Nutrigenetics of antioxidant enzymes and micronutrient needs in the context of viral infections

Ruth Birk

Department of Nutrition, Faculty of Health Sciences, Ariel University, Ariel, Israel

Abstract

Sustaining adequate nutritional needs of a population is a challenging task in normal times and a priority in times of crisis. There is no ‘one-size-fits-all’ solution that addresses nutrition. In relevance to the COVID-19 (coronavirus disease 2019) pandemic crisis, viral infections in general and RNA viruses in particular are known to induce and promote oxidative stress, consequently increasing the body’s demand for micronutrients, especially those related to antioxidant enzymic systems, thus draining the body of micronutrients, and so hindering the human body’s ability to cope optimally with oxidative stress. Common polymorphisms in major antioxidant enzymes, with world population minor allele frequencies ranging from 0.5 to 50 %, are related to altered enzymic function, with substantial potential effects on the body’s ability to cope with viral infection-induced oxidative stress. In this review we highlight common SNP of the major antioxidant enzymes relevant to nutritional components in the context of viral infections, namely: superoxide dismutases, glutathione peroxidases and catalase. We delineate functional polymorphisms in several human antioxidant enzymes that require, especially during a viral crisis, adequate and potentially additional nutritional support to cope with the pathological consequences of disease. Thus, in face of the COVID-19 pandemic, nutrition should be tightly monitored and possibly supplemented, with special attention to those carrying common polymorphisms in antioxidant enzymes.

Key words: Nutrigenetics: Viral infections: Oxidative stress: Antioxidant enzymes

(Received 12 May 2020; revised 13 September 2020; accepted 14 October 2020; accepted manuscript published online 21 October 2020)

Introduction

Tight interaction exists between nutrition and the immune system. The necessity of optimal nutrition for the function, efficiency and capability of the immune system to cope with external and internal insults is well known⁽¹⁾. Consequently, poor nutrition states predispose the body to a compromised immune state^(2,3). Macro- and micronutrient deficiencies and suboptimal nutritional intakes are common worldwide in both developing and developed countries, and may adversely affect the individual’s immune system. Furthermore, specific sub-populations are more vulnerable to nutritional deficiencies at different time points in the cycle of life (infants, adolescents, pregnant women, elderly) and in specific states (hospitalised patients, chronic diseases)⁽⁴⁾. Although undernutrition clearly predisposes to immune deficiencies, overnutrition and obesity have also been shown to alter immunocompetence⁽⁵⁾. In fact, obesity is characterised by chronic, low-grade inflammation, which significantly contributes to the pathogenesis of obesity co-morbidities and to increased susceptibility to various infections^(6–8). The interaction between the immune response and nutritional status is highlighted in the context of oxidative stress during viral infections. While redox balance is critical to life and highly dependent on nutritional factors, viruses trigger by different mechanisms pro-oxidative and unbalanced redox states, which both

aggravate the host response and promote virus survival. In fact, viral infections are characterised by a spectrum of clinical phenomena, with oxidative stress being one of their hallmarks⁽⁹⁾.

One clear illustration of the strong link between nutrition and immunity in the context of viral infection is the case of Se. Se is an essential micronutrient that, through its incorporation into selenoproteins, takes part in the regulation of oxidative stress, redox balance and other crucial cellular processes, including the innate and adaptive immune response. Se has been shown to be involved in T-lymphocyte proliferation and in the humoral system⁽⁴⁾. Se deficiency was found to enhance the virulence or progression of some RNA viral infections, while Se supplementation was shown to augment antiviral immunity against endemic coxsackievirus and to prevent viral genomic RNA adaptations that lead to increased virulence and cardiac pathology in Keshan disease⁽¹⁰⁾. Similarly, another RNA virus, influenza A, was shown to undergo increased mutational alterations in genomic RNA due to Se deficiency⁽¹¹⁾. Among HIV-1-infected individuals, lower serum Se concentrations have been associated with lower CD4⁺ T cell counts, greater HIV-1 disease progression and higher HIV-1-related mortality⁽¹²⁾. Interestingly, human subjects vaccinated against poliovirus antigens showed more rapid clearance of the poliovirus, with lower number of the poliovirus mutations and more robust Th1 immune

Abbreviations: CAT, catalase; GPx, glutathione peroxidase; HCV, hepatitis C virus; MAF, minor allele frequency; ROS, reactive oxygen species; SOD, superoxide dismutase.

