Review Article

Nutrigenomics and Cancer

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Abstract

Cancer incidence is projected to increase in the future and an effectual preventive strategy is required to face this challenge. Alteration of dietary habits is potentially an effective approach for reducing cancer risk. Assessment of biological effects of a specific food or bioactive component that is linked to cancer and prediction of individual susceptibility as a function of nutrient-nutrient interactions and genetics is an essential element to evaluate the beneficiaries of dietary interventions. In general, the use of biomarkers to evaluate individuals susceptibilities to cancer must be easily accessible and reliable. However, the response of individuals to bioactive food components depends not only on the effective concentration of the bioactive food components, but also on the target tissues. This fact makes the response of individuals to food components vary from one individual to another. Nutrigenomics focuses on the understanding of interactions between genes and diet in an individual and how the response to bioactive food components is influenced by an individual's genes. Nutrients have shown to affect gene expression and to induce changes in DNA and protein molecules. Nutrigenomic approaches provide an opportunity to study how gene expression is regulated by nutrients and how nutrition affects gene variations and epigenetic events. Finding the components involved in interactions between genes and diet in an individual can potentially help identify target molecules important in preventing and/or reducing the symptoms of cancer.

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Introduction

It is believed that dietary habits as an important modifiable environmental factor, influence cancer risk and tumor behavior. It is estimated that diet influences about 30-40% of all cancer cases, however, the actual percentage is not known and depends on the specific type of cancer and the specific components of diet [(1)].

Many studies indicate that breast, prostate, liver, colon and lung cancers are linked to the dietary intakes [(2)]. However, the linkage has not shown to be consistent perhaps due to the multifactorial and complex nature of cancer and the specificity of dietary constituents and their effects on genetic pathways. Although excess calories are generally

linked to enhanced cancer risk, many bioactive components in food can potentially provide protection at several stages during cancer development [2]. Some of these bioactive components such as calcium, zinc, selenium, folate, vitamins C, D and E, carotenoids, flavonoids, indoles, allyl sulfur compounds, conjugated linoleic acid and N-3 fatty acids may influence carcinogen metabolism, cell signaling, cell cycle control, apoptosis, hormonal balance and angiogenesis [3]. Studies of variations in cancer incidence among and within populations under similar dietary habits suggest that an individual's response to food may reflect genetic predisposition of an individual as well as differences in gene and protein expression patterns in the individual. Recently the effects of nutrition on DNA methylation and the role of epigenetic events in cancer prevention have also been reviewed [4].

Biology of cancer

Malignant cells are characterized by the upregulation or activation of many signaling pathways that are involved in proliferation, apoptosis, invasion and angiogenesis [5]. In malignancy, many proteins and pathways are observed to be up regulated and opposing malignant behavior of cells.

Hanahan and Weinberg [6] have summarized the derangements in signaling that are required for the formation of a fully invasive tumor. These include:

1. Self-sufficiency in growth signals or activation of growth signals without the need for exogenous signals
2. Insensitivity to proliferation inhibiting signals
3. Activation of survival pathways
4. Indefinite replication which leads to avoidance of terminal differentiation or sensecence
5. Angiogenesis initiation
6. Invasion and metastasis

During the carcinogenic process, multiple oncogenic mutations occur that are often functionally redundant. It has been suggested that no single pathway appears to be the cause of cancer, therefore, multiple dietary and/or chemical interventions are likely to prevent cancer growth [5,7].

