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Short Communication

Nutrigenomics Coupling with other OMICS Platform Enhance Personalized Health Care in Metabolic Disorders

genes which are regulated by diets and can cause or contribute to metabolic/chronic diseases could bring about development of diagnostic tools, individualized intervention and strategies for maintaining health. The genetic makeup of an individuals inherited from their parents are responsible for each variation in response to food and their susceptibility to chronic disease as T2D. Familiar variation in gene sequence include single nucleotide polymorphism (SNPs) brings about differences in complex traits such as food-gene interaction, height or weight potential, food mechanism [2,4,5]. There is the need to understand systemic disease monitoring platform such as the define risk concept, detection risk and validation disease involved in nutrigenomics; how the omics can be applied to monitoring health include prevent and treat disease: how can the correlation between gene expression and metabolic process, at the cellular level influence individual's health and will the understanding of the outcome between gene and nutrients lead to personalized/individualized nutrition. To consider those questions, integration of diverse omics as a disease-care, prevention, and monitoring module is essential understanding the role nutrients plays on health and disease.

T2D, as a polygenic, multifactorial disease can serve as a model for cancer, obesity, cardiovascular disease and other chronic diseases that are influenced by diet and environmental factors. Epidemiological studies showed that about 90% of T2D are as a result of five major lifestyles which include diet, physical activity, smoking, obesity and alcohol consumption [1-3]. But among these diet is essentially given that T2D disease rooted in dysfunctional metabolism and energy fuel utilization. Imbalance diet in both quality and quantity is a risk factor that had been established for obesity which is closely linked to T2D. Both epidemiology and clinical studies indicated that insulin sensitivity or other glycemic character are affected by dietary pattern. A better understanding of these molecular events can give a basic clues about T2D pathogenesis and understanding the molecular impact of different dietary patterns with nutrient man aid the development of nutritional remedies, as well as preventive strategies for curbing prediabetes and epidemics. Four category of molecular based Omics platform such as

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Diabetes is a multifactorial of diseases characterized by high blood glucose levels which occur as a result in the body's inability to produce and/or use insulin. Both type 1 and 2 diabetes are thought to be complex disease which developed by the influence of many susceptibility and protective genes, in relation with negative and positive environmental factors. Though type 1 diabetes is distinguished by common beta-cell loss which is mediated by an autoimmune process to extent that all patients with overt type 1 diabetes will essentially need insulin. Multiple genetic factors have been connected to type 1 diabetes which can define individualized plan for type 1 prevention. This review has focused on type 2 diabetes (T2D) which has become more and more a challenging health burden as a result of its degree of morbidity, mortality and heightened prevalence worldwide. According to World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC), T2D is among the top ten leading cause of death in USA and the world at large, while prediabetes is prevalent among children and young adults. T2D also known as hyperglycemia result from compromised insulin utilization (insulin resistance-IR) linked with insufficient compensatory insulin production. Long term consequence and comorbidities of T2D are nephropathy, neuropathy, retinopathy, hypertension, cardiovascular disease, dyslipidemia, cerebrovascular and peripheral vascular disease [1-3].

Recently, dietary and nutritional imbalances had been known as key risk factors for T2D but the underlying mechanism remains ill-defined. Since diets and genes changes one's health and susceptibility to diseases therefore, identifying

transcriptomics, epigenomics, proteomics, metabolomics, and microbiomics could enhance health caring surveillance system which people suffers metabolics disorder would be implemented [2,4,6].

This is the most successful technology applied to nutrigenomics. It covers the step of passing information from DNA to RNA. It is a simultaneous measurement of almost all gene expressed in a given cell, tissue or organism. The commonly used transcriptomics tools in nutrition studies are DNA microarrays analysis and the high-throughput NA sequencing (RNA-Seq) technologies (Illumina platform, Pacific Biosciences single-molecule real time sequencing). Microarray has the ability to measure the levels of expression of thousands of genes simultaneously through hybridizing total mRNAs from biological samples to predesign gene-specific probes, while RNA-Seq is more sensitive with a broader band than microarrays tools. Moreover, whole genome DNA microarrays has been applied exploring therapeutic marker to treatment of T2D [5,7-9]. It can detect gene transcript signals from previously annotated genes and also allowing the analysis of transcripts from either the forward or the reverse strand, thereby offering a much higher discovery potential.