Corresponding author: Professor Ruth Birk, email ruthb@ariel.ac.il

responses, when supplemented with Se, as compared with human subjects with low Se status⁽¹³⁾. One of the human body's fundamental anti-oxidative systems is the antioxidant enzymes. Antioxidant enzymes need nutritional factors, mainly micronutrients, as co-activators for optimal function. Major antioxidant enzymes have common polymorphisms related to altered enzymic function with world population minor allele frequencies (MAF) ranging from 0.5 to 50 %, which could substantially affect the body's ability to cope with viral infection-induced oxidative stress. Thus, in light of the COVID-19 (coronavirus disease 2019) pandemic, there is a critical need to consider personalised nutritional needs related to one of the fundamental viral pathological mechanisms, oxidative stress.

Reactive oxygen species: antioxidant defence system and related nutritional needs

The redox balance, or the anti/pro-oxidative balance in human cells, is of utmost importance to survival. Reactive oxygen species (ROS), typically oxygen and NO radicals, are consistently produced in and by cells in normal physiological processes, serving an important role in cellular and physiological functions, such as cellular signalling, regulation of cytokines, growth factors, transcription, immunomodulation and apoptosis, as well as in other processes⁽¹⁴⁾. The cellular ROS levels are tightly maintained by complex intracellular regulatory systems. However, an unbalanced, uncontrolled pro-oxidative redox state results in damage to DNA, lipids and proteins, as well as loss of cellular integrity, and is linked to the initiation, development, progression and outcome of most human diseases, including infectious diseases. To keep cellular homeostasis and prevent a deleterious oxidative state, a sophisticated and synergistic antioxidant defence system, consisting of both enzymic and non-enzymic factors, is continuously activated. Non-enzymic antioxidants are mainly dietary components, classified generally as essential vitamins and minerals; and non-essential components, including phytochemicals – such as polyphenols, carotenoids and organosulfur compounds. The endogenous enzymic antioxidant system is comprised mainly of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) as well as other enzymes. The major antioxidant enzymes SOD1–3 catalyse the dismutation of superoxide (O_2^-) oxidative radicals into O_2 and H_2O_2 . Followed by SOD activity, two other antioxidant enzymes, CAT, a tetrameric haemoprotein, and GPx, convert H_2O_2 to water and O_2 . The importance of these enzymes to human health is evident through numerous studies, demonstrating that abnormal SOD is linked to several diseases, including amyotrophic lateral sclerosis, Down's syndrome and carcinogenesis^(15,16). Similarly, studies have shown the involvement of GPx in cancer, diabetes, angiogenesis, endothelial dysfunction, atherosclerosis, and cardiac dysfunction^(17,18). The majority of detoxification enzymes depend on dietary minerals as cofactors for optimal activity. For example, of the three human SOD isoforms, the cytosolic SOD1 uses Cu or Zn ions, the mitochondrial SOD2 uses Mn, the extracellular SOD3 also uses Cu/Zn, and GPx uses Se. Furthermore, as elimination of ROS is usually an orchestrated process, where the activity of one enzyme is followed by

another, if the activity of one enzyme is not optimal and balanced by that of the following enzyme, the generation of ROS is accelerated.

Fruits and vegetables are a rich source of exogenous antioxidants, such as vitamins C and E and minerals (Mg, Zn, Mn and Se) and also of non-essential phytochemicals (polyphenols and carotenoids). Numerous studies have shown that a diet rich in fruits and vegetables is associated with reduced risk of chronic diseases^(19,20). In fact, it has been shown that during oxidative stress, dietary components can modify total antioxidant capacity, an analyte frequently used to assess the antioxidant status of biological samples, improving redox status and consequently delaying or preventing progression and onset of diseases. Dietary total antioxidant capacity has been shown to be associated with risks of several chronic diseases, such as diabetes, hypertension and CVD, etc.^(21–30).