Individual foods and their constituents

Evidences suggest that foods offer advantages over their isolated constituents in treatment of cancer. This may be due to presence of multiple bioactive compounds within the food that exert additive or synergistic effects. For example, in treatment of human lung cancer cells which undergo apoptosis, whole green tea is more effective than the individual constituents of the green tea in inhibiting TNF-α release [8]. These effects appear to be mediated through enhanced incorporation of the tea polyphenols into the cells. In a rat study in which prostate carcinogenesis was induced by N-methyl-N-nitrosourea (NMU)-testosterone, tomato powder was shown to inhibit carcinogenesis. These effects were suspected to be at the levels of absorption, retention, or metabolism [9]. In another study a fat-soluble extract from vegetable powder was found to be more efficacious than ß-carotene in inhibiting cell proliferation in a lung cancer cell line [10]. There have been also cases wherein, the foods were found not to be as effective as their isolated components, suggesting that the food may contain constituents that inhibit the cellular response. Although the mechanisms involved in these processes are not known yet, it may be due to modification of components involved in absorption, metabolism, or site of action of the bioactive food constituent in the body. An example for this may be the reduced ability of soy flour and full fat soy flakes to inhibit aberrant crypt foci compared to isolated genistein [11]. At the present time, there is not much known about the food matrix and the bioactive components in them and how they influence cancer prevention.

Nutrigenomics

Nutrigenomics is a new field of science which attempts to study the genome-wide effects of nutrition.

From a nutrigenomics point of view, nutrients are dietary signals that are detected by the cellular sensor systems that can regulate gene and protein expressions and affect metabolite productions [12].

Accordingly, patterns of gene, protein and metabolite expressions in response to particular nutrients or dietary protocols can be viewed as 'dietary signatures'.

Nutrigenomics studies these dietary signatures in specific cells, tissues and organisms. Nutrigenomics also attempts to understand how nutrition influences homeostasis. Furthermore, nutrigenomics aims to identify the genes that affect the risk of diet related diseases at the genome level and understand the mechanisms that underlie genetic predispositions in individuals.

Two strategies are used in molecular nutrition research. The first strategy is the traditional hypothesis-driven approach in which the expression of specific genes and proteins influenced by nutrients are identified [12]. In this approach genomic tools such as transcriptomics, proteomics and metabolomics are used to identify specific regulatory pathways which are affected by diet [12,13]. Also transgenic mouse models and cellular models are also used which can allow new genes and pathways to be identified. In future, the use of such models may lead to better understanding of the interactions between metabolic and inflammatory signaling routes.

In the second strategy, systems biology approach is used. In this approach gene, protein and metabolite signatures that are linked with specific nutrient or dietary protocols are systematically organized to serve as molecular biomarkers for early detection of diseases in response to nutrient induced changes in the body. The first strategy provides detailed molecular data on the interaction between genome and nutrition. The second strategy will potentially provide variety of biomarkers to stage and track the health of an individual at any time point during his/her lifetime.

In summary, the goals of nutrigenomics are defined as:

1. Identification of transcription factors (as nutrient targets) and the genes they target;
2. Identification of signaling pathways involved at the cellular level and characterization of the main dietary signals;
3. Measurement of specific micronutrients and macronutrients inducing cell and organ specific gene expression signatures;
4. Identification of interactions between nutrient related regulatory pathways and pro-inflammatory stress pathways for a better understanding of diet related diseases;
5. Identification of genotypes which can be risk factors for the development of diet related human diseases (such as diabetes, hypertension or atherosclerosis);
6. Use of nutritional systems biology to discover biomarkers for early detection of disease and susceptibility (stress signatures) that are changed in response to diet [14- 16].

Many of the techniques used to unravel nutritional genomics are the same as those used in modern molecular genetics research. These techniques are used to study the interrelations between diet and cancer risk and tumor behavior [13,14, 17,18,]. Application of such techniques lead to a better understanding of genetics and associated polymorphisms in diet related diseases, nutrient-induced changes in chromatin structure, nutrient-induced changes in gene expression, and altered formation and/or bioactivation of proteins as they relate to nutrient-induced effects in an individual. The response to a bioactive food component may be very subtle; therefore, characterization and quantification of small cellular changes are very important.