One of the major application had been in the study of high fat diet (HFD) and high sugar diet. Complex diseases or condition such as insulin resistance (IR), obesity and diabetes are linked to the high intake of HFD as compared to lean, healthy diet low in fat and carbohydrates. Many studies had investigated the HFD-induced gene expression changes in different T2D-related tissues such as liver, adipose, muscle, islet and the hypothalamus. As a result of the differences the length of intervention, the amount of fat in the diet used, the individual tissues examined and also the animal model involved, there is a variability in the top differentially expressed genes detected between studies. A more tissue-specific pattern had emerge, an example is inflammatory and immune processes are capture more in the adipose frequently while lipid mechanism, oxidative phosphorylation, peroxisome proliferator-activating receptors (PPARs) signaling and insuling signaling showed more in the liver. It also revealed that HFD induced lipid overload may initiate inflammation via its various effect on inflammasomes, innate receptors, nuclear receptors, cell death, ER stress and gut microbiota. The liver transcriptome of C57BL/6J (sensitive to HFD) and BALB/c (resistance to HFD) revealed opposite expression pattern in genes that are involved in proteasome and ubiquitin-mediated proteolysis pathways. Islet transcriptome study showed a vivid differences between C57BL/6J (IR sensitive) and BALB/c (resistance to HFD-induced IR) in pathways related to cell cycle, growth, proliferation, inflammation and insuling secretion. The transgenerational effect of HFD was examined and it was discovered that transcriptomics studies collaborate with the increase susceptibility of offsprings to metabolic diseases [9]. Moreover, high sugar diet had been recognised as a potential risk of metabolic syndrome and diabetes with no dependent on energy intake. Though a recent study revealed that the consumption of high fructose corn syrup demonstrated a remarkable 20% increase in T2D incidents. Consistent with

this study finding by which cellular ATP depletion can result in an arrest in synthesis of protein and induce inflammation and pro-oxidative changes, transcriptomics studies showed that high fructose intake encourage fatty acid synthesis, endoplasmic reticulum stress and stress-related kinase, apoptotic activity and mitochondria dysfunction in the liver. In addition to protein study in T2D, most especially in context of protein restriction in pregnancy which had been connected to hypertension, endothelial dysfunction and blood glucose levels in offerings. Transcriptomics analysis of the liver from a porcine model unveiled that maternal protein restriction diets changes a diverse set of pathways which include cell cycle regulation, Wnt signaling, fatty acid elongation, steroid biosynthesis, glucocorticoid, mTOR signaling etc. Micronutrient such as vitamin D and Iron plays a major in glucose metabolism, insulin signaling and beta-cell function and high rate of micronutrient deficiencies had been observe in obese and T2D individual [9]. A recent transcriptomic study of islet responded to vitamin D implicated pathways including lipid metabolism, cell cycle, cellular assembly and organization, cell function and maintenance etc, while Iron overload and deficiency had been connected to impaired pancreatic function and glucose homeostasis.

Epigenetic studies

Epigenetic studies the modification of DNA and protein, thereby linking the DNA and histones, that may result in changes in the chromatin structure without changing the sequence of the nucleotides. It is the information transmitted which is based on gene expression as it changes started slowly though progressively and potentially reversible. One example is the metabolism of folate, where folic acid as a nutrient related to genetic integrity ensures a balanced amount of deoxyribonucleotides for DNA replication. It also act as a cofactor for enzyme linked to the biosynthesis of nucleotides and thymidylate (protein found in RNA molecule), as a universal donor of methyl and DNA methylation reaction. In a study, genome-wide DNA methylation analysis of sperm which involved male mice fed with either folate poor or folate rich diet all through their span, the result showed that the two groups had differential methylation pattern at genes linked with various chronic disease including cancer, diabetes etc. Also during a genome-wide assay of approx. 16,000 CpG methylation in the liver tissue, maternal obesity, 276 CpG loci in T2D [7], was discovered to trigger small but a wide spread of methylation changes. Metabolic malfunctions also involve different types of modification or organisation of the DNA which include DNA methylation, histone modification (acetylation, methylation, phosphorylation, DP-ribosylation etc.) and chromatin modeling [5]. These effect gene expression majorly by changing the accessibility of DNA to the transcriptional machinery. Epigenome is dynamic and respond to external stimuli like dietary changes and consist of chemicals compounds that can modify or mark the genome in a way it can indicate which cell can do and where and when to do it. An epigenetic marks could be passed from one cell to another when they divide themselves and so are passed from one generation to another. These marks are influenced by the

genotype in the surrounding media such as environment, diet and drugs and this will determine the phenotype.