Reactive oxygen species, viral infection and antioxidant enzymes

In the context of viral infections, many human viruses, including HIV, herpes simplex virus type 1, hepatitis B virus, hepatitis C virus (HCV), respiratory syncytial virus, influenza viruses and SARS (severe acute respiratory syndrome) coronavirus, produce ROS by diverse mechanisms^(31–35). As SARS-CoV-2 virus has 80 % homology to SARS coronavirus, it probably uses similar mechanisms⁽³⁶⁾. In recent years, several reviews summarised the involvement of ROS in the pathogenesis of viral infections in general and in RNA viruses in particular^(37–39). Although not the focus of this review, in brief, during viral infections, one of the virus's infection strategy to promote viral pathogenesis is to modulate the intracellular redox state as a byproduct of survival efforts and as part of their replication mechanism. Ultimately, virus-induced host cells, as a mechanism of pathogen elimination and viral spread limitation⁽⁴⁰⁾, secrete cytokines, which trigger host ROS production⁽³⁹⁾. Host-triggered phagocytes activate the NADPH oxidase complex and NO synthase, resulting in simultaneous release of ROS and pro-oxidant cytokines, such as TNF and IL-1⁽¹⁴⁾. In turn, TNF and IL-1 trigger a chain of cellular events, such as mitochondrial pro-oxidant activity and stimulation of neutrophils to release lysosomal proteins, including lactoferrin, which may result in an elevated production of ROS. As viral multiplication progresses, more ROS are formed, causing an imbalance in cellular redox homeostasis, thus contributing to the severity of the inflammatory responses, cell death, weight loss and other typical phenomena^(37,38). The cellular redox homeostasis imbalance can in turn further contribute to viral survival by selecting for certain viral mutants and activating transcription factors, such as NF- κ B, which increases viral replication⁽³⁹⁾.

In general, viruses, although varying in the production of ROS, share a common pathogenic pathway which results in host antioxidant system depletion⁽³⁸⁾. For example, patients infected by hepatitis B virus show a reduction in Cu/Zn-SOD and GPx enzymes⁽³⁹⁾; patients with dengue fever exhibit alteration in oxidative stress status as the disease progresses, with decrease in the glutathione and total antioxidant status following

infection⁽¹⁵⁾; and HIV patients show significantly reduced levels of GSH, cysteine, vitamin C, GPx and SOD in plasma and leucocytes, and an increase in levels of lipid peroxidation^(17,41,42).

The critical importance of both antioxidant enzymes and nutritional components to the course of viral infection is clearly demonstrated by numerous *in vivo* and *in vitro* studies (mostly in animals), highlighting the therapeutic potential but also the limitations of this therapy^(43,44). Some examples in a nutshell: injecting SOD conjugated with a pyran copolymer protected mice against a potentially lethal influenza virus infection⁽⁴⁵⁾; the administration of recombinant human CAT to mice infected with H1N1 influenza A virus decreased inflammatory cell infiltration, inflammatory cytokine levels and the mRNA levels of the Toll-like receptors and NF- κ B⁽⁴⁶⁾. Moreover, it was demonstrated that oxidative stress positively affects viral RNA replication and that antioxidant treatment can significantly impair viral RNA replication, altering the amount of capped viral RNA⁽⁴⁷⁾. Clinical studies have shown that the addition of antioxidants can decrease liver injury caused by oxidative stress, suggesting that this could be a potential treatment for HCV infection^(48,49). Studies have also shown that the administration of exogenous GSH inhibits dengue virus-2 viral production by modulating NF- κ B activity and reducing ROS production^(50,51). Vitamin and micronutrient supplementation has been shown to improve outcomes in HIV-infected patients either alone or with antiretroviral treatment^(52,53). Vitamin E supplementation decreased lung virus titres in mice infected with influenza^(54,55). SOD, CAT and GPx were significantly increased in rats after oral dosage of astaxanthin⁽⁵⁶⁾. A vitamin C supplement was demonstrated to have a beneficial effect in influenza infections, mainly in experimental models; however, this effect has not been reported in patients⁽⁵⁷⁾. Herpes zoster infection patients receiving intravenous vitamin C supplement had a significant reduction in pain scale scores⁽⁵⁸⁾. However, it should be noted that the role of antioxidants in viral infections is more complex than the mere antiviral host defence and viral survival strategies, as it includes many other effects related to metabolic regulation both of host and viral survival. Thus, viral infection simultaneously increases the demand for micronutrients and causes their loss, which leads to an antioxidant deficiency that should be monitored and addressed as an essential part of viral treatment. However, due to the complexity of the viral–host interaction, the complex effects of ROS–antioxidant interactions and the lack of clinical studies, well-designed clinical trials are required to study the use of antioxidants as a therapy in viral infections.

In the context of the present review, one of the overlooked areas which requires scientific and clinical attention is the existence of functional polymorphisms in genes encoding antioxidant enzymes, which alter the function of the enzymes, with possible implications on antioxidant nutritional requirements and treatment (Table 1).

