REVIEW

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The philosophy behind exo/endo/existing antioxidants and our built-in oxidant and antioxidant system

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Free radicals (FRs) and oxidants (Os) have different vital activities in our bodies. Biological redox reactions are the major source for FRs-Os. In normal cases, they are under the control of our body's existing antioxidant (antiO) system. If their amounts exceeds a certain limit, they start to attack and damage various macromolecules and cells. In the case of DNA damage, dangerous diseases such as cancer "the human killer" can be elevated. The expression and regulation of the genes coding for the endogenous (endo) antiO enzymes are important for our health. Genetic polymorphism between different populations reflects the differences between individuals and populations abilities to produce antiOs. This review will discuss general aspects about different types of FRs-Os and antiOs as well as their direct and indirect interaction with genetic materials. The benefit of the antiOs, which can do a lot for our health, will be highlighted.

"*Variation is a unique criterion in the biological system." "A certain level of balance is required in all aspects of the life including food." When you start to read this review you will find something different! Is it the style? Or it may be something else! Each of us has his fingerprint, and our genes are different too. This is the life. The author.*

1. Introduction

1.1. Free radicals and oxidants, our enemies or friends?

Harman (1956) was the first to describe the damage caused by Free radicals (FRs) and oxidants (Os) to life processes. He correlated the damage in tissues and cells, especially during ageing processes, with the activities of FRs-Os.

FRs-Os in the bio-system gain their importance from their ability to damage key biological sites (Pacher et al. 2007; Sies 1997). However, they are involved in many essential and vital processes. They prevent diseases by assisting the immune system during phagocytosis process, mediating cell signaling, and playing an essential role in apoptosis as a part of normal aerobic and xenobiotic metabolism (Bahorum et al. 2006; Valko et al. 2004, 2007; Droge 2002; Seifried et al. 2007). FRs-Os are formed from different molecules via the breakage of their chemical bonds. Each fragment keeps one electron, by cleavage of a radical to give another radical and via redox reactions (Bahorum et al. 2006; Valko et al. 2004, 2007; Droge 2002; Seifried et al. 2007).

1.2. Enzymatic and non-enzymatic FRs-Os formation

FRs have at least one unpaired electron and are capable of independent existence (Ghafourifar and Cadenas 2004). They are high-energy particles that ricochet wildly and damage cells. FRs include hydroxyl ($OH^{\bullet}$), superoxide ($O_2^{\bullet -}$), nitric oxide ($NO^{\bullet}$), nitrogen dioxide ($NO_2^{\bullet}$), peroxyl ($ROO^{\bullet}$) and lipid peroxyl ($LOO^{\bullet}$). Os such as hydrogen peroxide (H_2O_2), ozone (O_3), singlet oxygen ($1O_2$), hypochlorous acid (HOCl), nitrous acid (HNO_2), peroxynitrite ($ONOO^-$), dinitrogentrioxide (N_2O_3), and lipid peroxide (LOOH) are not FRs but they are unstable molecules (Pacher et al. 2007; Sies 1997; Bahorun et al. 2006; Valko et al. 2004; Willcox et al. 2004; Genestra 2007). They cause damage to our biological system. When this damage exceeds the existing antiOs system [the endogenous (endo) antiOs plus the exogenous (exo) antiOs supplemented through diet] as well as the system for DNA regeneration and correction, different health problems begin to appear and vital organs will be affected (Bahorum et al. 2006; Valko et al. 2004, 2007; Droge 2002; Seifried et al. 2007). Those dangerous FRs-Os could appear as a result of excessive exercise, stress, alcohol, cigarettes smoking, air pollution, food etc. (Bahorum et al. 2006; Valko et al. 2004, 2007; Droge 2002; Seifried et al. 2007; Ghafourifar and Cadenas 2005). When the sources of the FRs-Os are irremovable, exo-antiOs should be supplemented through diet or drugs (Ghafourifar and Cadenas 2005). The endo/exo FRs-Os sources could be controlled or reduced by different strategies. The deficiency in one or more of the antiOs gene(s), FRs-Os controlling systems, essential pathway(s), as well as loss of precursor(s) or mutation(s), will result in an increase in FRs-Os. The amount of antiOs and their related precursors in our bodies could be optimized through diets. Food is the most promising candidate as a safe source of antiOs. "From *vivo* to *vivo* is usually better than from *chemo* to *vivo*". However, the simplest solution will be to stop all the sources of FRs-Os as causative agents. Adequate amounts of exo-antiOs will compensate for any deficiency in the endo-antiOs. Key genes are responsible for both FRs-Os and antiOs production and control (Valko et al. 2007).