The methylation status of DNA loci can be measured simultaneously by sequencing-based technologies. Sequencing coupled with chromatin immunoprecipitation (ChIP-seq), formaldehyde-assisted isolation of regulatory element (FAIRE-seq) and DNase-seq can be used for histone modifications and chromatin organisation. The detection of T2D related DNA methylomic patterns makes it possible to compare these pattern with those affected T2D-associated diets or factors to later understand the mechanistic connections of nutrition to T2D [9].

Epigenetic mechanism through the changes in chromosome structure can cause modulations in gene expression. An example is DNA methylation and histone acetylation, from a recent study it is shown that DNA methylation is closely related to the remodeling of chromatin, which in turn is induced by the enzyme DNA methyltransferase (DNMT). DNMT catalyses the transfer of methyl group from S-adenomethionine to specific site on the DNA. S-adenomethionine metabolises compounds from food such as folic acid, vitamin B6, B12, B2, choline and methionine. but when there is a deficiency of these it can lead to alteration in metabolism of carbon resulting in impair DNA methylation, thereby increasing the risk of development of NTCD. Hypermethylation of DNA tend to suppress the gene that is responsible for transcription, though hypermethylation is linked to malignancy such as prostate cancer and hepatocellular [4,5].

Proteome studies

Proteome studies in nutrigenomics detected both well-studied and novel regulators and pathways providing a good review on nutrient excess and alteration in the mitochondria proteome and function in diabetes which may contribute to neurodegeneration. In diabetic neurons, proteins that are involved in mitochondrial complex I-V, tricarboxylic acid cycle, heat shock, fatty acid utilization were said to be altered. From a mouse study, it was proposed that excess nutrient may have triggered diminished NAD⁺/NADH ratio which in turn switches off the AMP kinase and /or SIRT1 signaling cascade, leading to a impaired expression or activity of PGC-1 alpha thereby reducing the activity of the mitochondria. Another earlier studies on mouse liver reported that the HFD affected the protein that are involved in branched-chain amino acid degradation, fatty acid oxidation, TCA cycle, oxidative phosphorylation and retinol metabolism. Also the relationship of proteins alteration due to fructose consumption with diabetes was examined in hamsters using a matrix-assisted laser desorption/ionization-based proteomics approach and it was discovered that the distinctively expressed proteins were enriched in fatty acids metabolism, protein folding, fructose catabolism, antioxidation, cholesterol and triglyceride metabolism which agreed with the transcriptome study in nutrigenomics findings discussed before that high fat and high sugar diets affects proteins that are involved in lipid metabolic processes.

Proteomic changes by dietary fatty shifts was examined

using nano-HPLC-ESI-MS/MS and by comparing the proteomics between two diets involving polyunsaturated fatty acids of omega-3 and omega-6, by varying their amount it was observed that the proteins involved in mitochondria, metabolic processes and response to stimulus were said to be perturbed in the liver tissue by fatty acids shifts.

Imbalances in vitamins and minerals had been found to exert a significant effect on the functions and activity of proteins. They acts as substrates, cofactors and ligands of protein which are directly involved in catalytic or transport activities. An example which was reported, showed that maternal vitamin B12 deficiency induced distinctive levels of proteins which are involved in the regulation of amino acid, lipid and carbohydrate metabolism, so also the enzymes in the beta oxidation pathway in the liver of the offspring. Metabolic changes was proposed to be mediated by the PPAR signaling pathway [4]. The resultant effect of transcriptomic and epigenomic changes are expected to be reflected in protein level alteration. Proteomics studies the complete set of proteins in the biological processes of a certain species. This had been used in the study of diabetes showing an increasing number of enzymes and metabolic pathways that are related to the development of IR. Common proteomics method for measurement and monitoring include one- and two-dimensional gel electrophoresis (2D-GE), protein chip, HPLC, MS, prefractionation of samples by extraction sequences and organellar proteome analysis [9]. They gives information from static to dynamic measurements, from measuring protein abundance to obtaining translational levels and measuring posttranslational effects and from population level to single cells. This methods makes the monitoring of protein markers for physiological deregulation and the effects of nutrition easier.