Nutrigenetics and personalized diet

As indicated, nutrigenomics is the study of the effects of nutrients at the genomic level. However, nutrigenetics studies the effect of genetic variation on the interaction between diet and disease. Based on a number of studies on population differences in single nucleotide polymorphisms (SNPs), it is

thought that genetics plays a major role in determining an individual's risk of developing a certain disease [19]. Inter-individual genetic variation is also likely to be an important factor in nutrient requirements. For example, it has been shown that individuals with a C→T substitution in the gene for methylene-tetrahydrofolate reductase (MTHFR) might require more folate than those with the wild-type allele [20]. Several studies have indicated that diet has an important influence on the risk of developing certain diseases and genetic predisposition has been shown to play a role in these cases [21,22,23,24].

One interesting example of the complex interactions between genetics, diet and disease is from a study on the occurrence of hepatocellular carcinoma in Sudanese population. It was reported that a stronger relationship existed between the risk of developing the disease and the consumption of peanut butter contaminated with aflatoxins in Sudanese people with the glutathione *S*-transferase M1 null genotype compared to those lacking this genotype [25].

With the recent availability of the human genome sequence and the cataloguing of human genetic variations, the investigators in the field of nutrigenetics can identify specific polymorphisms linked to altered risk of disease or sensitivity to diet [26, 27].

In recent years, a high-resolution recombination map of the human genome has provided and increased the information on the genetic order of polymorphic markers and the SNP map of the human genome [28]. It is hoped that the map of SNPs in the human genome will provide powerful molecular tools to decipher the role of nutrition in human health and disease and help defining optimal diets.

Advanced genetic analysis in combination with twin studies [29] may provide opportunities to understand the basis of complex traits and the role of individual genotypes on the development of polygenic diet related diseases such as cancer and diabetes. Such findings in the future, might lead to specific dietary recommendations on the basis of genotypes of individuals. Although using such data to develop specific protocol for a personalized diet is still unclear, progress in this field is rapid and several biotechnology companies have been founded on the concepts of nutrigenomics/ nutrigenetics and the commercialization of personalized diets.

Diet and cancer prevention

Cancer prevention studies have shown that all of the major signaling pathways deregulated in different types of cancer, are affected by nutrients. Pathways studied include: carcinogen metabolism, DNA repair, cell proliferation/ apoptosis, differentiation, inflammation, oxidant/antioxidant balance and angiogenesis [30]. So far, more than 1000 different phytochemicals have been identified with cancer preventive activities [31].

Although in recent years much effort has been made in elucidating the molecular mechanisms underlying the activities of these agents, the response has been shown to be complicated, since the effects of nutrients can be cell type-specific and dose-dependent. One of the major difficulties in such studies is that data is obtained in cell culture studies in which the results are obtained with physiologically unachievable concentrations of a single agent, making extrapolation to human subjects difficult. Interpretation of the results from in-vitro studies, must take into consideration the dose, cell type, culture conditions, and treatment time because each of these factors can affect the biological out come. Identification of any process involved in causing a change in incidence and behavior of a given tumor is of considerable importance as many of these processes are likely to be influenced by several food components which may have synergistic and antagonistic interactions accordingly.

To exert their carcinogenic effects almost all dietary or environmental carcinogens undergo enzymatic biotransformation which is known as metabolic activation. Xenobiotic or drug metabolizing enzymes, are important mediators in regulating the mutagenic and

neoplastic effects of chemical carcinogens and metabolizing endogenous compounds such as steroid hormones [32,33,34].

There are two types of enzyme systems involved in metabolizing drugs in the body: Phase I cytochrome P-450 enzymes (oxidation and reduction) and phase II enzymes which perform glucoronidation, sulfation, acetylation and methylation.

It has been shown that the activities of phase II enzymes are mediated by the antioxidant response element (ARE), which is located in the promoter region of specific genes [35]. Dietary components can also induce many enzymes through activation of signal transduction pathways. The three known signaling pathways, mitogen activated protein kinase (MAPK), protein kinase C (PKC), and phosphatidylinositol 3-kinase (PI3K) pathways are known to be modulated by dietary components [35].