AntiO genes are the major players for maintaining our health (Valko et al. 2007).

The balance between beneficial and harmful effects of free radicals is achieved by mechanism(s) called "redox regulation". The process of "redox regulation" protects living organisms from various types of FRs-O stresses and maintains "redox homeostasis" by controlling the redox status *in vivo* and during human diseases (Droge 2002; Valko et al. 2007). FRs-Os are generated from end sources such as mitochondria, respiratory chain, immune system activity, inflammation, mental stress, excessive exercise, ischemia, infections, cancer, change in the intestine microflora, ageing, genetic susceptibility, phagocytosis, and Cytochrome enzymes 450 (CYP450) (Valko et al. 2004, 2007; Droge 2002; Seifried et al. 2007; Ghafourifar and Cadenas 2004). FRs-Os can also be generated from exo-sources such as air and water pollution, cigarette smoke, alcohol, heavy or transition metals (Cd, Hg, Pb, Fe, As), certain drugs such as ciclosporine, tacrolimus, gentamycin and bleomycin, industrial solvents, cooking (smoked meat, used oil, fat) and radiation (Pacher et al. 2007; Bahorun et al. 2006; Valko et al. 2004; Genestra 2007; Davis et al. 2009; de Oliveira et al 2009; Halliwell 2007; Young 2001; Valko et al. 2005; Parthasarathy 1999). After their penetration into the body by different routes, these exo-compounds are decomposed or metabolized into FRs-Os (Valko et al. 2004, 2007; Drog 2002; Seifried et al. 2007 Ghafourifar and Cadebas 2005). Diet, lifestyle, and the exposure levels are important factors in determining the capacity of an organism to mount a protective response (Valko et al. 2004; Droge 2002). Different diseases have been associated with FRs-Os such as cancer, artherosclerosis, pulmonary disease, cardiovascular diseases, neurodegenerative diseases, allergies, metabolic diseases, aging, insulin resistance, Down's syndrome, familial amyotrophic lateral sclerosis (ALS), transplantation complications, and many other conditions (Pacher et al. 2007; Bahorun et al. 2006; Valko et al. 2007; Droge 2002; Young 2001). It is important to highlight that any new disease will be an additional source of FRs-Os! Chemoprevention by nutrients, CYP450 inhibitors, and antiO enzyme inducers, nutraceutical food, good life style, etc., have been successfully used to inhibit the formation of reactive species (Wender et al. 1981).

1.3. Our food and the problems

In both plants and animals, energy is extracted from food molecules by a process of gradual oxidation or controlled burning. Mitochondria harness the energy from the oxidation of food molecules, such as sugars, to produce adenosine triphosphate (ATP), the basic chemical fuel that powers most of the cell's activities (Valko et al. 2007; Droge 2002; Davis et al. 2009; de Oliveria et al. 2009; Raha and Robinson 2000). The mitochondria as a major source for FRs-O generation shows that we have a built-in and a continuous source of FRs-Os. Unfortunately, food is the major source for both antiOs and FRs-Os. Food is transformed to energy and FRs-Os, which results in the inverse correlation between metabolic rate and the ageing process (Valko et al. 2007; Nakabeppu et al. 2006; Stadtman 1992; Raha and Robinson 2000; Davies 1995; Chui and Carol 2008; McCann 1997; Schrauzer and Peter 2009).

When the existing-antiO system starts to work, it needs energy, which is derived from different metabolic pathways. Some of these intermediate pathways are the source of FRs-Os, too. Continuous activation of the endo-antiO system is an extra load on genetic material, which could cause DNA damage. The DNA damage could be dŭe to guanine residues resulting in 8-oxo-deoxyguanosine (8-oxo-dG). These induce G:C to T:A transversions that have been observed in oncogenes and tumor suppressor genes (eg p53) known to have significant roles in carcinogenesis. The mutant generation rate in the presence of high levels of FRs-Os is greater than that produced in normal cases (Valko et al. 2005; Droge 2002; Davies 1995).