Superoxide dismutase polymorphisms and diseases

The human *SOD1* gene is located on chromosome 21q22, *SOD2* on chromosome 6q25^(30,59) and *SOD3* on chromosome 4q21^(60,61). Due to their essential role in conserving cellular integrity and

redox balance, functional alterations in SOD1, SOD2 and SOD3 have been linked to common diseases, including inflammatory bowel disease^(62,63), obesity^(64,65), diabetes and hypertension^(30,66–70), chronic obstructive pulmonary disease^(71–75) and CVD⁽⁵⁹⁾, etc. Surprisingly, although polymorphisms in the antioxidant genes may determine cellular oxidative stress levels, with significant implications for the pathogenesis of viral infections and their complications, scarce research exists on this issue. Farawela *et al.*⁽⁷⁶⁾ studied 100 Egyptian patients with B cell-non-Hodgkin lymphoma and 100 controls to test the association between HCV infection, oxidative stress gene polymorphisms and B cell-non-Hodgkin lymphoma risk. Concomitant HCV infection and *GPx1* gene polymorphism (Pro¹⁹⁷Leu) had a synergetic effect on non-Hodgkin lymphoma risk with an OR of 15. *SOD2* (Val16Ala) and *CAT* (C-262T) genetic polymorphisms were not found to confer increased non-Hodgkin lymphoma risk. Similarly, Ezzikouri *et al.*⁽⁷⁷⁾ found a significant association between homozygosity of the *SOD2* (Val16Ala) variant polymorphism and hepatocellular carcinoma occurrence in HCV-infected Moroccan patients.

In humans, at least 111 SNP have been identified for *SOD1* and 100 for *SOD3*; however, information regarding these polymorphisms in the context of chronic diseases is lacking^(75–78). Most of the SNP, summarised in a recent review, are not known to be functional, yet are located in non-coding intronic genetic regions with possible regulatory implications⁽⁷⁵⁾. Of clinical significance is the functional SNP rs1799895 (worldwide MAF 0.5–10%), which changes arginine to glycine at position 213 (R213G) at the *SOD3* carboxy-terminus, resulting in alteration of the positive charge of the terminus, and consequent release of SOD3 from the extracellular matrix to the extracellular fluids such as plasma and epithelial lining fluids⁽⁷⁹⁾. SOD3 is highly expressed in arteries⁽⁸⁰⁾, lungs, airways⁽⁸¹⁾ and alveolar macrophages⁽⁸²⁾. Studies in both human subjects and mice have shown that SOD3 plays a key role in decreasing lung injury by reducing oxidative stress⁽⁸³⁾. In fact, *SOD3* R213G carriers have reduced risk of exacerbations of chronic obstructive pulmonary disease⁽³⁵⁾. In a recent elegant study, Gaurav *et al.*⁽⁷⁹⁾ showed that knock-in mice analogous to the human *SOD3* R213G SNP had lower airway hyper-responsiveness, inflammation and mucus hypersecretion with decreased IL-33 in bronchoalveolar lavage fluid and reduced type II innate lymphoid cells in the lungs. This study suggests the potential benefit of *SOD3* R213G SNP carriers, as they highly express SOD3 in the airway-lining fluid, thus ameliorating allergic airway inflammation by diminishing the innate immune response, including IL-33-mediated changes in innate lymphoid cells⁽⁷⁹⁾. Of note, the *SOD3* R213G SNP was also reported to increase the risk of IHD in The Copenhagen City Heart Study⁽⁸⁴⁾.

The nuclear *SOD2* gene is translated in the cytoplasm with a mitochondrial targeting sequence; the enzyme is then transported into the mitochondria, processed, and assembled into an active homo-tetramer⁽⁵⁹⁾. *SOD2* is present in the mitochondria, the major ROS production organelle in aerobes, thus playing a pivotal role in health and disease⁽⁷⁸⁾. In humans, at least 190 SNP have been identified for *SOD2*^(30,59). The most studied *SOD2* functional SNP is Ala16Val (rs4880) in exon 2, which causes a conformational change in the mitochondrial targeting domain,

