Nutrigenomics – a new approach for cancer prevention and treatment

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ABSTRACT

Diet is a major environmental factor which maintains metabolic balance and body homeostasis. The aim of the study was to present the latest reports on the biological activity of the food compounds in a critical review. It has been shown that bioactive substances supplied with food e.g. polyphenols, flavonoids or phenolic acids exhibit immunomodulatory and anti-inflammatory functions. What is more, they favourably downregulate major oncogenes and enhance suppressors' expression. Studies show that these substances can be an important component of cancer prevention and treatment. However, there are micronutrients like iron or copper which elevated levels in cancer cells occurs and should be considered as a therapeutic targets.

Keywords: Bioactive food compounds, cancer, treatment, prevention

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INTRODUCTION

Nutrigenomics focuses on the influence of diet bioactive compounds on the expression or silencing specific genes. It determinates the role of variate food ingredients in homeostasis and metabolic pathways. This study area combines many complexed issues from genetics (heredity and variability), molecular biology (properties of nucleic acids and proteins), transcriptomics (localization and time of gene activity), metabolomics (metabolic changes present in tissue or cell), proteomics (structure, function of proteins, and relationships between them) to genomics (functions and structure of genes) [1].

The biological activity of a protein depends on its transcriptional quality and amount. Studies indicate that with most diseases, diverse molecular defects can be associated with each stage of protein biosynthesis. In case of length mutation, shortened protein can occur or protein is not formed at all (so-called zero mutation). When changes make sense, the protein is present in a sufficient amount, but its function is disturbed. Genetic mutations can be inherited (e.g. congenital hypercholesterolemia) or initiated during pregnancy, mature life, as in case of spontaneous cancer caused by e.g. smoking [2].

For the first time, in 1917 Friedrich Goppert confirmed the food-related metabolism disorder underlying pathophysiology of galactosemia [3]. Another mile stone was the explanation of phenylketonuria symptoms by Ivar Asbjørn Følling in 1934 [4].

The phenomenon of genetic variability is caused by the adaptation of organisms to survive in unfavourable conditions. In consequence, pathophysiology of non-infectious diseases is usually the result of complex interactions between environmental factors and multiple genes. Genetic variability is caused by the presence of different polymorphisms: numerous single nucleotide (SNPs), variant number of copies (CNVs) or copy number polymorphisms (CNPs). Human genome contains approximately 10 million SNPs - this means that on average, every 300 nucleotides a change in SNP appears [5].

Certain polymorphisms have the ability to influence transcriptional activity of genes, leading to protein amount intracellular differences, while others are capable of causing structural changes leading to functional ones. Well studied SNP, for example in prostate cancer, is A-290G substitution of 1B allele in promotor region of *CYP3A4*, a gene involved in the oxidation of testosterone to 2B-, 6B, or 15B-hydroxytestosterone [6].

Bioactive substance metabolisms include three different stages: intestinal absorption, absorption efficiency, and organ or functional storage. The general measure of the utilization (assimilation) of components is their body retention, determined by means of isotopes, taking into account intake and excretion balance. For every element, there are also metrics that reflect body stock level of minerals (for example, plasma ferritin reflect body iron accumulation) and its functional pool (activity of specific enzymes or incorporation into biologically important structures). Regardless of the SPNs presence, food bioactive ingredients influences the regulation of chromatin structure, which activate or repress transcription process or regulate activity of cellular receptors, consequently indirectly influencing gene expression [7]. Therefore, the aim of this review was to verify the potential application of selected bioactive compounds macro- and microelements, polyphenols, flavonoids, lignans and carotenoids in case of carcinogenesis prevention and treatment.

MACROELEMENTS

Calcium acts as a cofactor in the mitotic cell division process and chromosome segregation [8]. Milk and its products (mainly yellow cheese), fish preserves (especially whole fish eaten), white beans, cabbage leaves, parsley and hazelnuts are tremendous source of calcium in the diet. Study shows that in patients with differentiated thyroid carcinoma, selective supplementation of calcium after thyroidectomy is essential for its proper serum concentration and prevents osteoporosis [9].

Magnesium, the second most abundant intracellular cation in the body, takes part in more than 300 biological reactions [10]. Without the presence of magnesium, microtubule polymerization can not occur. Magnesium deficiency leads to reduction of accuracy DNA replication process. In case of carcinogenesis, lack of magnesium causes abnormalities during chromosome segregation. The sources of magnesium in the diet are buckwheat groats, nuts, pulses, cocoa, soybeans, chocolate, seafood and bran [11]. Study shows that high dietary intake of magnesium is inversely associated with the risk of all-cause mortality among women with breast cancer and what is more, magnesium intake may improve overall survival in this group of patients [12].