1.4. CYP450 one coin with two faces

CYP450 s is another built-in FRs-O generator. The CYP450 enzymes convert organic chemicals to a more hydrophilic metabolite, while the concomitant reduction of the other oxygen atom forms water molecules. As some of most potent precarcinogens are converted into their ultimate carcinogenic form by the CYP450 system, these electrophilic metabolites can exert their biological effect by covalent interaction with cellular macromolecules, with the critical target most likely being DNA to yield DNA adducts. However, the action of CYP450 enzymes are not usually hazardous. These enzymes also play a central role in the detoxification of foreign compounds by increasing their water solubility and facilitating their excretion. The case of CYP450 is a good example of FRs-Os/antiOs possible interaction with the exo/endo effective candidates. CYP450 is able to detoxify large amounts of toxic material and exotic chemicals; it is also able to convert some pre-carcinogenic compounds to carcinogenic ones (Awney et al. 1997). We should not forget that although our biological system is intelligent, it is not intelligent enough to cover all our mistakes.

1.5. AntiOs, the hidden soliders

AntiOs are substances that slow down or prevent oxidation and reactions promoted by FRs-Os (Sies 1997; Bahroun et al. 2006; Valko et al. 2007; Seifried et al. 2007; Willcox et al. 2004; de Oliveira et al. 2009). In our bodies, there are different types of endo antiO enzymes such as superoxide dismutase (SOD), which was the first antiO enzyme to be discovered (McCord and Fridocich 1969; Wang 2009). Catalase (CAT), glutathione peroxidase (GPx) (both of which reduce peroxide to water), glutathione S-transferases, hemeoxygenase-1 (HO-1), thiol-specific antiO enzyme and macrophage stress protein all play a central role in protection against FRs-Os (Siow et al. 1995; Yim et al. 1994; Sachdev and Davies 2008; Vertuani et al. 2004; Chaudiere and Ferrari-Iliou 1999; Sies 1993). As a network, glutathione and vitamin C can act in concert to alleviate a variety of O stresses. Vitamin C is able to regenerate tocopherol in the lipid phase (Jindal 2008; Joyner 2009). β-Carotene and tocopherol act synergistically against lipid peroxidation. Polyphenols, such as flavonoids, provide antiO protection, which is enhanced by vitamin C. AntiO vitamins play major roles in the protection against FOs-Os and different related diseases (Jindal 2008; Platz 2009; Rayman et al. 2009; Schrauzer 2009; Shaw and Wan-Hsuan 2009).

Exogenous antiOs will be of great benefit to the body. They will save cellular energy and genetic materials, and will improve our health significantly. In the presence of a continuous extra dosage of FRs-Os, antiOs could give reverse results. Studies, which have been conducted on cigarette smokers, proved that β-carotenes could induce cancer rather than prevent it (De Luca and Ross, 2009).

This shows clearly who the players in the FRs-Os/antiOs struggle are: the FRs-Os and exo/endo/existing antiOs. Macromolecules under attack are also included. When attacked, they cause changes in their own cell system. The time of exposure to FRs-Os is another important factor. However, the most important part is the genetic material, which cannot be easily recovered. Other candidates, such as nutrients, environment, mental disorder, stress, different physiological and pathological disorders,

etc., are involved. The antiOs/FRs-Os struggle is individually based and should be studied case-by-case (Ortega 2006).

1.6. Is our endo-antiOs system able to stand-alone?

In fact, our endogenous antiO system is diet dependent. Most of our endo-antiO systems' platforms are derived from our diet (Traber and Packer 1995).

Other candidates are involved in protecting us from FRs-Os. Melanin is increased in the skin as a response to exposure to ultraviolet light (Cutler 1984). Human antiO defenses are effective but they are not infallible, and oxidative damage to key biological sites occurs, accumulates with age, and contributes to senescence and age-related diseases (Benzie 2003; Ames et al. 1993; Beckman and Ames 1998; Halliwell and Gutteridge 1999; Vasdev and Gill 2006).

The level of glutathione, the major cellular antiO in the body, declines with ageing. Glutathione is a protein, which is easily digested and cannot be effectively supplemented orally. Food, which contains high amounts of cysteine, will be better than that which does not contain cysteine. The cell membrane transports cysteine ten times faster than cystine. This shows how food and its constituents are efficacious in support of the antiO system (Vasdev and Gill 2006). Niacin is required for synthesis of nicotinamide adenine dinucleotide hydrogen (NADH)/NADPH and sulfur (methionine and cysteine) for synthesis of GSH (Jacob 1995).

