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Genetic and Epigenetic Biomarkers on the Personalized Nutrition

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ABSTRACT

Nutritional genomics is a new field of study of how nutrition interacts with an individual's genome or individual responds to individual diets. Systematic approach of nutritional genomics will likely provide important clues about responders and non-responders. The current interest in personalizing health stems from the breakthroughs emerging in integrative technologies of genomics and epigenomics and the identification of genetic and epigentic diversity in individual's genetic make-up that are associated with variations in many aspects of health, including diet-related diseases. Microarray is a powerful screen system that is being also currently employed in nutritional research. Monitoring of gene expression at genome level is now possible with this technology, which allows the simultaneous assessment of the transcription of tens of thousands of genes and of their relative expression of pathological cells such tumor cells compared with that of normal cells. Epigenetic events such as DNA methylation can result in change of gene expression without involving changes in gene sequence. Recent developed technology of DNAarray-based methylation assay will facilitate wide study of epigenetic process in nutrigenomics. Some of the areas that would benefitfrom these technologies include identifying molecular targets (Biomarkers) for the risk and benefit assessment. These characterized biomarkers can reflect expose, response, and susceptibility to foods and their components. Furthermore the identified new biomarker perhaps can be utilized as a indicator of delivery system for optimizing health.

INTRODUCTION

The biology of disease progression is a complex multiple-step process leading to phenotypic change as consequence. This process requires sequential molecular events such as gene expression changes and altered signal and metabolic pathways. The completed human genome sequence allows the study of the function of all individual human genes and their interaction. We begin to realize that all events may serve as potential biomarkers, can be used to detect a disease or indicate the biological exposure to environmental substances including those encountered by dietary intake. Nutritional biomarkers should indicate nutrient status with respect to the intake or metabolism of dietary constituents.

In this presentation, genetic and epigenetic research data related gene expression and promoter methylation generated through microarray-based technology will be addressed with emphasis of development of technology.

DNA Microarray

When a gene is turned on or expressed, it produces mRNA. In any particular cell type, only about 10~30% of the genes in the genome are active. The genes expressed in normal and diseased tissue differ. By analyzing which genes are expressed in a cell or tissue, and to what level, it can be determined which physiological pathways are active in the cell, and to what degree. Expression profiling monitors the level of mRNA for each gene within a

cell (1). It has been recognized that DNA microarray is the most promising expression profiling technologies allow the monitoring of tens of thousands of gene's activity. This is made possible by arranging either unique DNA fragments, called cDNAs, or shorter single-stranded DNA pieces, called oligonucleotides, in a dense grid known as a DNA microarray. Each cDNA or oligonucleotide in a microarray binds to the mRNA of a specific gene, thereby providing a report on that gene's expression level. Many diseases result from a malfunction of the genetically programmed protective response to environmental insults, such as infection, stress or an inherited mutant gene. That malfunction may result in inadequate, misguided or exaggerated gene expression. Identifying genes that are differentially expressed in particular diseases or patient populations allows identification of new targets and validation for which new therapies can then be developed. By understanding when and where abnormal gene expression occurs and the changes in expression that a drug or nutrients can cause, the physiological pathways implicated in disease and drug action can be pinpointed.

Differential Gene Expression

Many chemicals in foods are nutrients and so metabolized to energy or involved in key metabolic reactions like vitamins. Nonetheless, some chemicals in foods are ligands for transcription factors and directly alter gene expression, whereas other dietary chemicals alter signal transduction pathways and chromatin structure to indirectly affect gene expression.

Health benefit of resveratrol is well known for its connection with cancer prevention. It seems the anti-cancer properties of resveratrol work on several different levels. Studies show that resveratrol has the ability to inhibit the process that leads to the growth and spreading (metastasis) of cancer. Resveratrol helps to neutralize the oxidation of free radicals, which keeps them from penetrating the cell membrane and destroying the protein and DNA inside healthy cells. Resveratrol also shows properties of tumor suppression by preventing the production of new blood vessels, which can help limit the growth of tumors by cutting off their supply of nutrients. While evidence shows that small daily amounts of resveratrol have positive health benefits, some concern exists that large amounts may have adverse effects (2). Limiting the amount of the antioxidants to those in red wine, peanuts, blueberries and cranberries may offer the most health benefit. More research is moving in the direction of using resveratrol as a chemopreventive (cancer preventing) agent. Therefore, it is necessary to determine proper amount of resveratrol needed for this.

Along with this I will address the study designed to further understand the pleiotropic effect of resveratrol by identifying the genes differentially expressed after resveratrol treatment in the human ovarian cancer cell (3). Not surprisingly, results showed that highly up-or down regulated genes by resveratrol treatment were related with apoptosis. More detail categorized gene groups will be discussed.