MICROELEMENTS

Zinc is one of the most important microelement underlying oxidative balances – it builds superoxide dismutase (SOD). SOD along with other antioxidant enzymes, maintains the state of cell equilibrium by removing reactive oxygen species [13]. Zinc is also essential for building proteins with so called “zinc fingers” (protein domain directly involved in the DNA binding

process) [9]. Zn fingers stimulate receptors activated by peroxisom proliferators in p53 protein (PARP). Zinc deficiency can lead to increased oxidation, DNA degradation and loss of *P53s'* proper function. Over 50% of identified cancers are caused by mutations of tumour suppressor *P53* gene. *P53* acts as transcription factor - inhibit autophagy, regulate mitochondrial function and apoptosis. Inactivation of *P53* contributes to cancer initiation, progression and chemotherapy resistance [14]. Zinc is found in such products as dark bread, meat, rennet cheese, liver, buckwheat or pulses.

Inadequate levels of selenium can result in the growth of numerous DNA strands brakes, DNA oxidation, and telomeres shortening. A rich source of selenium is meat, meat products, kidneys, fish, garlic, pulses and mushrooms. Selenium is a part of antioxidant protein - selenocysteine. The prooxidative role of selenium in the pathophysiology of civilization diseases is mainly due to its presence in the active center of antioxidant enzymes such as thioredoxin reductases (TrxR) or glutathione peroxidase (Gpx). Gpx and TrxR, also dismutase and superoxide catalase, are part of an enzymatic system that protects cells against damage associated with oxidation of lipoproteins, lipids and nucleic acids. Thirteen different SNPs have been detected in the selenobacterial *S* gene, among which at least one, influence changes in inflammatory markers (such as TNF-α) and immune system (IL-1β). Selenium is a builder component of the glutathione peroxidase selenomethionine, methylselenic acid (MSA) and hydrogen selenide, which have been reported to exhibit chemopreventive effect against different types of cancer. Recent *in vitro* study shows that MSA inhibits angiogenesis by down-regulation of β3 integrin pathway [15].

Manganese is another primary component of superoxide dismutase (SOD), which catalyzes the reactions of dismutation and removal of cell metabolites [16]. SOD is found in different body cells, although it highest concentration is in hepatocytes. New mechanistic studies have revealed that SOD inhibits oncogenic activity and subsequent metabolic shifts during early tumorigenesis. It was shown that cellular higher MnSOD expression has an inverse relationship with p53 status and tumour promotion. Dark bread, buckwheat, pulses and nuts resonate with manganese [17].

Iron builds ribonucleotide reductase enzyme (RNR) and mitochondrial cytochrome (the group of proteins involved in the electron transport during cellular phosphorylation of the respiratory chain). The consequence of RNR shortage is: reduced DNA repair capacity and an upward tendency for mitochondrial DNA to the oxidative damage. There are some concerns about supplementation of iron due to both, tumour initiation and tumour growth; recent work has also shown that iron has a role in the regulation of tumour microenvironment and metastasis. Pathways of iron acquisition, efflux, storage and regulation are all modified in cancer, suggesting that reprogramming of iron metabolism is a crucial aspect of tumour cell survival. Signalling through hypoxia-inducible factor (HIF) and through cell surface receptors pathways (WNT) may contribute to altered iron metabolism in cancer. Good sources of iron in the diet are: offal, parsley, pulses, red meat and coarse grain products [18].

The liver, oysters, baker's yeast, sesame seeds, cocoa and chocolate are copper-rich products. Cu is a component of ceruloplasmin, a glycoprotein produced in the liver, which binds about 95% of plasma copper [19]. Copper is also a component of monoamine oxidase – an enzyme responsible for regulating the level of biogenic amines. What is more, this microelement builds: metallothionein (involved in the metabolism of xenobiotics and some heavy metals), superoxide dismutase (responsible for superoxide radical inactivation), cytochrome c oxidase (involved in energy production and respiratory chain processes) lysine oxidase (participates in the formation of elastin and collagen) as well as tyrosinase, which mediates the production of melanin [20]. Interesting is the influence of copper on the process of carcinogenesis. Evidences show that copper cell accumulation is dependable from carcinogenesis statement. Cu has been shown to be an important angiogenic factor necessary for tumour growth and metastasis [21]. Breast, colorectal, prostate, brain, and lung cancer cells are characterized by elevated copper levels [22]. As a result of this discovery, strategies for reducing tumour-specific excess of copper have been designed e.g. chelating agents (change in oxidation state). It seems that the excess of this element is manageable and its reduction affects the inhibition of angiogenesis, metastasis, and tumour growth [20,23]. Cu complexes can regulate the activity of the nucleus. It binds non-covalently to the DNA molecule, and also causes the phosphodiester double bonds of the DNA helix to break, leading to destruction of tumour cells. Another mechanism of interaction of copper complexes with DNA is the penetration of this molecule between the base pair in the nucleic acid structure, which changes the twist angle of double helix and the diameter of DNA molecule.