Scurvy is a clear example about our body's demand for antiOs (Valko et al. 2005, 2006, 2007; Davies 1995).

2. Classification of human antiOs

While the major classification for the antiOs is the endo/exo/existing system, other classifications for the biological antiOs will be of great importance. There are four other major classifications for antiOs.

2.1. Enzymes and low molecular weight antiOs (LMWA)

Biological antiOs may be classified into two principal groups; enzymes such as CAT, Prx and SOD or as LMWA, such as tocopherols, ascorbic acid and glutathione. Metal-containing SODs, including Cu, Zn-SOD (SOD1), Mn-SOD (SOD2), and extracellular Cu, Zn-SOD (SOD3). SOD provides the first line of defense against oxidative stress and catalyzes the dismutation of superoxide anion to molecular oxygen and hydrogen peroxide. SOD1 is mainly expressed in astrocytes and neurons, whereas SOD2 is predominantly localized in neurons (Jacob 1995; McCord and Fridovich 1969; McCord 1976; Marklund 1982; Johnson and Giulivi 2005). Catalase is an intracellular antiO enzyme that catalyzes the conversion of H_2O_2 into water and molecular oxygen (Dringen et al. 2005).

The family of Prx's consists of six thio-specific antiO proteins that are involved in the enzymatic degradation of H_2O_2, organic hydroperoxides, and peroxynitrite (Rhee et al. 2005).

Prx's are abundantly expressed in the cytosol; however, several isotypes can also be found in mitochondria, peroxisomes, nuclei, and membranes (Hofmann et al. 2002).

The glutathione system is one of the most important antiO systems for most tissue types *in vivo*. It has been demonstrated in astrocytes that when hydrogen peroxide clearance by catalase is inhibited, the glutathione system almost completely compensates for this (Liddell et al. 2006 a,b). Neuronal cells contain high concentrations of the tripeptide glutathione (GSH) and display high GPx and glutathione reductase activity (Rhee et al. 2005). Inducible hemeoxygenase-1 (HO-1) and constitutive HO-2 belong to the family of heat shock proteins and protect brain cells from oxidative stress. NADH quinine oxidoreductase (NQO1) is mainly expressed in astrocytes and brain endothelial cells and, together with NQO2, prevents the generation of FRs-Os (Siegel and Ross 2000; van Muiswinkel et al. 2004; van Horssen et al. 2006).

Micronutrients play an important role in the antiO defense system such as vitamin C (ascorbic acid) which is an effective quencher of many oxyradicals in the body and a protector against scurvy. Vitamin E (tocopherol) provides antiO protection in the body, especially the protection of the unsaturated fatty acids of the cell membrane. Carotenoids in fruits and vegetables are also believed to provide antiO protection to lipid rich tissues; glucose, pyruvate, bilirubin, carnosine, and the methyl rich compounds carnitine, choline, betaine, and methionine are involved. A variety of minor plant constituents such as flavonoids, liminoids and procyanins exhibit antiO activity (Valko et al. 2005, 2007; Droge 2002; Davies 1995; Halliwell and Gutteridge 1999; Lauterburg et al. 1984).

2.2. AntiO classification based on action

AntiOs have three main modes of actions include preventing, chain-breaking/scavenging and chelating mechanisms. In the case of preventing the production *ab initio* of FRs-Os and their destruction, catalase is an example. Chain- breaking/scavenging the radicals examples are vitamin E and C, as well as enzyme systems to control FRs-Os (Hammadeh et al. 2008). Carnosine as a chelating agent is an efficient singlet-oxygen scavenger, quenching singlet oxygen more effectively than histidine. Carnosine, anserine, and histidine have a protective effect against (γ-irradiation, which gives rise to oxidative DNA damage, protects against oxidative stress, and suggests that it and related compounds may serve as natural antiOs in skeletal muscle and brain (Gulewitsch and Amiradzibi 1900).

2.3. AntiO classification based on solubility in water or lipids

Vitamin C is present in the body's aqueous compartments such as the blood plasma and cell cytosol. Vitamin E (tocopherol) is present in the body's lipid phases. Carotenoids in fruits and vegetables are also believed to provide antiO protection to lipid rich tissues (α-Lipoic acid (ALA)) has the ability to exist in both aqueous and lipid phase. ALA has a role in the increase in cellular GSH concentration. ALA is readily absorbed from the diet and is converted rapidly to its reduced form, dihydrolipoic acid (DHLA) (Smith et al. 2004). Both ALA and DHLA are powerful antiOs and exert their effects by scavenging free radicals, metal ion chelation and antiO recycling. DHLA as an antiO is stronger than ALA and can act synergistically with other antiOs such as glutathione, ascorbate and tocopherol (Jacob 1995; Navari-Izzo et al. 2002).

