wants to get information on dietary factors that modulate the expression of a particular gene, she/he just needs to input the name (or ID) of the gene to retrieve the experimental conditions under which its expression is affected. The benefits of using the database will increase when large sets of reference data are available. We therefore have been accumulating 'reference data' for nutrigenomics research, including gene expression profiles in response to fasting, high fat diet, protein malnutrition, and caloric restriction (described below).

Another accomplishment made by the authors' group is the development of a novel tool for the visualization of nutri-omics data. The web-based tool Keggle is an overviewer of omics data that was designed to visually compare the responses of multiple metabolic pathways simultaneously. It maps transcriptome and metabolome data onto KEGG (Kyoto Encyclopedia of Genes and Genomes, http://www.genome.jp/kegg/) pathways on the web. The feature of Keggle is implemented in the Nutrigenomics Database so that the stored data can be effectively utilized. Only a 3-step process is needed to obtain results. The pathway images can be intuitively expanded, minimized, and moved seamlessly across the screen. The pathways/genes that are activated or repressed among the multiple metabolic pathways can be visually and intuitively found. Annotation information is instantly shown in popup windows. A snapshot of a Keggle analysis is shown in Figure 1. Keggle has become an essential tool in the integrated omics research of the authors' group, and we welcome researchers to try its functions and provide inputs.