Copper compounds have been shown to induce apoptosis in cancer tumor cells [24]:

- MDA-MB-231
- MCF10
- MCF-7 breast cancer as well as PC-3 prostate cancer.

STILBENES

Stilbenes belong to one of polyphenol subgroups and are presented in a small amount in the average person diet. They consisted of two phenyl molecules linked by a double carbon bridge and are synthesized during defensive reactions in response to infection or damage. Stilbenes have strong antioxidant properties and possess a number of therapeutic effects [25].

Red wine is a rich source of resveratrol – a major stilbene representant. *In vitro* experiments have shown that the antitumour potential of resveratrol is based on inhibition of proliferation, invasion, metastasis, angiogenesis and other signaling pathways in prostate cancer cells [26]. *In vivo* experiments have also revealed that resveratrol reduced tumour growth in atypical *nu/nu* immuno-deficient mice via inhibition of angiogenesis and induction of apoptosis. Moreover, resveratrol have been shown to prevent the development and growth of prostate cancer *in vivo* by reducing the expression of androgen receptors. Antitumour potential of resveratrol is also based on induction of apoptosis by activation/inhibition of such factors as nuclear factor kappa-light-chain-enhancer of activated B cells (NfκB), mitogen-activated protein kinases (MAPK) and epidermal growth factor (EGF) [27,28,29].

Resveratol also stimulates the expression of two suppressor genes, that products are involved in cell cycle regulation: the retinoic acid receptor beta (RARβ) and the phosphatase and tensin homolog (*PTN*) gene. These sequences encode protein - RARβ, which is involved in the transcription of cyclin-dependent kinase inhibitor 1 (P21), as well as phosphatase, an enzyme catalyzing oncogenic signaling pathways. *P21* competes with the (DNA-cytosine-5)-methyltransferase 1 gene (*DNMT1*) to bind to the nuclear cell proliferating antigen, thereby inhibiting methylation RARβ and *PTEN* genes. Stimulation of *p21* gene expression, as a result of resveratrol abundance, has been observed in bladder and breast cancer cells. A similar effect of regulation to the transcriptional activity of suppressor genes by demethylation of genes promoters by resveratrol was also found in prostate and esophageal cancer cells [30].

PHENOLIC ACIDS

Phenolic acids are found mainly in red fruits, red onions and radishes. These compounds have both hydroxy and carboxy groups. The most common sources of phenolic acids in the diet are proteins - phenylalanine and tyrosine. Whereas, chlorogenic acid can be found in yerba mate, coffee, hawthorn, artichoke, black berry, nettles and raw potatoes [31].

Chlorogenic acid was also shown to inhibit the initiation and progression of chemical induced tumours. Coffee acid, inhibits the production of angiogenic factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factor bFGF (basic fibroblast growth factor) in both *in vivo* and *in vitro* studies. VEGF affects vascular permeability, and is responsible for the formation of: new vascular vessels and peritoneal effusion (ascites) [32].

Coffee acid is found in legumes, tomatoes, nuts, cereal grains, sunflower seeds, coffee, olive oil, wine and tobacco leaves. This phenolic acid has the ability to block the mutagenic effects of carcinogens that are produced on the metabolic pathway - for example, 4-nitroquinoline-1-oxides. Studies have found that metabolites of coffee acid (8-5-dihydrobenzofurans) exhibit cytotoxic effects on colorectal, breast and leukemia cancer cells [33]. Thanks to its antioxidant properties, this compound prevents collagen degradation. Coffee acid prevent lipoprotein oxidation and protects endothelial cells from damage caused by oxidized LDL fraction [34].