Table 1. Summary of oxidative enzyme polymorphism and nutrition interactions

Gene	Polymorphism	Minor allele frequency	Nutrition interaction	Reference
<i>SOD2</i>	Val16Ala	11.7 % East Asian, 50 % European, 62 % Latin American	Alcoholic cirrhosis patients that have at least one Ala16Val allele are at increased risk for hepatocellular carcinoma occurrence and death	(93)
			Premenopausal women homozygous for the <i>SOD2</i> Ala16Val allele have a 4-fold increased risk for breast cancer compared with women that are homozygous or heterozygous for the common allele (OR 4.3; 95 % CI 1.7, 10.8). This association was found to be most evident among women whose intake of fruits and vegetables and dietary ascorbic acid and α -tocopherol is below the median	(94-97)
			Men homozygous for the variant allele had a 70 % increased risk for prostate cancer compared with men homozygous for the wild-type allele (OR 1.72; 95 % CI 0.96, 3.08). Supplementation with α -tocopherol had no impact on the <i>SOD2</i> -prostate cancer association	(98)
			Significant interaction between prostate cancer risk, <i>SOD2</i> homozygous variant genotype and low baseline plasma antioxidant levels, where homozygote genotype and low antioxidant levels incurred almost 4-fold increased risk of prostate cancer. Men homozygous for the variant allele genotype had a 10-fold increased risk for aggressive prostate cancer across quartiles of antioxidant status	(99)
			Reduced risk of cervical carcinogenesis subtype was associated with the variant allele only among those with above median levels of serum β -carotene and γ -tocopherol	(100)
			Women carriers of at least one <i>SOD2</i> variant allele who had a high vegetable intake have lowered breast cancer risk by almost half compared with those with a low vegetable intake	(101,102)
			Greek-Cypriot women carriers of at least one <i>SOD2</i> variant allele, with high vegetable intake, have lowered breast cancer risk by almost half compared with women with low vegetable intake	(103)
			Women homozygous for the common C allele who consumed high-fruit diet showed a significantly lower risk for breast cancer (OR 0.59; 95 % CI, 0.38, 0.89)	(116)
			Women with at least one <i>CAT</i> -262C allele and high vegetable intake had lower breast cancer risk (OR high v. low for -262CC = 0.66, 95 % CI 0.47, 0.92; for -262CT = 0.53, 95 % CI 0.35, 0.81) ⁽⁸³⁾	(103)
			Women with low vegetable and fruit intake (< median), the low-risk <i>CAT</i> CC (OR 1.33; 95 % CI = 0.89, 1.99) genotype appeared to be associated with higher breast cancer risk, with significantly increased risks observed in those with ≥ 4 low-risk alleles compared with participants with ≤ 2 low-risk alleles (OR 1.77; 95 % CI 1.05, 2.99; $P_{\text{interaction}}$ 0.006)	(116)
<i>CAT</i>	C-262T (rs1001179)	8–26 %	Inter-individual variation in antioxidant genes, including the <i>CAT</i> rs12807961 SNP, could interact with dietary intake to influence pancreatic cancer risk	(118)
			The frequencies of both allele -21A and -21AA <i>CAT</i> genotypes were higher among asthmatics than among healthy controls	(109)
			Low fruit and vegetable consumers (once per d or less) possessing the <i>CAT</i> -21AA genotype were at increased risk of both allergic and non-allergic asthma	(118)
			Inter-individual variation in antioxidant genes, including the <i>CAT</i> rs12807961 SNP, could interact with dietary intake to influence pancreatic cancer risk	(130)
<i>GPx1</i>	Pro ¹⁹⁸ Leu (rs1050450)	28 %	<i>GPx1</i> Pro ¹⁹⁸ Leu variant allele results in lesser response to the stimulation of <i>GPx1</i> enzyme activity during Se supplementation compared with the common allele	(133-135)
			<i>GPx1</i> Pro ¹⁹⁸ Leu genotypes differentially affected the Se status and <i>GPx</i> activity	(137)
			Brazil nut supplementation significantly increased <i>GPx1</i> mRNA expression only in subjects with the CC genotype ⁽¹¹⁷⁾	(141)
<i>GPx4</i>	718 T/C (rs713041)	35–44 %	Homozygotes for the variant allele had higher colorectal cancer risk with alcohol consumption and homozygotes for the common allele with higher dietary vitamin C intake had reduced risk of colorectal cancer ⁽¹²⁰⁾	(139)
			Elevated adhesion levels in HUVEC and monocytes in individuals homozygous for the T-variant compared with carriers of the C-variant. This effect was modified by Se and PUFA ⁽¹³⁹⁾	(140)
			Se supplementation for 6 weeks in non-smokers, both lymphocyte <i>GPx1</i> protein concentrations and plasma <i>GPx3</i> activity increased significantly in individuals homozygous CC in the <i>GPx4</i> 718 T/C (rs713041) SNP but not in homozygote TT participants. After Se withdrawal, there was a significant fall in both lymphocyte <i>GPx4</i> protein concentration and activity in the homozygote TT, but not in homozygote CC participants	(140)