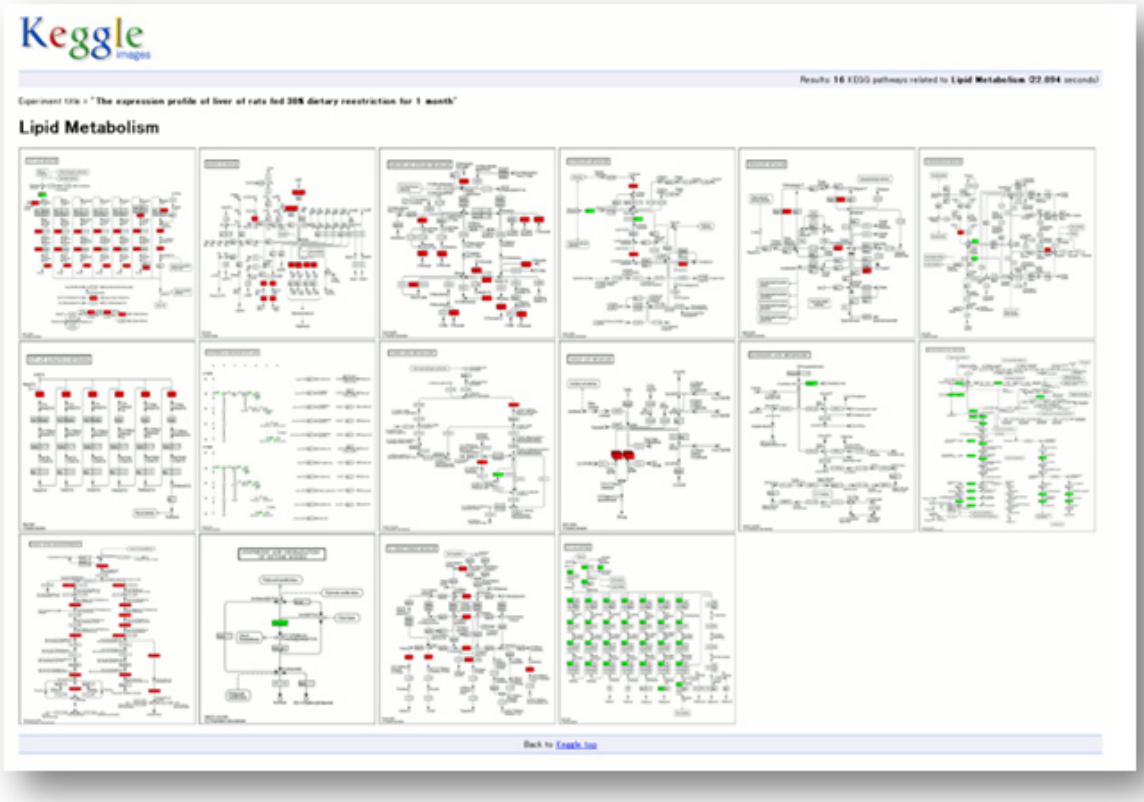


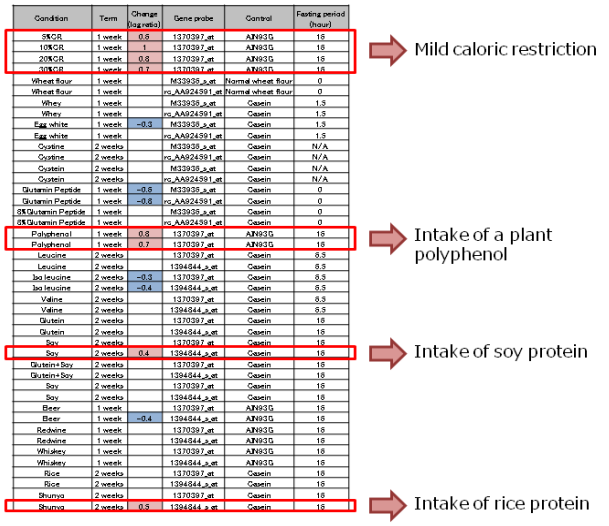

**Figure 1.** Snapshot of a result of Keggle analysis of transcriptome data
Up- and down-regulated genes can be simultaneously viewed on multiple pathway maps of KEGG. Red and green boxes correspond to up- and down-regulated genes, respectively, following the mild caloric restriction in the rat liver (Saito et al. 2010).

## Transcriptomics

Among all omics platforms, transcriptomics is most widely employed in food research because of the many advantages of the DNA microarray technology over other omics methodologies, including the comprehensiveness of the expression data, established protocols, and high reliability and reproducibility of the data. We have also reported the alterations of global gene expression in response to various dietary interventions such as nutritional deficiency, fasting, excessive intake of a nutrient, and ingestion of specific food factors (Endo et al., 2002, Kamei et al., 2010, Matsuzaki et al., 2005, Nakai et al., 2008, Ohta et al., 2006, Saito et al., 2010, Tachibana et al., 2005). As one example of our attempt to acquire reference data we made a transcriptome analysis of the liver of rats treated with mild caloric restriction (Saito et al., 2010). A modest reduction of food intake or altered intake pattern is sometimes encountered in animal experiments whose purpose is the examination of food functionality. Therefore, it is significant to discriminate between the direct effects of the food component and the secondary effects caused by the change in eating behavior. In our experiment, rats were fed a diet with 5 to 30 percent less food than that consumed by an ad libitum-fed group for 1 week or 1 month. Among the genes whose expression exhibited restriction level-dependent changes was *cyp4a14*. The fact that the *cyp4a14* gene was induced by even a low level of caloric restriction suggests that this gene can be used as a biomarker for the beneficial effects of food factors on energy metabolism. As shown in Figure 2, a search of the Nutrigenomics Database indicated that the ingestion of other factors such as soy protein, rice protein, as well as a particular polyphenol resulted in the induction of the *cyp4a14* gene.