2.4. AntiO classification based on life span

Melatonin, once oxidized, cannot be reduced to its former state because it forms several stable products upon reacting with FRs-Os. Therefore, it has been referred to as a terminal (or suicidal) antiO (Tan et al. 2000). Ascorbic acid and tocopherol have long life spans. Ascorbic acid is able to regenerate tocopherol (Valko et al. 2005, 2007; Droge 2002; Davies 1995; Tan 2000). Melatonin reduces oxidative damage caused by ischemia in heart, liver, and kidney (Sewerynek et al. 1995; Reiter and Tan 2003; Sewerynek et al. 1996; Okatani et al. 2003; Sener et al. 2002).

3. Regulation and expression

Different studies proved that the endo-antiO system could respond to the presence of end/exo source of FRs-Os. Different individuals show different response based on their age, gender, genetics, and structural complexity of the organ, health condition, and nutritional status as well as different tissue specific responses. Human studies indicate that environmentally induced FRs elicit antiO responses in different tissues, which should have some link to the tissue gene specificity. The role of antiO proteins in their responses to FRs-Os was investigated using knockout animals (Kensler et al. 2007; Kobayashi and Yamamoto 2006; Itoh 2004). Various factors including cell stress lead to an increase in the expression levels of the antiO enzyme in tissues; however, coordinated expression does not necessarily occur in response to stimuli. As an example, NF-E2-related factor 2 (Nrf2) induces the expression of endo-antiOs enzymes. Nrf2 belongs to a subset of basic leucine-zipper (bZip) genes sharing a conserved structural domain, called the CNC domain. In mammals this CNC family is composed of four closely related proteins, p45-NFE2, Nrf1, Nrf2, and Nrf3, which function as heterodimeric transcription factors by pairing with other bZip proteins, including small Maf proteins (Kensler et al. 2007; Kobayashi and Yamamoto 2006; Itoh 2004).

Nrf2–antiO responsive element (ARE) activation induces the production of a battery of endogenous enzymes, such as SODs, CAT, GPx's, Prx's, NQOs and HOs (Harris 1992; Jaiswal 1994; Wasserman and Fahl 1997).

Transcriptional regulation appears to be the most common form of regulation over antiO enzyme expression (McCord 1976; Rhee et al. 2005; McCord and Edeas 2005; Mills 1957; Kim et al. 2007; Li and Jaiswal 1992; Long and Jaiswal 2000; Iskander et al. 2006; Jaiswal 2000; Ishii et al. 2000; Wagener et al. 2003; McCord 1976; Maier and Chan 2002; Harris 1992; Nanji et al. 1995; Wilson and Johnson 2000).

4. Medicinal food

Humans are one of the few vertebrates that cannot Synthesise vitamin C because the gene for the flavoenzyme, L-gulono-1,4-lactone oxidase is not transcribed and is highly mutated (Chatterjee 1973).

The importance of foods which have high amounts of active compounds such as those used in modern medicine is often underestimated. There is an increasing need for more knowledge about the biological activities and/or chemical constituents of that neutraceutical food, especially for the discovery of new therapeutic drugs and novel chemical structures. In addition to this, neutraceutical food serves as an alternative medicine. Scientists are intensively investigating different plants for active compounds. Dubick (1986) reported that the medical use of herbs is deeply rooted in human history and folklore. He describes gineseng and garlic, which are plants having active compounds that are widely used in traditional medicine and food. Ginseng and garlic are well known for the existence of large amounts of antiOs (Dubick 1986; Cumming et al. 2000; Wesnes et al. 2000). Masella et al. (2004) reported that extra virgin olive oil biophenols inhibit cell-mediated oxidation of low-density lipoprotein (LDL) by increasing the mRNA transcription of glutathione-related enzymes

Awney et al. (1997) report a study on the effect of 12 different plant extracts on the aryl hydrocarbon hydroxylase (AHH) activity and H_2O_2 production by lindane induced mice hepatic microsomes. The different plant crude extracts which contain different antiOs show significant H_2O_2 and AHH inhibition, especially edible ones including *Sesamum indicum*, *Nigella sativa*, *Cinnamomum zeylanicum*, *Ficus carica*, *Curcuma longa* and *Zingiber officinale* (Awney et al. 1997). The same extracts are able to inhibit tumor formations using *Agrobacterium tumefaciens in vivo* potato disk antitumor bioassay which have a significant correlation to the 3PS (*in vivo*, murine leukemia) (Awney et al. 1997; Amara et al. 2008; Galsky and Wilsey 1980; 1981 a,b).