Epigenetic Influence: The Epigenetic Ability Such as a DNA Methylation to Change the Expression of Genes Without Actually Altering Their Sequence Is a Very Xritical Event on Perturbation

When a cancer starts to develop in a human body, a tumor suppressor gene normally initiates a series of events that generates proteins designed to suppress further duplications of tumor cells. In normal state, a tumor suppressor gene is eventually copied onto a suppressant protein is called gene expression.

One of the ways a cell controls its gene expression activities leading to protein synthesis is through chemical modification of its genes, or methylation. More specifically, a methylation refers to the addition of a methyl group to the cyclic carbon 5 of a cytosine nucleotide of a gene. When methylated, a gene is essentially turned off and

it cannot be expressed to synthesize a protein. For that reason, it's been known that one of the most efficient gene-silencing mechanisms is methylation. Analogously, it is essential that tumor suppressor gene to have unmethylated promoter, if it were to remain actively potent to being expressed to produce tumor suppressant protein. Research results provide corroborating evidence that CpG islands found methylated in tumor cells are rarely or never found to exhibit methylation in normal cells. Hypermethylation of CpG islands inhibits initiation of mRNA synthesis, which results in tumor suppressant proteins not being produced. Since methylation of CpG islands in promoter of tumor suppressant gene occurs during the very early stage of cancer development, evidences of methylation in promoter of those genes can provide a stable biomarker for early detection of cancer (4). Further, a panel of biomarkers enables cancer classification for samples from patients with different cancer types and also provide information on developmental stages of cancer for monitoring purposes. In order to use methylation patterns as novel biomarkers in clinical applications, researchers would first have to identify methylation-associated tumor suppressor genes. Unless a gene is identified and validated as a tumor suppressor, its methylation pattern provides to no conclusive evidence towards clinical detection of cancer. However, researchers in search of tumor suppressor genes have historically been challenged by a sheer number of genes present in a human body.

Early Environmental Factors Can Alter Gene Expression Without Mutating Gene Itself

There was an interesting related report of study published in the Aug. 1, 2003, issue of Molecular and Cellular Biology (5). The authors in study showed they could change the coat color of baby mice by feeding their mothers four common nutritional supplements before and during pregnancy and lactation. Moreover, these four supplements lowered the offspring's susceptibility obesity, diabetes and cancer. Pregnant mice that received dietary supplements with vitamin B_{12}, folic acid, choline and betaine gave birth to babies predominantly with brown coats. In contrast, pregnant mice that did not receive the nutritional supplements gave birth predominantly to mice with yellow coats. The non-supplemented mothers were not deficient in these nutrients. Those nutrients are all known to serve as methyl donors in a number of metabolic pathways. A study of the cellular differences between the groups of baby mice showed that the extra nutrients reduced the expression of a specific gene, Agouti, to cause the coat color change. The mechanism that enabled this permanent color change was happened by DNA methylation on gene. During DNA methylation, methyl group attaches to a gene at a specific point and alters its function by leading chromatin configuration change. In the treated mice, one or several of the four nutrients caused the Agouti gene to become methylated, thereby reducing its expression and potentially that of other genes as well. It is interesting to note about the role of folic acid in here. In addition to above influence of folic acid on offspring of mice, it is know as folic acid catalyzes pathways that will lower blood homocysteine and thereby leading to reduction of risk of heart disease So, recently lots of people are try to get more folic acid in their diets. However, if increased folic acid changes status of DNA methylation we are going to eventually see some unexpected changes in health on lifetime. The growing body of data implicates epigenetic events, including DNA methylation, in cancer. The discovery that DNA methylation silences tumor suppressor genes, coupled with the fact that small molecules can reverse this silencing, suggests DNA methylation as an appropriate target for therapeutic intervention. So, I will introduce the development of methylation-biomarker using proprietary microarray-based assay and show a promoter-methylation pattern in colon cancers.

Future Direction

Biomarkers in health disease could provide useful method and information for nutritional studies. Nonetheless,

it is frequently difficult to establish the relation of cause and effect between health states and specific dietary constituents in the first place. To achieve successful interpretation regarding nutritional expose and outcome, it is essential to obtain appropriate biomarkers (near perfect panel of biomarkers) to assess conditions that can evaluate nutritional status and external factors effectively. Eventually, the true value of a biomarker depends on how much it can be used to measure the influence of diet on health. Biomarker research investigating the connection of between diet and health will open new window of chance to disease prevention and cure.

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