## Proteomics

Proteome analyses are generally comprised of separation, quantification, and identification of proteins (Kussmann et al., 2008). A conventional method for the separation of proteins in biological samples is two-dimensional gel electrophoresis (2-DE), in which separated proteins are visualized and quantified after staining with reagents for silver stain or fluorescent stain. A more sophisticated strategy based on the same principle is the differential imaging gel electrophoresis




| Condition | Term | Change (log ratio) | Gene probe | Control | Fasting period (hour) |
|---|---|---|---|---|---|
| 5%CR | 1 week | 0.6 | 1370397_at | AIN93G | 18 |
| 10%CR | 1 week | 1 | 1370397_at | AIN93G | 18 |
| 20%CR | 1 week | 0.8 | 1370397_at | AIN93G | 18 |
| 30%CR | 1 week | 0.7 | 1370397_at | AIN93G | 18 |
| Wheat flour | 1 week | | M33938_s_at | Normal wheat flour | 0 |
| Wheat flour | 1 week | | rc_AA924591_at | Normal wheat flour | 0 |
| Whey | 1 week | | M33938_s_at | Casein | 1.3 |
| Whey | 1 week | | rc_AA924591_at | Casein | 1.3 |
| Egg white | 1 week | −0.3 | M33938_s_at | Casein | 1.3 |
| Egg white | 1 week | | rc_AA924591_at | Casein | 1.3 |
| Cystine | 2 weeks | | M33938_s_at | Casein | N/A |
| Cystine | 2 weeks | | rc_AA924591_at | Casein | N/A |
| Cystein | 2 weeks | | M33938_s_at | Casein | N/A |
| Cystein | 2 weeks | | rc_AA924591_at | Casein | N/A |
| Glutamin Peptide | 1 week | −0.6 | M33938_s_at | Casein | 0 |
| Glutamin Peptide | 1 week | −0.6 | rc_AA924591_at | Casein | 0 |
| 8%Glutamin Peptide | 1 week | | M33938_s_at | Casein | 0 |
| 8%Glutamin Peptide | 1 week | | rc_AA924591_at | Casein | 0 |
| Polyphenol | 1 week | 0.8 | 1370397_at | AIN93G | 18 |
| Polyphenol | 1 week | 0.7 | 1370397_at | AIN93G | 18 |
| Leucine | 2 weeks | | 1370397_at | Casein | 6.5 |
| Leucine | 2 weeks | | 1394844_a_at | Casein | 6.5 |
| Iso leucine | 2 weeks | −0.3 | 1370397_at | Casein | 6.5 |
| Iso leucine | 2 weeks | −0.4 | 1394844_a_at | Casein | 6.5 |
| Valine | 2 weeks | | 1370397_at | Casein | 6.5 |
| Valine | 2 weeks | | 1394844_a_at | Casein | 6.5 |
| Glutein | 2 weeks | | 1370397_at | Casein | 18 |
| Glutein | 2 weeks | | 1394844_a_at | Casein | 18 |
| Soy | 2 weeks | | 1370397_at | Casein | 18 |
| Soy | 2 weeks | 0.4 | 1394844_a_at | Casein | 18 |
| Glutein+Soy | 2 weeks | | 1370397_at | Casein | 18 |
| Glutein+Soy | 2 weeks | | 1394844_a_at | Casein | 18 |
| Soy | 2 weeks | | 1370397_at | Casein | 18 |
| Soy | 2 weeks | | 1394844_a_at | Casein | 18 |
| Beer | 1 week | | 1370397_at | AIN93G | 18 |
| Beer | 1 week | −0.4 | 1394844_a_at | AIN93G | 18 |
| Redwine | 1 week | | 1370397_at | AIN93G | 18 |
| Redwine | 1 week | | 1394844_a_at | AIN93G | 18 |
| Whiskey | 1 week | | 1370397_at | AIN93G | 18 |
| Whiskey | 1 week | | 1394844_a_at | AIN93G | 18 |
| Rice | 2 weeks | | 1370397_at | Casein | 18 |
| Rice | 2 weeks | | 1394844_a_at | Casein | 18 |
| Shunyo | 2 weeks | | 1370397_at | Casein | 18 |
| Shunyo | 2 weeks | 0.5 | 1394844_a_at | Casein | 18 |

**Figure 2.** The result of a Nutrigenomics Database search
Nutritional manipulations or food factors that affect the expression of the *cyp4a14* gene were searched using the transcriptome data in the database.

