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The Role of Nutrigenomics in Cystic Fibrosis: A Mini Review

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Abstract

Cystic fibrosis is an autosomal recessive genetic disease with the mutant gene located on chromosome 7 and it encodes the dysfunctional cystic fibrosis transmembrane conductance regulator (CFTR) protein. It largely affects the Caucasian community while documented report of occurrence in African countries is scarce.

Nutrigenomics can be defined as the study of interactions between the genome and diet, taking into cognizance the mode in which nutrients affect the transcription and translation process as well as subsequent proteomic and metabolomic changes, including differences in response to dietary factors based on the genetic makeup of the individual. Although advances in this area are scanty in the application to the treatment of cystic fibrosis, exploring existing reports may serve as an additional avenue of developing more efficient nutritional based therapies in combating and improving the prognosis of the disease and further extending the life expectancy of this population.

This review documents existing reports of nutrition based applications of nutrigenomics in the treatment of cystic fibrosis.

Keywords: Cystic fibrosis; Nutrigenomics; Curcumin; Choline-related compounds

Abbreviations: CF: Cystic Fibrosis; CFTR: Cystic Fibrosis Transmembrane Conductance Regulator Protein; SNP: Single Nucleotide Polymorphism; BMI: Body Mass Index; SAH: S-adenosyl Homocysteine; SAM-S-Adenosyl Methionine; SERCA: Sarcoplasmic/Endoplasmic Reticulum Calcium Pum; PPAR:Peroxisome Proliferator-Activated Receptor; ONS: Orafl Nutrfitfionafl Suppflements

Introduction

Cystic fibrosis (CF) is an aberration to health as a result of mutations in the gene that codes for the cystic fibrosis transmembrane conductance regulator (CFTR) protein. It is therefore a single nucleotide polymorphism (SNP) gene disease. The occurrence ranges from 1:1353 in Ireland to 1:4000 in USA to 1:6100 in Argentina to 1: 350000 in Japan with marked incidences in some isolated populations such as the Amish population in Ohio (1:569) and limited available data for African countries [1].

CFTR, a cyclic adenosine monophosphate (cAMP)-regulated chloride ion channel, is well expressed in various epithelia and at much lower levels in many other cell types. It is found abundantly in the pancreas, lungs, intestine and gall bladder. The characteristic phenotypic manifestations of cystic fibrosis include intussusception, acidity in the intestinal tract, microbial dysbiosis, pulmonary inflammation, systemic inflammation, intestinal dysmotility, malnutrition, immune dysfunction, appendiceal aberrations and obstruction [2]. CFTR mutations could be classified into six classes based on the severity of the aberration of protein function: mutations in classes I, II, and III are usually associated with a classical severe form of CF while mutations in classes IV, V, and VI are related to a milder phenotype (being mild mutations) characterized by pancreatic sufficiency and ultimately bacterial colonization [1].

Moreover, Blackman et al. [3] have shown that genes independent of CFTR play a role in the average lifetime nutritional status of the CF patient. Also, Bradley et al. [4] demonstrated that the nutritional status of young twins and siblings with CF possess genes other than the CFTR gene that influence the variation in body mass index (BMI). These genes are genetic modifiers located at loci on chromosomes 1 and 5 which contribute to a considerable percentage of the BMI variance. These CF-modifier genes, which can also provide greater insight into the pathophysiology CF, may serve as targets for future nutritional therapies.

In recent years, there has been significant improvement in the life expectancy of the cystic fibrosis population. Factors which have contributed to this include standardization of care, with management of patients in specialized centers by multidisciplinary teams, better control of pulmonary infection with the development of new inhaled therapies, better control of Pseudomonas aeruginosa colonization, aggressive nutritional supplementation with pancreatic enzymes, early diagnosis through newborn screening, and lung transplantation [5]. Moreover, the emergence of mutation-specific therapies is evolving to further help the disease condition.

With the advent of the Human Genome Project, various areas related to genetics have evolved, one of which is nutrigenomics. Simply, nutrigenomics seeks to investigate the effect of nutrients on gene expression.