Bioactive components present in fruits and vegetables can prevent carcinogenesis by several mechanisms such as blocking metabolic activation through increasing detoxification. In-vitro studies and preclinical models have shown many constituents of plant foods can modulate detoxification enzymes; examples are flavonoids (e.g. quercetin, rutin, and genistein), phenols (e.g. curcumin, epigallocatin-3-gallate and resveratrol), isothiocyanates, allyl sulfur compounds, indoles, and selenium [36, 37].

As a result carcinogen activation, covalent adducts with the individual nucleic acids of DNA or RNA are formed. It has also been found that reactive oxygen species (ROS) such as superoxide anions, hydrogen peroxide, and hydroxyl radicals attack DNA bases [38], resulting in potential mistranscription of DNA sequence.

Such disruptions can interfere with DNA replication and thus produce mutations in oncogenes and tumor suppressor genes. ROS can also result in breakage of DNA strand, resulting in mutations or deletions of genetic material [39]. In cells, many DNA repair pathways exist and prevent the persistence of damage to DNA and help maintaining the genome stability which would in turn lead to cancer prevention [40].

There are many different DNA repair mechanisms which include: base excision repair, direct repair, nucleotide excision repair and double strand break repair [41].

Deficiency of dietary components have been found to disrupt DNA repair pathways and many dietary components such as flavonoids, vitamins E and C, and isothiocyanates that scavenge ROS, have been shown to stimulate repair of oxidative DNA damage [42]. Dietary supplementation with cooked carrots have been shown to increase the repair of 8-oxodG (an indicator of oxidative DNA damage) in white blood cells [43].

Such observations may indicate that whole food products rather than single bioactive components are important in mediating effects in the body. However, it may also indicate that interactions between antioxidants and other components in food matrix are important in mediating the effects [44]. In cancer prevention, changes in DNA repair capacity, steps in cell cycle progression and apoptosis including important molecular targets for dietary components. In general, the growth rate of preneoplastic or neoplastic cells is much faster than that of normal cells, because of malfunctioning of their cell growth machineries [45]. Thus, introducing an arrest in cell cycle or inducing apoptosis by dietary bioactive compounds is an approach which can be used to prevent cancer [46]. Cell cycle progression goes through a sequence of steps and checkpoints, and thus provides opportunities for intervention by dietary components which can potentially affect and block the proliferation of neoplastic cells [47]. Some of the dietary components that regulate cell proliferation include phenolic compounds such as genistein and epigallocatechin-3-gallate which cause cell cycle arrest [48]. Isothiocyanates can also regulate the expression of p21 and inhibit cell proliferation at the G2-M checkpoint in the cell cycle [49]. Many dietary compounds such as selenium, epigallocatechin-3-gallate,

phenylethyl isothiocyanate, retinoic acid, sulforaphane, curcumin, apigenin, quercetin and resveratrol have their cancer preventive effect by apoptosis inhibition [50,51]. Apoptotic events in the normal physiological process are distinct and mediated mainly by the interaction between death receptors and their specific ligands [52]. However, there is another apoptotic pathway which is mediated through the mitochondria and many bioactive dietary components appear to induce apoptosis using this pathway. Dietary compounds have been shown to generally down-regulate antiapoptotic molecules and upregulate proapoptotic molecules [46]. The imbalance between anti-apoptotic and proapoptotic proteins cause the release of cytochrome C from mitochondrial membranes, which in turn forms a complex with caspase-9 and subsequently lead to activation of caspases-3, –6, and –7 [53].

When the caspases are activated, degradation of many intracellular proteins occurs leading to morphological changes that are normally associated with apoptotic cells [54]. To enhance this mitochondria mediated apoptosis, dietary components play an important role in activation of proapoptotic c Jun N-terminal kinase (JNK) and inhibition of antiapoptotic NF-κB signaling pathways [46]. Involvement of mitochondria, caspases and other apoptosis related proteins allow monitoring of the cytotoxic effects of dietary components on cells.