(DIGE) method, in which proteins of different samples are pre-labeled with different fluorescent dyes (Swatton et al., 2004). Gel-free separation usually relies on chromatography, including 2-D chromatography. Mass spectrometry is most widely used for the identification of proteins with evaporation of peptides and proteins by matrix-assisted laser desorption/ionization (MALDI) and electrospray ionization (ESI). Many food and nutrition research studies have been published that used proteomics approaches.

The effect of mild caloric restriction described above was also studied by proteomics (Takahashi et al., 2011). The comparison of the proteome of the liver of rats treated with 30% food restriction with those of control rats identified 9 significantly up-regulated proteins and 9 down-regulated proteins. Ten percent restriction resulted in the up-regulation of 9 proteins and the down-regulation of 2 proteins, as far as our 2-DE method could detect. An interesting finding was the up-regulation of prohibitin, whose involvement in the regulation of longevity was recently discovered (Artal-Sanz and Tavernarakis, 2009). This result suggests that prohibitin can be used as an effective biomarker of the beneficial effects of food factors. Although the current stage of proteomics research is much less exhaustive compared with that of transcriptomics, the study described here together with other nutritional proteomics studies indicate that proteomics is a highly promising tool for the discovery of biomarkers (Kussmann et al, 2010a).

## Metabolomics

No more than ten thousand kinds of major metabolites exist in animal bodies, while the number of proteins is thought to well exceed 100,000. This feature of metabolites is likely to result in more comprehensive features of metabolomics analysis than proteomics analysis. However, exhaustive analysis of metabolites is in fact fraught with difficulties and usually requires the use of techniques requiring a high skill level, due to the diversity of the chemical properties of metabolites, which is much greater than those of transcripts and proteins. Another difficulty derives from the width of the abundance of metabolites. Despite these difficulties, metabolomics analysis is a powerful tool in food and nutrition science (Zivlovic and German, 2009, Oresic, 2009). The authors' group is also employing metabolomics analyses in our research (Matsuzaki et al., 2005).

Metabolome analysis relies on multiple techniques, of which nuclear magnetic resonance (NMR) and mass spectrometry (MS) are major choices. Generally NMR is easier to perform and applicable to a wider range of compounds, although it is less sensitive compared to MS-based techniques. Gas chromatography (GC)-MS and liquid chromatography (LC)-MS are used, depending on the property of the target molecules. As capillary electrophoresis (CE)-MS provides metabolite profiling of up to several thousands of ionic compounds, its use in metabolomics is increasing rapidly.

## Other omics

As shown in Table 1, many other omics platforms are the target of nutri-omics research. Here we discuss just two intriguing areas.

Epigenomics is the genome-wide analyses of the alterations at the level of epigenetics, a term that refers to the changes of chromatin structure such as DNA methylation and histone modification without changes in DNA sequence (Kussmann et al., 2010b). Epigenetic changes affect the expression of genes located at the respective region. An interesting example of epigenetic modification is the effect of nutrition during fetal development on the susceptibility to life style-related diseases in later life. That is, children of mothers who underwent over- or undernutrition during pregnancy have increased risk of developing obesity, diabetes, hypertension, cardiovascular diseases, and so on (Lusis, 2008). Many studies have presented evidence of the involvement of epigenetic alterations

in such acquired predisposition. Moreover, thanks to the development of new technologies, including the next generation sequencer, genome-wide analyses of the alteration of epigenetic status (epigenomics) has become an intriguing area in the kingdom of nutritional omics (Hawkins et al., 2010). Thus, the influence of the nutrition of early stages of life such as the fetal, suckling, and growing period on the health during later stages may be delineated by chromatin modification in the future.