This review seeks to highlight the application of nutrigenomics in the treatment of cystic fibrosis in view of the fact that more effective nutrition based therapies can be developed in addition to the personalized or precision medicine that already exists to further improve the quality of life of the population.

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Literature Review

Nutrigenomics

Nutrigenomics aims at dealing with the genetic basis for susceptibility to various diseases and the diverse responses to foods [6]. It can also be said to be the science of the integration of genomic science with nutrition dealing with the study of the effects of food and food constituents on gene expression [7]. It focuses on locating and understanding molecular level interaction between nutrients and other dietary bio-actives (dietary signals) directly or indirectly with the genomic structure and function, and metabolite concentration [7-10]. Nutrigenomics seeks to promote rational means to optimize nutrition with respect to the subject's genotype. It is linked with personalized nutrition based on the individual's genome by looking at certain biomarkers [11].

Nutrigenomics uses an integrated framework of technologies to simultaneously examine the genome-wide effects of the nutrients and nutrient-regimes (diet) on genetic and cellular processes thus affecting human health (ie, transcriptomics, proteomics, and metabolomics) [7,9,10,12,13]. This is carried out by investigating interactions of bioactive food compounds with genes and their effect on transcription factors (transcriptome), protein expression (proteome) and metabolic profile (metabolome) [14,15].

It has been suggested by investigators that these technologies can be used to build an ideal diet/intake of certain nutrients or a 'nutriome' that ensures proper functioning of all pathways involved in genome maintenance[7]

Simply, nutrigenomics can be viewed as a snapshot portraying the cellular details of metabolism taking place at a given point in time under defined dietary and nondietary conditions. The dietary signal (s) produced in these conditions can be compared with one expressed in an altered state (such as proinflammatory condition, specific disease) as a means of identifying potential disease biomarkers [9]. Moreover, changes in nutrient composition, which could lead to the identification of nutrition intervention strategies that reduce disease onset, incidence, or progression, can be compared to response as a result of dietary signals or signatures [16].

Nutrigenomics could serve as a guide for the design of novel foods that will be genotype dependent for the prevention and management of chronic diseases as well as the promotion of health [17].

German et al. [6] defined nutrigenomics as the combination of three complementary areas: (a) the direct relationship between nutrients and DNA to modify genetic expression, (b) epigenetic interactions in which nutrients modify the structure of DNA (DNA methylation and chromatin remodeling), affecting gene expression, and (c) genetic variations within humans that relate to the variations between humans in their response to diet (single nucleotide polymorphisms).

Kaput and Rodriguez [10] reviewed the principles of nutrigenomics to be as follows: a) gene expression or DNA structure is modified by the action of nutrients and bioactive food components on the human genome with the modification occurring directly or indirectly, b) in some individuals, diet is a risk factor for certain diseases under certain circumstances, c) diet-regulated genes and their common variants (i.e. single nucleotide polymorphisms, SNPs) are likely to be affected by chronic disease onset, incidence, progression, and/or severity, d) genetic makeup is likely to affect the influence of diet on health and disease, and e) prevention or alleviation of the consequences of chronic disease can be afforded by nutritional intervention tailored to an individual's nutritional status, genotype, current health status, and nutritional requirements.

Nutrigenomics and cystic fibrosis

The application of nutrigenomics in the treatment of cystic fibrosis is still in its infancy. Paediatric CF patients tend to manifest hepatic steatosis, triacylglycerol accumulation and fat malabsorption; high plasma S-adenosyl homocysteine (SAH), adenosine and homocysteine levels; and lower levels of methionine, reduced glutathione, S-adenosyl methionine (SAM), and docosahexaenoic acid [18-20]. Innis et al. [19] carried out trials of supplementation with soy lecithin, betaine, or choline in CF children and showed that these choline-related compounds can significantly increase plasma methionine, S-adenosyl methionine (SAM), and reduced glutathione while decreasing SAH and homocysteine levels. The choline-related compounds may influence the enzymes that catalyze the synthesis of these thiol products either at the level of gene expression or their activity.