Diets containing antiOs are usually derived from vegetables and fruits including grape seeds, isothiocyanate from cruciferous vegetables, catechins from green tea, and curcumin from turmeric (Awney et al. 1997; Keum et al. 2004; Surh et al. 2005; Son et al. 2008).

Plant antiOs activate the Nrf2-mediated adaptive response (Surh et al. 2005; Son et al. 2008; Surh 2003; Kohle and Bock 2006). Studies show that consumption of fruits and vegetables containing antiOs provides protection from cancer (Surh 2003). An oversupply of antiOs results in a reducing intracellular environment, which keeps more Keap1 molecules in the reduced configuration. With less oxidized Keap1 molecules present, ubiquitination and degradation of Nrf2 increases. A decline in Nrf2 would lead to impairing the endo-antiOs (Kohle and Bock 2006; Bjelakovic et al. 2004; Bairati et al. 2006; Hercberg et al. 2007; Omenn 2007; Plummer et al. 2007; Lin et al. 2009). Taking low-dose prooxidants should be beneficial (Calabrese 2001). Low-doses of isothiocyanate and its related antiOs may activate the Nrf2 antiO system, providing protection (Calabrese 2001).

While "protection is usually better than treatment" is a common idiom and a correct scientific fact, there is a general developing theory among scientists concerning protection against and treatment for diseases using edible plants, food, or nutraceuticals. Herpecious plants could have unique types of active constituents, but usually there is a risk of the presence of detectable or hidden harmful compounds (Awney et al. 1997). In contrast, edible plants prove historically that they have nearly no side effects (Amara et al. 2008; Galsky and Wilsey 1980; Galsky et al. 1981 a,b).

Active combination between the different types of neutraceutical foods in most cases leads to better treatment. To maintain health, a particular food diet should be used for each age/situation, especially if there is an expectation for the presence of particular or inherited diseases, or if there is an expected interaction between food and our DNA. In the case of nutraceutical foods, their composition of antiOs should be calculated (Valko et al. 2007; Droge 2002; Valko et al. 2005; Davies 1995).

5. FRs-Os/antiO/food interaction

There is convincing evidence that genetics have a crucial role in impairing the balance between AntiO/FRs-O systems. The genetic differences could affect the exo/endo/existing antiO and FRs-O systems and their interaction with nutrients and active compounds in food including mutations, impaired genes, methylated genes, single nucleotide polymorphism (SNP) and damaged genes. Homozygotic twins having identical alleles at corresponding chromosomal loci are considered genetically identical. The genetic differences will be clearer between individuals other than twins. However many exo/endo factors are not inherited and could affect our genes, such as the environment, food, and imprinting processes during fetal development which can cause methylation. Other differences across entire regions of an individual's genome result from various nutrient imbalances and deficiencies. Genetic variation between individuals is the rule not the exception (Marklund 1982; Rhee et al. 2005; McCord and Edeas 2005; Mills 1957; Kim et al. 2007; Li and Jaiswal 1992; Long and Jaiswal 2000; Iskander et al. 2006; Jaiswal 2000; Ishii et al. 2000; Wagener et al. 2003; McCord 1976; Maier and Chan 2002).

Minor changes in our genetic material could cause dangerous diseases. In most cases those changes are static. There are different mechanisms which can cause a genetic change in a person who is born normal. Cancer is an example of the interaction between food (which is either an inducer or a protector) and the genetic materials (Valko et al. 2004; Droge 2002; Chui and Carol 2008). "Cancer is a detectable internal modification that happens in our gene(s), However many other forms are undetectable or neglectable"

6. Our genes are susceptible

Is there is a real interaction between food and our DNA? In other words, what influence has food on our DNA? There is increasing evidence that nutrients have a direct effect on our genomic DNA, especially during the infant stage. To simplify this, what could be the affect of nutrients on our DNA. Examples from lower eukaryotes and prokaryotes should be considered. Studies on the human genome are rather complicated and in many cases incontinuous in regard to many aspects including time, environment, lifestyle, nutrients sources, tradition, etc. (Valko et al. 2006, 2007; Droge 2002; Davies 1995).