Another emerging target of omics approaches in food science is related to the RNA transcripts that do not encode proteins. MicroRNA (miRNA) is a subtype of these non-coding RNAs. Precursors of miRNAs (pri-miRNA) are longer products of transcription and are cleaved to yield mature miRNAs of 22 nucleotides in length. Mature miRNAs regulate the expression of genes at the levels of mRNA degradation, mRNA translation, and even gene transcription. In the case of human cells, about 1,000 miRNAs are known to exist and are thought to regulate the expression of more than half of the protein-coding genes. Considering the accumulating evidence supporting the importance of miRNA in the development of diseases and the maintenance of health, the information on the status of miRNAs is no doubt essential for the understanding of the interaction between food components and the body. Global miRNA analysis is now easily performed by the use of commercial miRNA arrays. The promise of miRNA in nutritional omics is reviewed elsewhere, in which a new term, NutrimiRomics, is proposed (Sen, 2010).

## Concluding remarks

The tactical use of particular food components or their combination as well as nutritional manipulations is surely a major strategy in complementary medicine. The demand for an omics-based approach will continue to grow in food and nutrition science. As depicted in Figure 3, the goals of nutrigenomics research ranges widely, encompassing the discovery of new functionality, elucidation of the mechanisms of action, and safety issues. Although exhaustive analysis of one particular omics will help deepen our knowledge of the food-body interaction, the combination of different omics data will provide more concrete information on what happens inside the body in response to the consumption of food components. Figure 4 shows a snapshot of Keggle analysis in which transcriptomics and metabolomics results are viewed simultaneously. It is a common recognition of

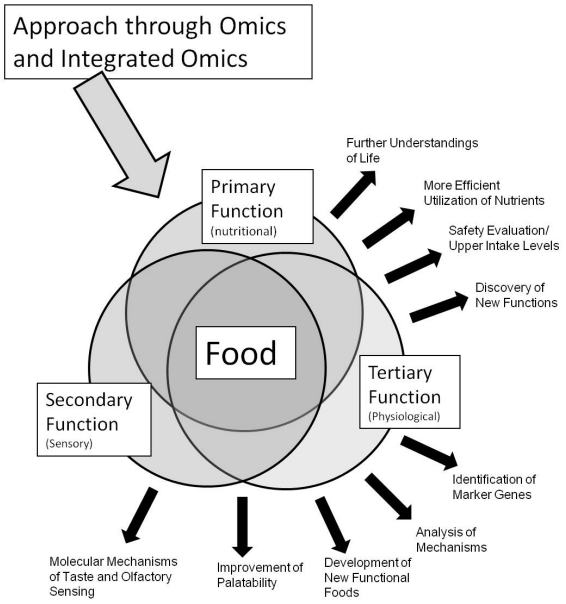



**Figure 3.** Functions of food and outputs of omics research

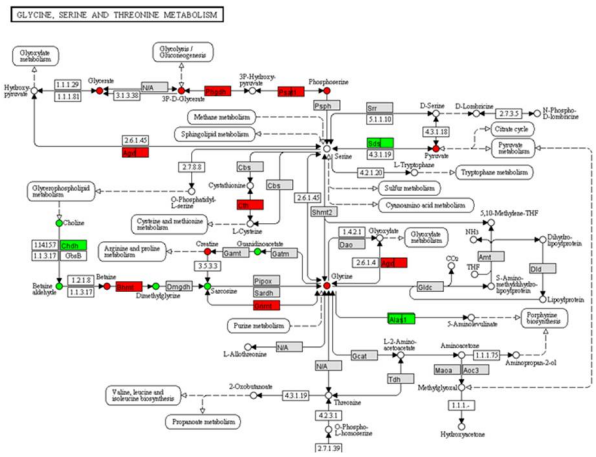



**Figure 4.** Combined visualization of transcriptome and metabolome data by Keggle

Colored boxes and nodes show affected genes and metabolites, respectively, where red means up-regulation or increase and green means down-regulation or decrease.

food researchers that the integration of different omics will increase the importance of omics research. As a consequence, further cooperation of researchers with different backgrounds and expertise is required. The formation of an international collaborative network is a matter of immediate importance (Kato, 2008).

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