A more recent study with an easily absorbed choline-rich supplemented structured lipid in children showed that the lipid improved dietary choline, increased plasma levels of choline, betaine, dimethylglycine, lysophosphatidylcholine and phosphatidylcholine while fecal phosphatidylcholine/phosphatidylethanolamine ratio was decreased. Muscle choline concentration was also increased and this was attributed to the improvement in the plasma choline status [21]. Other similar studies have been conducted and reviewed [22,23]. Moreover, Innis et al. [20] showed that normalizing the altered balance in the ratio of omega 6 fatty acid to omega 3 fatty acid and decreasing production of omega 6 fatty acid-derived inflammatory mediators would also control cystic fibrosis.

Discussion

Isoflavonoid compounds possess the ability to bind directly to the CFTR protein and alter its channel properties. Curcumin (a dietary supplement derived from the curry spice turmeric) exhibits structural similarities to this group of compounds [24,25]. It has been shown that the most common mutation, ΔF508, results in the production of a misfolded CFTR protein that is retained in the endoplasmic reticulum and targeted for degradation eventually. Egan et al. [26] observed that curcumin (a nontoxic Ca–adenosine triphosphatase pump inhibitor) when orally administered to homozygous ΔF508 CFTR mice in doses comparable, on a weight-per-weight basis, to those well tolerated by humans corrected these animals' characteristic nasal potential difference defect. These effects were not observed in mice homozygous for a complete knockout of the CFTR gene. The ΔF508 CFTR is known to be functional as a chloride channel with the mutation resulting in the abnormal protein being held by chaperone proteins in the endoplasmic reticulum of the cell and thus does not traffic to the cell surface [27]. It has been shown in vitro that some of the chaperone proteins involved in this hold up are calcium-binding proteins and addition of curcumin, which is known to be a low-affinity sarcoplasmic/ endoplasmic reticulum calcium (SERCA) pump inhibitor, inhibits the calcium pump in endoplasmic reticulum and culminates in the ΔF508 CFTR protein to be released and functional at the cell surface. Thus the authors proposed its potential as a new treatment of the ΔF508 CFTR mutation [26-28]. Moreover, curcumin induced the function of ΔF508 CFTR protein in the plasma membranes of transfected baby hamster kidney cells. Thus buttressing the observation that curcumin treatment may be able to correct defects associated with the homozygous expression of ΔF508 CFTR [26]. Furthermore, a marked increase in survival rate and in normal cAMP-activated chloride transport across nasal and gastrointestinal epithelia was observed when curcumin was supplemented to gene targeted mice homozygous for the ΔF508 [26]. Three major biochemical aberrations are usually observed in CF; diminished expression and activity of peroxisome proliferator-

activated receptor (PPARs), elevated levels in the production of PGE2, and increased tissue injury as a result of oxidation [24]. Mine et al. [24] suggested that curcumin should have the capacity to activate the PPAR anti-inflammatory pathway (characteristically underexpressed in CF), inhibit PGE2 synthesis, and protect against oxidative stress.

Other unconfirmed studies, which need the examination of clinically relevant outcomes, dose levels, timing and the elucidation of clear biological pathways, have been conducted using supplementation of antioxidant micronutrients (zinc, ß-carotene, selenium, vitamin E and vitamin C) or reduced glutathione and omega-3 fatty acids [25-35]. However, Contreras-Bolivar et al. [36] showed that with the use of oral nutritional supplements (ONS) by clinically stable cystic fibrosis adults, there was amongst others a lower BMI, significantly higher daily calorie intake, increased plasma levels of vitamin E and lower rate of vitamin D deficiency, but the components of the ONS was not specified.

Conclusion

Curcumin, choline, betaine and soy lecithin may be developed as more effective nutritional therapies to the treatment of CF as an alternative until direct gene or other therapies, which can correct the dysfunctional cystic fibrosis transmembrane conductance regulator protein, are elucidated.

Conflict of Interest

The author declares no conflict of interest.

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