6.1. Learning from prokaryotes

Perhaps one interesting example of prokaryotes is *E. coli* cell XL1-Red (end*A1,* gyr*A96,* thi-*1,* hsd*R17,* supE44*,* relA1*,* lac mutD5*,* mutS*,* mutT*,* Tn*10(*Tc^r*)*) Stratagene© (Bachmann 1987; Glickman and Radman 1980).

Strain XL1-Red is an *E. coli* strain deficient in three of the primary DNA repair pathways. They are: *mutS* (error-prone mismatch repair), *mutD* (deficient in 3′-to 5′- exonuclease of DNA polymerase III) and *mutT* (unable to hydrolyse 8-oxodGTP). This strain grows extremely slowly in rich media (e.g. LB media), having a doubling time of ∼90-120 min (Glickman and Radman 1980; Scheuermann et al. 1983).

This deficiency enables an irreversible DNA mistake causing mutations. If a specific gene comes under stress during replication or during the processes leading to a particular protein in absence of the repair mechanism, these conditions will lead to mutations. As an example Amara et al. (2002) established *in vivo* a random mutagenesis protocol for mutant screening, $phaC_{Ap}$ synthase was the target gene.

Why does normal *E. coli* cultivated under the same conditions not induce such mutations? Something is different. In our case, we know the main difference between normal *E. coli* and *E. coli* XL1 Red. *E. coli* XL1 Red is a sick cell with impaired DNA repairing genes, which enable mutagenesis (Glickman and Radman 1980; Scheuermann et al. 1983; Amara et al. 2002).

Human cells under similar conditions could give the same results. When there is a deficiency, in particular essential genetic materials such as DNA repairing genes or those genes responsible for expressing essential enzymes including antiO enzymes, the problem will be exponential. The nutrients used for cultivating *E. coli* XL1 Red will start its growth, replication and the DNA mutagenesis process. The nutrients in our food could do the same job and will follow the same steps. If we have a problem in one or more of the essential genes, which could be in interaction or under the influence of a particular nutrient, this gene will be under pressure. When an external or a mutagenic factor such as FRs-O exists, more damage to the target gene(s) could occur.

When AntiOs are preventing or decreasing the amount of FOs-Os in our bodies, they are doing a vital activity (Albanes 2009; Bandera et al. 2009; Block 2009 a,b; Chen et al. 2009).

Eliminating the stress source(s) will give better results for healthy individuals, and this will always be best for those who have genetic problems. On other hand, normal *E. coli* and *E. coli* XL1-Red are examples of the genetic polymorphism, which is a real fact in the bio-system especially those that reproduce sexually or have inherited disease(s).

6.2. A real example

DNA damage and base change can affect gene transcription, mRNA stability, or protein function (McCann 1997; Dringen et al. 2005; Cha et al. 2004).

Detrimental amino acid changes and altered gene regulation have been the focus of the most attention so far. Genetic variation in oxidative stress-related genes could reveal the degree of variability that is tolerated in healthy life (e.g., acatalasemia). Furthermore, the effect of antiOs on expression levels needs to be determined. In the eukaryotic system, the results will be of course more complicated. Cancer is a clear example of above normal DNA/Protein interactions. Different proteins are working as antiOs to control the FRs-Os from damaging cell macromolecules. Among the three isoforms of SOD (SOD1, SOD2 and SOD3), SOD2 polymorphisms have largely been implicated with cancer risk. The most commonly studied polymorphism of Mn-SOD is Val 16 Ala on mitochondrial target sequence. Other examples like Pro 197 Leu SNP of the GPx1 (GPx) gene have been associated with FRs-O related diseases (Ambrosone et al. 1999; Grasbon-Frodl et al. 1999; Hu and Diamond 2003). CAT SNP is responsible for Japanese acatalasemia (Hirono et al. 1995). The CAT C-262T SNP is the most widely studied to date; it has been associated with a decrease in CAT activity and an increased or decreased risk of developing FRs-Os (Nadif et al. 2005). Other SNPs located within this region include G-844A, which has been associated with hypertension (Jiang et al. 2001; Gavalas et al. 2006).

These SNP regions can influence either nutritional status or the renutrition process because renutrition becomes progressively more difficult with age (Nadif et al. 2005).

