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Review Article

Advances in Nutrigenomics and its Application in Poultry

Azmat Alam Khan[1,2], Abdul Majeed Ganai[1,3] and Zulfqar ul Haq[1,4]*

[1]Faculty of Veterinary Sciences and Animal Husbandry, Sher-e-Kashmir University of Agricultural Sciences & Technology of Kashmir, India
[2]Division of Livestock Production and Management, SKUAST-K, India
[3]Division of Animal Nutrition, SKUAST-K, India
[4]Poultry Seed Project, SKUAST-K, India
**Corresponding author*

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A B S T R A C T

Nutrigenomics is the science which helps to understand the interaction between nutrients and molecules in an organism, the implementation of molecular biology and biochemistry in classical nutrition research, followed by the technological revolution of the omics technologies which will greatly affect nutritional sciences. Although the complexity of this proposed integration is exceeding the current bioinformatics tools and capacities, its implications for nutritional research can be enormous. Thus, nutrition by its nature *needs* to be studied in an integrated way. So far, most of the tools for this integration were lacking, thus maintaining an unbridgeable gap between classical nutrition (studying physiology with a focus on biochemical pathways) and biomedical sciences (determination of disease-related molecular mechanisms). In applying Systems Biology to nutritional sciences, these paradoxal extremes are bridged and the complexity of the relationship between nutrition and health can be met by the complexity of the integrated approach. Nutrition research in the future will increasingly focus on the ways in which our genes are affected by what we eat or how our animals genes are affected by what we feed them. Foods and feeds that are safer and more nutritious, new treatments, and novel ways to help maintain the environment are potential benefits expected to result from these research efforts and its further application will be discussed in detail.

Introduction

Nutrigenomics as the word implies is the study of genomic influence of nutrition on an animal. From this perspective, nutrients are dietary signals detected by the cellular sensor which in turn influence gene and protein expression and subsequently metabolite production. Thus patterns of gene expression, protein expression and metabolite production in response to particular nutrients can be viewed as 'dietary signatures'. Nutrigenomics seeks to examine these dietary signatures in specific cells, tissues and organisms to understand how nutrition influences homeostasis (Benitez and Ovilo, 2017). The interaction of an organism with its diet is an intimate and complex physiologic affair that is based on multiple organ systems working in concert. Classic animal nutrition research has involved the determination of nutritional requirements, feed formulation and animal performance. Historically, specific nutrition research often involved the assessment of targeted pathways such as carbohydrate or lipid metabolism where biochemical and enzyme assays monitored the effects of diet. More recently with the development of the field of molecular biology, researchers have been able to study the impact of diet on the organism at the molecular level. The vision

behind application of nutrigenomics is to develop foods and feeds that can be matched to genotypes of animals in order to have its positive impact on health and enhance normal physiological processes in them. Using gene chips that contain the genetic code of animal, researchers can measure the effects of certain nutritional supplements, and how they alter the gene interactions of the body. The main target of it is to alter the activity of genes and results in more activation of good genes and suppresses the activity of bad ones. Through nutrigenomics we are carefully selecting nutrients for fine-tuning genes and DNA present in every cell and every tissue of an animal.

The research analysis based on nutrogenomics reveal that essential nutrients and other bioactive food components can serve as important regulators of gene expression patterns. Macronutrients, vitamins, minerals, and various phytochemicals can modify gene transcription and translation, which can alter biological responses such as metabolism, cell growth, and differentiation, all of which are important in the disease process. The functional integrity of gene is mainly depends on metabolic signals that the nucleus receives from internal factors, e.g. hormones, and external factors, e.g. nutrients, which are among the most influential of environmental stimuli. Genomes evolve in response to many types of environmental stimuli, including nutrition. Therefore, nutrogenomics explains in better aspect, the expression of genetic information and its regulation by dietry composition of feed such as nutrients, micronutrients and photochemicals (Van, 2004) found in feed.

Concept of nutrigenomics in poultry

As the demand of broiler chicken is increasing rapidly, feed optimization in chicken farm is a very crucial job in term of health and production which would not be possible without considering nutrigenomics research. Nutrigenomics play a critical role in poultry production like correlating nutrition and genetics in breeding programs, helps to improve bird performance, increase feed efficiency, deliver better health and increase meat quality. For past few years, several nutritional programs have been conducted to explore the effect of diet on neonatal and early-life periods. Researchers have demonstrated that fasting in post hatch chicken for a period of 24 h has adverse effects which reduce body weight and meat quality in adult broilers. Particularly, nutrigenomics research will lead to the implementation of improved precision feeding strategies by the poultry industry. Recently, in a study carried out by Jiang *et al*. (2014) reported that nicotinic acid plays an important role in lipid metabolism in female chicken of two brioler strain. The result of their investigation also correlates the expression pattern of hepatic genes apolipoprotein A-I (ApoA-I) and apolipoprotein B (Apo B) with varying amount of nicotinic acid in feed. Apart from bioactive material in feed, several trace elements and vitamins are also considered to be the determinant factors for health. Vitamin E also acts as a transcriptional regulator of gene involved in lipid oxidation and antioxidant gene expression in broiler chicken which reduce stress and enhance meat quality. Nutrigenomics data analysis also showed that algae based diet can reduce the stress profile in chicken through nutrigenomics data analysis. Like vitamin E, different types of minerals such as zinc can actively regulates the transporter gene in intestine of broiler chicken and the expression pattern is directly related to the amount of zinc in feed. Whereas, selenium was reported to be a key regulator of gender specific gene regulation in chicken. Several

others research also reported various diet related gene expression in chicken (Table 2).