Inflammation, diet and cancer prevention

Inflammation is a physiological response to a variety of conditions in the human body. These conditions include invasion by micro-organisms, trauma, chemical irritation, or foreign tissues. Although acute inflammation is usually beneficial and helps body respond quickly to the foreign threats, chronic inflammation is often damaging and not beneficial to the host. In recent years, many experimental evidences and epidemiologic data have shown an association between chronic inflammatory conditions and malignant transformation [55]. Multiple mechanisms have been proposed to link inflammation to cancer and multiple targets have been shown for cancer prevention by bioactive dietary components. Free radicals and aldehydes are produced during chronic inflammation and can potentially induce DNA mutations and post translational modifications of proteins important in malignancy [56]. In response to an inflammatory insult, proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), Inter leukin-1 (IL-1), IL-6, IL-12, and Interferone-γ are synthesized and secreted, leading to an elevation of reactive oxygen species (ROS) and reactive nitrogen species. In response to this, anti-inflammatory cytokines (e.g., IL-4, IL-10, and TGF-ß) are secreted to reduce the accumulation of ROS. During the inflammatory process, activation of MAPK pathway and subsequently expression of nuclear factor-κB (NF- κB) and the c-Jun part of activating protein-1 (AP-1) lead to activation of genes for nitric oxide synthase (iNOS) and cyclo-oxygenase-2 (COX-2) among others. These enzymes are directly involved in production of ROS and eicosanoids that if not removed, can increase cancer risk [57].

Many animal models and cell line studies indicate that ROSs are likely to be involved in pathways which convey both intracellular and extra-cellular signals to the nucleus under different pathophysiological conditions. ROSs have been shown to modulate the activities of kinases, phosphatases, redox sensitive transcription factors and genes. Potential role of ROSs and oxidised lipids in signal transduction processes in cell and tissue pathophysiology have been discussed elsewhere [58].

During chronic inflammation, several changes have been observed in cells including increased DNA damage, disruption of DNA repair pathways, cellular proliferation, inhibition of apoptosis, and promotion of angiogenesis and invasion [55]. Any of these changes can be a potential target by dietary constituents. Many studies now exist that demonstrate selected dietary components, including conjugated linoleic acid, long chain omega-3 fattty acids such as those in fish oil, butyrate, epigallo-catechin-3-gallate, cur-

cumin, resveratrol, genistein, luteolin, quercetin, and vitamins A and D, may influence the inflammatory process at various sites [58-63]. In tumor pathogenesis, angiogenesis is a crucial step in sustaining malignant cells with nutrients and oxygen [64]. During angiogenesis, endothelial cells are stimulated by growth factors such as Vascular endothelial growth factor (VEGF) and Fibroblast growth factor (FGF). These growth factors are attracted to the angiogenesis site where the inflammatory cytokines and chemo attractants are also present [65,66,67].

Matrix metalloproteinases (MMPs) are important enzymes mediating the angiogenesis process [68,69]. Angiogenesis prevention resulting in tumor size reduction is another mechanism by which dietary components can affect and regulate tumor growth. Dietary components that inhibit angiogenesis include polyunsaturated fatty acids [70] and polyphenols such as epigallocatechin-3-gallate, resveratrol, curcumin and genistein [71-73].

Summary

Dietary components are likely to be major determinants of cancer risk in humans. Genetic polymorphisms lead to alteration of response to dietary components by influencing the absorption and metabolism. Epigenetic events can induce changes in DNA methylation patterns and thus influencing overall gene expression that can be modified in response to food components. Many dietary constituents affect post translational events and may account for at least part of the variations in response to dietary components. Bioactive food components may affect cellular and molecular events that are important in cancer prevention. Studies of dietary components using tissue/cell model systems can help have a better understanding of inter-relations among nutrigenetics, nutritional epigenomics, nutritional transcriptomics, proteomics and metabolomics in the near future. As the field of molecular nutrition expands and the functions of human genome are better understood, a greater understanding of how foods and their components influence cancer will ensue.

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