The success in using the new molecular biology tools such as genomics, proteomics and metabolomics (Young 2002; Fay and German 2008; Fiehn 2001) will map the interactions between genes, nutrients and environment and in this way will highlight their downstream effects on human health (Young 2002; Fabre et al. 2008).

6.3. Thank God our erythrocytes contain no DNA!

Erythrocytes transport large amounts of oxygen over their lifespan resulting in oxidative stress. Red cells have potent antiO protection consisting of enzymatic and nonenzymatic pathways that modify highly active FRs-Os into substantially less reactive intermediates (Çimen 2008).

DNA and RNA are the major sensitive macromolecules in the cell. The absence of DNA in our red blood cells enables maximum expected protection against FRs-Os. Three major hereditary conditions in the erythrocytes can cause major cell disorders including sickle cell anemia (SCA), thalassemia, and glucose-6-phosphate dehydrogenase (G6PD) deficiency (Comporti et al. 2002; Scott et al. 1993; Kakhlon and Cabantchik 2002; Scott et al. 1991; Kirkman and Gaetani 2007). However, increased oxidative damage to red cells is commonly associated with all three disorders and have been attributed to the accelerated red cell destruction in all cases. Food which contains antiOs is recommended for general health improvement for those patients (Valko et al. 2005, 2007; Droge 2002; Davies 1995).

7. Nutrient personalization

Currently there is increased interest in nutrient personalization. Do the differences between humans in response to their diet components enable the building of a genetically based diet? The increasing data from genomic, proteomic and transcriptome research prove this argument. Research on gender revealed that there are different effects of antioxidants on cancer risk (Higdon and Frei 2005; Waters et al. 2004). Providing nutritional foods for helping individuals recovering from diseases is a clear opportunity to develop parallel approaches along with personalized medicine. The different observations derived from different ethnic groups indicate that humans have long known about the interaction between food and health. Scurvy is an example. Linking the genome, proteome, and transcriptome with nutrients and with each other will match our aim of establishing the nutrient personalization science. Building database(s) about genetic polymorphisms and their interaction with food aiming to solve the existing gene/food based problems or protecting against expected diseases through supplying specific nutrient(s) is in demand (Marklund 1982; Rhee et al. 2005; McCord and Edeas 2005; Mills 1957; Kim 2007; Li and Jaiswal 1992; Long and Jaiswal 2000; Iskander et al. 2006; Jaiswal 2000; Ishii et al. 2000; Wagener et al. 2003; McCord 1976; Maier and Chan 2002).

8. Conclusion

FRs-Os are not always enemies but are an essential part of our biological system. They are involved in many vital and positive processes. They are controlled with the aid of our endo-antiO system as well as the exo-antiOs, which we gain during our normal daily diets. The antiOs are groups of compounds produced mainly by the biological system and are used to remove / control the FRs-Os. They can do this individually or work as a network. Because they are produced by the biological system, most of them have references in our genetic materials.

AntiOs can be classified according to their source, nature, solubility, life span and their mode of action. In special cases, our existing antiOs do not satisfy our demand and cannot remove the excess of FRs-Os, which are generated from different exo and indo sources. Therefore, we need external sources of antiOs, preferably gained from our diet. Foods that have an extra amount of antiOs usually are called neutraceutical foods. Neutraceutical foods supply us with adequate amounts of antiOs. They can, in most cases, reduce the amount of FRs-Os and satisfy our bodies' demands.

The study of individuals and population genetic polymorphisms will be a challenging task for scientists because they have to optimize their knowledge about the role of genomes and proteomes in our health status. Those who have inheritable diseases need to gain exo-antiOs to recover from deficiencies. The overcontinuous expression and induction of FRs-O or antiO systems could be a source of self-damage. Exogenous sources of antiOs will not only satisfy our need and cover any kind of deficiency but also will enable the cells to be more relaxed and to direct their power to other vital processes. AntiOs should be used wisely because free radicals also have essential roles in our life. FRs-O levels should always be under control to promote our best health. Personalizing food will show an increasing interest in *ab initio* protection based on the genetic polymorphisms between different individuals. We are not equal genetically. A case-by-case healthy nutrition regime is a key factor in our healthy future.

> "*With hundred of friends, one has problems! Reducing the number will be better! Treat FRs-Os as friends and not as enemies, but reduce their amounts." The author.*

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