SOD2, superoxide dismutase 2; *CAT*, catalase; *GPx*, glutathione peroxidase; HUVEC, human umbilical vein endothelial cells.

from α -helix to β -sheet secondary structure, consequently affecting *SOD2* activity in the mitochondria⁽³⁰⁾. Numerous studies have shown that the *SOD2* Ala16Val SNP is significantly associated with altered progression and risk of different diseases, such as diabetes and diabetes co-morbidities^(59,85–87), epilepsy⁽⁸⁸⁾, cancer⁽⁸⁹⁾, pre-eclampsia⁽⁹⁰⁾ and CVD^(59,78,91), etc. The *SOD2* Ala16Val (rs4880) mean allelic frequency is highly variable in different populations, ranging from 11.7 % in the East Asian population, to 50 % in European cohorts, to 62 % in Latin American population (BLAST⁽⁹²⁾).

Superoxide dismutase 2 Ala16Val SNP and dietary factors

Several known disease risk factors have been shown to interact with the *SOD2* Ala16Val polymorphism, including smoking and alcohol consumption. Alcohol promotes the generation of ROS through numerous processes, particularly in the liver, the main organ that metabolises and detoxifies alcohol. Nahon *et al.*⁽⁹³⁾ reported that alcoholic cirrhosis patients who have at least one Ala16Val allele are at increased risk for hepatocellular carcinoma occurrence and death.

Conflicting evidence exists regarding the interaction between the *SOD2* Ala16Val polymorphism and dietary components. Women homozygous for the *SOD2* Ala16Val variant allele have a 4-fold increased risk for breast cancer compared with women who are homozygous or heterozygous for the common allele (OR 4.3; 95 % CI 1.7, 10.8); this effect is particularly evident in premenopausal women. This association was found to be most evident among women whose intake of fruits and vegetables and dietary ascorbic acid and α -tocopherol is below the median^(94–97). The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study found that men homozygous for the variant allele had a 70 % increased risk for prostate cancer compared with men homozygous for the wild-type allele (OR 1.72; 95 % CI 0.96, 3.08)⁽⁹⁸⁾. However, supplementation with α -tocopherol had no impact on the *SOD2*–prostate cancer association. The Physicians' Health Study found significant interaction between prostate cancer risk, *SOD2* homozygous variant genotype and low baseline plasma antioxidant levels, where homozygote genotype and low antioxidant levels incurred almost 4-fold increased risk of prostate cancer. Men homozygous for the variant allele genotype had a 10-fold increased risk for aggressive prostate cancer across quartiles of antioxidant status⁽⁹⁹⁾.

Tong *et al.*⁽¹⁰⁰⁾ studied the interaction between *SOD2* genotypes and cervical carcinogenesis risk and the modulating effects of serum antioxidant nutrient status (β -carotene, lycopene, zeaxanthin/lutein, retinol, α -tocopherol and γ -tocopherol). They found that the reduced risk of cervical carcinogenesis subtype was associated with the variant allele only among those with above median levels of serum β -carotene and γ -tocopherol. Two meta-analyses have examined the association between the *SOD2* Val16Ala polymorphism, breast cancer risk and vitamin C, vitamin E and carotenoid⁽⁸²⁾ and fruit and vegetable consumption⁽¹⁰¹⁾. Their results suggest that the *SOD2* Val16Ala polymorphism may contribute to cancer development through a disturbed antioxidant balance; while both meta-analyses showed no independent effect of genotype on breast cancer risk,

intakes of antioxidants were shown to modify risk in premenopausal women⁽¹⁰¹⁾, while fruit and vegetable consumption did not⁽¹⁰²⁾. Similarly, Kakkoura *et al.*⁽¹⁰³⁾ showed that in Greek-Cypriot women who were carriers of at least one *SOD2* variant allele, high vegetable intake lowered breast cancer risk by almost half compared with low vegetable intake. Taken together, despite inconsistencies, the overall results suggest that the *SOD2* Ala16Val SNP can be modulated by dietary factors. However, further studies are needed to establish the nature of this association^(30,59).

Catalase polymorphisms and dietary factors

The *CAT* gene, mapped to chromosome 11p13, encodes a tetrameric haemoprotein expressed in all aerobes; the highest levels of the enzyme are found in the liver, kidney and erythrocytes. Numerous *CAT* polymorphisms have been described in the promoter, 5' and 3' untranslated regions, exons and introns^(104,105). Significant associations were found between *CAT* polymorphisms and the risk of various diseases, including diabetes^(106,107), hypertension⁽¹⁰⁸⁾, asthma^(109,110), breast cancer⁽¹¹¹⁾ and others. However, results of the various studies are inconsistent, explained at least in part by different populations, methodologies and disease course.