The gut system and the antibiotic dilemma

The poultry GIT plays a central role in nutritional state of the animal. During the first weeks after hatching, there is allometric growth of the intestine compared with the rest of the body, at such a high rate that supplementation in the first 96 h after hatching can have a long term effect on the animal. Maintaining a healthy digestive system is important to exploit the full genetic potential of these animals. Scientists have taken advantage of modern nutrigenomics technologies to study the interaction of diet with gut immune system to enhance understanding of mechanisms and efficacy of different nutritional management approaches. Microarray analysis and bioinformatics have been widely used in broiler nutrigenomics studies. Phytonutrients with immunomodulatory capacity have great potential in modern poultry diets to help maintain a healthy and robust digestive system. Transcriptomic analysis of the tissue itself or the intestinal mucosa leukocytes clearly revealed that products such as carvacrol, cinnamaldehyde, and oleoresin from *Capsicum* spp., anethole, garlic metabolites, or turmeric are efficacious on the GIT immune response and protection. These compounds can modulate the expression of genes regulating immunity and physiology (e.g., energy and protein metabolism), supporting the idea that plant-derived phytochemicals possess immune enhancing properties in chickens. Prebiotics, such as yeast cell wall products, regulated the expression of oxidative phosphorylation and other genes important in cellular stress response in jejuna tissue. When tested against a common antibiotic (i.e., bacitractin), the gene expression profiles in yeast cell wall supplemented broilers revealed that biological functions and pathways related to improved health and metabolism were activated. The study of the enterocyte proteome in broilers fed *Enterococcus faecium* revealed several differentially expressed proteins related to immune and antioxidant systems, indicating that these chickens used less nutrients and energy to deal with immune and antioxidant stresses (Luo *et al.,* 2013). These recent findings from nutrigenomics studies clearly offer new avenues for developing effective drug free alternative strategies for disease control for poultry infectious diseases.

Gene expression- transcriptomics

Focusing on the analysis of RNA (the transcriptome), transcriptomics aims at measuring the level of expression of all or a selected subset of genes based on the amount of RNA present in a sample. Currently, the most powerful tools available are DNA array and next Gen sequencing technologies. Using one array the expression level of greater than 80,000 transcripts can be measured in parallel, and 100s of samples can be screened per day. In these studies, hundreds to thousands of genes are usually detected as varying in expression. The difficulty is to organize the results in such a way that they can be used to elucidate biological mechanisms, or to derive biological markers for a given physiological situation. Such data treatment is obviously an essential requirement if one wants to understand the overall consequences of nutrient intake. The main limitation lies in the sensitivity of the assay as well as in data analysis. Statistically significant measurements can sometimes only be obtained for the most abundantly expressed genes, and when expression differences are changed by a factor of two or more. When smaller changes need to be detected, the

measurement has to be repeated several times, making studies rather costly.

The advent of next Gen sequencing technologies in the last several years has rapidly reduced the cost to sequence cloned RNAs to the extent that it is now practical to investigate changes in gene expression by simply sequencing vast numbers of clones from cDNA libraries constructed form RNAs extracted from experimentally manipulated samples. Complete transcript sequencing (termed RNAseq) provides a detailed analysis of gene expression in a sample. One key advantage RNAseq has over a microarray approach is that there in no prior knowledge required of the transcripts present in a sample. For a microarray tha transcripts must be known to be included in the construction of the array. RNAseq is based on high throughput sequencing of cDNA prepared from poly-adenylated RNA, with transcript counting being the method of quantifying gene expression levels. Consequently, RNAseq is also a discovery platform identifying most transcripts expressed in a given sample. Since the method relies on sequence determination, RNAseq readily identifies alternative splicing events in mRNAs, allele specific expression and RNA editing sites (Chris 2011).