Grapes are great source of gallic acid. This compound has the ability to counter or abolish the effects of environmental mutagens and carcinogens. Gallus acid inhibits the synthesis of N-nitrosine - compound that leads e.g. to gastric cancer development. The antioxidant properties of gallic acid allow it to be used during the initiation phase of carcinogenesis but also at a later stage of promotion. Gallic acid could be a support in antineoplastic therapy as it induces enzymes involved in the second phase metabolism (e.g. superoxide dismutase and glutathione S-transferase) [35].

LIGNANS

Arctigenin was first isolated from the rhizome of *Ipomoea cairica*. Arctigenin acts anti-inflammatory via inhibiting the expression of intercellular adhesion molecule 1 (ICAM-1).

In addition, it down-regulates cyclic AMP phosphor-diesterase (participates in many biochemical reactions as a signal mediator). Arctigenin also has immunomodulatory properties due to its ability to inhibit tumour necrosis factor α (TNF-α) secretion [36,37].

VITAMINS

Vitamins (with little exceptions), like other previously mentioned bioactive substances, are not synthesized in the body, so they must be supplied with the diet. Vitamins are regulators of chemical reactions, necessary to maintain cellular homeo-stasis. They also control enzymatic and metabolic

reactions [38].

Folate belongs to vitamins B group. In larger amounts folic acid can be found in yeast, liver, broccoli, parsley root, wheat bran, spinach, lentils and peas [39].

Folacin acts as a cofactor in the transport and activation of carbon atoms in the purine biosynthesis process, participates in remethylation of homocysteine to methionine. Purines are necessary for DNA synthesis and adenosine methionine for genome methylation. Moreover, folic acid deficiency affects higher levels of atherogenic homocysteine, increased risk of thromboembolic events, stroke, and myocardial infarction [40].

Methionine biosynthesis is the most sensitive pathway in the entire metabolism of folic acid, and its impairment significantly distorts: the accuracy of deoxyribonucleic acid synthesis and its repair, cellular response and genomic stability [40].

A diet rich in folates (e.g. Mediterranean diet) may lower homocysteine levels in the carriers of the mutated allele of the methylenete-trahydrofolate reductase gene (*MTHFR*), where the SNP mutation is in 677 where C> T [40].

This gene encodes the enzyme - methylenetetrahydrofolate reductase and catalyses the reduction of 5,10-methylenetetra hydrofolate to 5-methyltetrahy-drofolate. 5-methyl-tetrahydrofola-te is essential for the conversion of homocysteine to methionine by methionine synthase [40].

Folic acid consumption has an effect on the expression of the *MTHFR* gene, resulting in less homocysteine accumulation (homocysteinuria therapy supplementation) [40].

Carotenoids are widespread among plant products (carrots, sweet potatoes, pumpkin, parsley, cauliflower, apricots). Both *in vivo* and *in vitro* studies have confirmed the protective antioxidant effect of β-carotene on DNA. This compound is a key source of retinol (provitamin A). Retinol prevents eye macular degeneration and reduces the risk of cardiovascular disease. Lycopene exhibits strong chemopreventive properties [41].

The main source of this carotenoid in the diet is tomatoes. The red dye possesses antioxidant, anti-inflammatory and immunomodulating properties, and also influences the expression of the antioxidant response gene (*ARE*) [42].

Lycopene inhibits the proliferation of tumor cells, induces their apoptosis, and prevents angiogenesis. In addition, this compound competes with estrogen for an active site on estrogen receptors in breast cancer cell, thereby reducing the expression of estrogen response gene (*ERE*) [42].

Niacin (vitamin PP, B3) is also classified into B group vitamins. It is found in yeast, fish, liver, meat, wheat bran and legumes. PP is essential to maintain the adequate length of telomeres (fragments of chromosomes, located at its ends to protect against copy damage) [43].

Telomeres are shortened at each cell division. Telomere shortening is believed to be the main cause of aging of the cell and its programmed death when there is a risk of amplification of abnormal DNA. Niacin deficiency results in increased susceptibility to mutagenic factors [43].

CONCLUSIONS

Nutrigenomic is essential discipline for the understanding of gene-nutrient relation underling development of a disease. Studies indicate the outstanding role of bioactive food substances in the preventing and treating cancer from both *in vitro* and *in vivo* studies. There is a need to assess the adverse effects of food supplements and evaluate health benefit doses in clinical studies. Currently, there is not enough solid long-term evidence for the use of minerals, vitamins, and antioxidants food supplements in cancer patients.

Conflicts of interest

None declared.

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