Of the *CAT* SNP presented in the National Center for Biotechnology Information (NCBI) database, the most studied in relation to human diseases is CAT C-262T (rs1001179), with mean world population frequency ranging from 8 to 26 %. The common CAT C262T polymorphism is located in the gene promoter region and its correlation with CAT activity is controversial^(111–113). However, the CAT C262T polymorphism was linked to host response to oxidative stress⁽¹¹¹⁾. Indeed, variant CAT T alleles have been associated with increased risk for conditions related to oxidative stress, such as hypertension⁽¹¹⁴⁾ and vitiligo⁽¹¹⁵⁾. Ahn *et al.*⁽¹¹⁶⁾ (Long Island Breast Cancer Study Project) have shown that women homozygous for the common C allele had a 17 % reduction in risk of breast cancer compared with those with at least one variant T allele. Women homozygous for the common C allele who consumed a high-fruit diet showed a significantly lower risk for breast cancer (OR 0.59; 95 % CI 0.38, 0.89). In a follow-up study, Ahn *et al.*⁽¹¹⁶⁾ found that differences in CAT activity by genotype were most pronounced among those in the highest tertiles of fruit and vegetable consumption. Similarly, Kakkoura *et al.*⁽¹⁰³⁾ found that high vegetable intake lowered breast cancer risk in Greek-Cypriot women with at least one CAT -262C allele (OR high *v.* low for -262CC = 0.66, 95 % CI 0.47, 0.92; for -262CT = 0.53, 95 % CI 0.35, 0.81). Analysing the Cancer Prevention Study-II Nutrition Cohort, Li *et al.*⁽¹¹⁷⁾ studied the interaction of a combined haplotype of SNP of common antioxidant enzymes with the level of vegetable and fruit intake on breast cancer risk in postmenopausal women. They found joint effects of endogenous and exogenous antioxidants, where among women with low vegetable and fruit intake (< median), the low-risk *CAT* CC (OR 1.33; 95 % CI 0.89, 1.99) genotype appeared to be associated with higher breast cancer risk, with significantly increased risks observed in those with ≥ 4 low-risk alleles compared with participants with ≤ 2 low-risk alleles

(OR 1.77; 95 % CI 1.05, 2.99; $P_{\text{interaction}} = 0.006$)⁽¹¹⁶⁾. Similarly, Jansen *et al.*⁽¹¹⁸⁾ found that inter-individual variation in antioxidant genes, including the CAT rs12807961 SNP, could interact with dietary intake to influence pancreatic cancer risk.

Another CAT SNP in the gene promoter region (rs7943316, worldwide MAF 25–48 %), an A>T substitution at position –21 (A–21T), has been studied in relation to interaction with nutritional factors. Polonikov *et al.*⁽¹⁰⁹⁾ found that the frequencies of both allele –21A and –21AA CAT genotypes were higher among asthmatics than among healthy controls. Notably, no association of CAT genotype –21AA with asthma was found in high fruit and vegetable consumers, whereas low fruit and vegetable consumers (once per d or less) possessing this genotype were at increased risk of both allergic and non-allergic asthma.

Taken together, there is growing evidence pointing to a possible interaction between CAT polymorphisms and relevant nutrients, indicating that an individual's genome should be taken into consideration when planning nutrient intake and that interaction between dietary components and the personal genome is a significant factor in health and disease.

Catalase polymorphisms and viral infection

Most of the quite limited publications regarding CAT polymorphisms and viral infection are related to either HCV and hepatic carcinoma or to HIV, with only initial and conflicting findings, warranting much needed future studies^(76,119,120). SNP have been associated with airway diseases, including asthma and chronic obstructive pulmonary disease⁽¹²¹⁾; however, little is known in this context regarding virus-induced lung disorders. Chambliss *et al.*⁽¹²²⁾ have shown that respiratory syncytial virus infection is associated with oxidative lung injury, decreased levels of antioxidant enzymes and degradation of the transcription factor NF-E2-related factor 2, a master regulator of antioxidant enzyme expression. Additionally, Chambliss *et al.*⁽¹²²⁾ demonstrated that the CAT rs1001179 (–262C/T) polymorphism in the lung may play an important and protective role in respiratory syncytial virus-associated lower respiratory tract infections in children heterozygous or homozygous for the variant allele. Similarly, the presence of the CAT rs1001179 (–262C/T) T allele has been previously associated with a decreased risk of asthma in non-smokers in the Hong Kong Chinese population⁽¹²³⁾, yet with an increased risk of new-onset of asthma among Hispanic and Caucasian children⁽¹²⁴⁾. To the best of our knowledge, no research has been conducted on the interaction between CAT polymorphism, viral infection and nutrition. Due to the important and proven interaction between CAT and nutritional factors, future such studies are needed.