The study of metabolomics

The study of metabolomics makes it possible to conduct high resolution characterization of thousand of metabolites. Metabolites plays a major role in IR and T2D, since diabetes is a metabolic disorder. It studies the changes in metabolites with the aim to isolate and characterize them. The two major analytical methods used in metabolomics analyses are MS and NMR. Each analytical method has its own inherent advantages and disadvantages, for example high reproducibility but low sensitivity in NMR-based methods compared to MS-based techniques. These metabolomics tool helps to comprehensively measure key metabolites in signaling, receptor binding, translocation and biochemical reaction pathways. In general, various metabolomics approaches could detect known biomarkers of diabetes such as sugar metabolites (1,5-anhydroglucitol), ketone bodies (3-hydroxybutyrate) and the branched chain amino acids. Recent metabolomics studies had revealed a diet-specific changes in metabolites. An example is that HFD increases lipid metabolites (phosphatidylcholines and fatty acids) but which decreases lipid metabolism intermediates (several acyl carnitines) and the NAD⁺/NADH ratio, which indicates a decrease in beta oxidation and abnormal lipid and energy metabolism. In addition, the levels of metabolites associated with obesity-related diseases which include

serotonin, pipercolic acid, uric acid and the branched chain amino acid valine were all altered by HFD. Tissue and nutrient-specific metabolite alteration were observed in low protein, high fructose, vitamin B6 and D.

Growing evidence had shown supports that microbiome in our body, most especially in the gut, is altered in diabetes. It was identified that approximately 60,000 diabetes related microbial gene markers uses the gut microbial DNA during a landmark metagenome-wide association research which involve 345 T2D patients and nondiabetic controls. It was discovered that T2D patients had a decreasing abundance of butyrate-producing bacteria (*Clostridiales* sp. SS3/4, *Eubacterium rectale*, *Faecalibacterium prausnitzii*, *Roseburia intestinalis* and *Roseburia inulinivorans*) and an increasing opportunistic pathogens (*Bacteroides caccae*, *Clostridium hathewayi*, *Clostridium ramosum*, *Clostridium symbiosum*, *Egerthella lenta* and *Escherichia coli*). The changes in the microbiota can significantly influence nutrients acquisition, energy harvest and various metabolic pathways in the organism [9]. For instance it is discovered that microbiome associated with obesity are more effective in harvesting energy from the diet, altering the organism metabolic pathways such as fatty acids metabolism and lipid peroxidation and activate inflammatory pathways, that are closely related to IR and diabetes. The strong influence of dietary on guts microbiota revealed the potential therapeutic avenues by modulating bacterial metabolites, fecal transplantation and probiotics. It is also observed that oral administration of butyrate or fecal transplantation showed an improved insulin sensitivity, increase energy expenditure and reverse metabolic syndrome in mice. Three major types high-throughput sequencing-based technologies are widely used to study whole communities of prokaryotes in many niches, namely; Amplicon, Shotgun Metagenome and Metatranscriptome sequencing. The amplicon sequencing amplifies and sequences specific variable regions of highly conserved genes (e.g. 16S rRNA gene and type 1 chaperonin gene cpn60) to determine which organism are in a sample and how organism vary between different condition, while Shotgun metagenome and metatranscriptome sequence aim to sequence DNA and RNA in a sample to decide which genes are transcribed to what levels. They can detect changes in the microbiome spectrum and distinctively expressed bacterial genes. Some of the problem associated with the whole technologies include low coverage, difficulty in assembly and potential ambiguous interpretation.

In conclusion, the overview of the application of omics platform in metabolic disease such as diabetes(T2D) testifies

to the ability of molecular-based detection technologies in determining novel biomarkers which can be used to diagnose, predict, monitor the progress of diabetes and to develop preventive and therapeutic strategies along with relevant bioinformatics. Omics study in T2D had shown a broad outcome of dietary imbalance on the molecular systems. The studies in high fat diet (HFD) revealed a detrimental shift in dietary components leading to a critical metabolomics changes and promoting gut microbiomic dysbiosis, which to a great extent aggravate metabolomic dysfunctional. This changes in key metabolites can modify the epigenome and perturb circadian rhythm to promote reprogramming of the transcriptome and proteome which can eventually lead to disruption in the diversity, amount, so also the movement pattern of genes and proteins involved in major metabolic pathways and immune processes necessary for T2D development.

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