Table.1 Diet related gene expression in chicken

Feed intake	Gene expression	Reference
Diet with immunomodulators like Corticosterone, ascorbic acid and 1,3-1,6 β-glucans.	Cytokine gene expression (ILreceptors 4 and 15) in spleen-1β, IL-2,toll-like	Kumar *et al.* (2011)
Comparison between organically grown feed and conventionally grown feed	The 49 genes were found to be differentially regulated in jejunum. Genes related to immune system (chemokine ah221, B-G protein, immunoglobulin heavy chain) were also differentially expressed	De Greeff *et al.* (2010)
Feed with mannan-oligosaccharides	Expression of 77 protein synthesis gene, including superoxide dismutase 1, lumican, β 2-microglobin, apolipoprotein A-1, fibronectin 1 etc	Xiao *et al.* (2012)
Poultry feed containing lead	Down regulation of all sugar, peptide and amino acid transporters. Up regulation of stress related genes	Ebrahimi *et al.* (2015)
Diet supplemented with high and low nutrient (HN and LN)	Different gene expression in two groups: Yellow-Feathered nutrient (HN and LN) Chicken (WYFC) and White Recessive Rock Chicken (WRRC). The gene expressions of Rheb, TOR, S6K1 and 4E-BP1 in muscle were the highest in the WYFC fed with low nutrient LN diets are optimal for the long-term housing of chickens	Wang *et al.* (2013)

Focused microarrays for nutrition research

Several groups have assembled microarrays containing subsets of chicken cDNA sequences. Many have (Affymetrix) have constructed a GeneChip Chicken Genome array covering almost 33,000 transcripts corresponding to more than 28,000 chicken genes (Antin and Konieczka, 2005). The GeneChip also contains probe sets for detecting 684 viral transcripts. An 8,000 feature metabolic/somatic system chip and a 7,000 feature neuroendocrine/ reproductive system chip are also available (Cogburn *et al.*, 2004). One limitation of all of these array formats is in their sensitivity for detection of differences in gene expression. Many of these arrays contain only a single spot or replicate for each gene in the array and require significant numbers of technical or biological replicates to detect statistically significant differences. North Carolina State University has designed a focused array that contains 320 specifically chosen long oligonucleotides enabling the accurate measurement of key genes and pathways of interest to several research groups. The array was customized for high replication number and provides a valuable, cost effective resource for the investigation of expression patterns in selected genes.

Utilization of microarray analysis to identify genes that are undergoing subtle changes in expression patterns, as in the chicken embryonic heart, requires a high degree of replication. Analysis with a traditional single-spot or paired-spot array is not sufficient to detect the small differences in gene expression that occur in some developmental processes. These small differences are akin to those that are expected to be encountered in similar studies involving subtle changes in growth rate, feed efficiency, and nutritional manipulation. These types of experiments are quite different from challenge or disease studies, which significantly perturb the biological system. With the inclusion of replicates in microarrays the increased power of sample size has a tremendous impact on the identification of differentially expressed genes as shown in our comparison of analysis methods. With detection limits using our focused microarray approach as low as ±7%, extremely small differences in gene expression can be detected and measured. The construction of a focused array is limited in its scope by the number of genes that can be printed on the substrate. Based on our current format of triplicate adjacent spots replicated four times on the array slide as many as 768 genes can be assayed simultaneously. The degree of accuracy with which the measurements can be made for this number of genes is far superior to any current technology for the cost involved (Wang et al, 2006). It is anticipated to expand the foundation of focused microarray to include supplementary pathways and processes for the evaluation of additional tissues and stages in the growth and development of poultry in future studies.

In conclusions, by helping to understand the interaction between nutrients and molecules in an organism, the implementation of molecular biology and biochemistry in classical nutrition research, followed by the technological revolution of the -omics technologies, will greatly affect nutritional sciences. Although the complexity of this proposed integration is exceeding the current bioinformatics tools and capacities, its implications for nutritional research can be enormous. Unlike biomedical interventions (drug therapy), nutrition is chronic, constantly varying, and composed of a very large amount of known and unknown bioactive compounds.

Furthermore, nutrition touches the core of metabolism by supplying the vast majority of ingredients (both macro- and micronutrients) for maintaining metabolic homeostasis. This homeostasis stretches from gene expression to lipid metabolism and from signaling molecules to enzyme cofactors. Thus, nutrition by its nature *needs* to be studied in an integrated way. So far, most of the tools for this integration were lacking, thus maintaining an unbridgeable gap between classical nutrition (studying physiology with a focus on biochemical pathways) and biomedical sciences (determination of disease-related molecular mechanisms). In applying Systems Biology to nutritional sciences, these paradoxal extremes are bridged and the complexity of the relationship between nutrition and health can be met by the complexity of the integrated approach. Nutrition research in the future will increasingly focus on the ways in which our genes are affected by what we eat or how our animals genes are affected by what we feed them. Foods and feeds that are safer and more nutritious, new treatments, and novel ways to help maintain the environment are potential benefits expected to result from these research efforts.

Application of nutrigenomics as tools can be utilized to efficiently investigate molecular events taking place in a genome receiving nutritional signals and responding to them through characteristic metabolic processes in the organism. The cumulative application of different molecular biological techniques in transcriptomics, proteomics and metabolic can lead to the essential survey of multi-factorial, nutritional influences on humans and livestock species. In last decade, microarray technology has been extensively utilized in livestock species as nutrigenomics research tool to improve food production, quality and their safety in dairy and meat industries. This widely utilized microarray or DNA chip technology in nutrigenomics research enables not only the screening of large numbers of genes simultaneously, giving a comprehensive picture of the variation of gene expression patterns, but will also provide explanations for complex regulatory interactions, such as those between diet-nutrients and genes.

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