Glutathione peroxidases

The glutathione peroxidases (GPx) are a family of Se-dependent enzymes encoded by discrete genes located on different chromosomes. The human genome harbours twenty-five selenoprotein genes, of which eight GPx paralogues have been identified, namely GPx1 (locus 3p21.3), GPx2 (locus 14q24.1), GPx3 (locus 5q23), GPx4 (locus 19p13.3), GPx5 (locus 6p22.1), GPx6 (locus

6p22.1), GPx7 (locus 1p32) and GPx8 (locus 5q11.2)⁽¹²⁵⁾. Five of these eight GPx paralogues contain a selenocysteine residue in the catalytic site (GPx1–GPx4, GPx6) and three have a cysteine instead (GPx5, GPx7 and GPx8)⁽⁹⁾. GPx1 and GPx4 are ubiquitously expressed; GPx1 (mostly abundant in erythrocytes, kidney and liver) is cytoplasmic, while GPx4 is localised to the cytoplasmic, mitochondrial and nuclear cellular compartments. GPx2 is present in epithelial tissues including the gastrointestinal tract, lung, skin and liver. GPx3 is secreted to the plasma and excreted mostly by the kidney. GPx6 is only found in the olfactory epithelium and embryonic tissues. The enzymic activity of GPx is directly proportional to Se intake; therefore, there is a strong link between Se deficiency and oxidative stress. Consequently, several GPx SNP have been shown to have significant association with both Se status biomarkers and health outcome⁽¹²⁶⁾. For example, the T allele for GPx1 SNP rs1050450 has been shown to have a significant impact on high-grade prostate cancer risk, over a range of plasma/serum Se concentrations^(127,128). Many SNP have been identified in human GPx isoforms: 46 in GPx1, 73 in GPx2, 120 in GPx3, 88 in GPx4 and 93 in GPx5⁽⁷⁸⁾. However, functional consequences have been demonstrated in *in vitro* and *in vivo* studies in only a small number of those SNP in genes encoding selenoproteins⁽¹²⁹⁾. GPx1 has four functional SNP, of which Pro¹⁹⁷Leu (rs1050450; worldwide MAF 22–35 %) has been studied most extensively in association with many diseases, including cancer^(78,116,130), diabetes^(131,132), kidney diseases and vascular diseases^(78,129). However, studies assessing the association between the GPx1 Pro¹⁹⁷Leu SNP genotypes and diabetes, stroke, brain tumours and prostate cancer are currently inconclusive.

Regarding functional consequences of SNP of the other GPx in relation to human diseases, there is at present very little conclusive data: GPx1 rs1800668 was studied in the context of cancer and was found to be associated with an increased risk of oesophageal cancer; three functional SNP of the GPx2 isoform, three of GPx3 and six of GPx3 coding regions have been scarcely studied in relation to disease⁽⁷⁸⁾.

Glutathione peroxidase polymorphisms and dietary factors

Evidently, the most studied nutrient in regard to GPx in general and GPx polymorphisms in particular is Se. Several SNP in selenoprotein-coding genes have been shown to be functionally significant and to affect the response of biomarkers of Se status to Se supplementation^(133–135). In particular, rs1050450 in GPx1, rs713041 in GPx4 and rs7579 in the selenoprotein-P gene are known to affect the expression of the respective selenoproteins. Of those, the GPx1 Pro¹⁹⁸Leu (rs1050450) SNP is the most studied. This polymorphism has been shown to affect GPx activity in some, although not all studies⁽¹⁰⁴⁾. Carriers of the variant allele have been shown to have significantly higher levels of lipid pre-oxidation components⁽¹³⁶⁾. This polymorphism has also been associated with several types of cancer, with conflicting results reported. A pilot study by Cardoso *et al.*⁽¹³⁷⁾ examined the effects of GPx1 Pro¹⁹⁸Leu in response to Se supplementation

via dietary Brazil nuts. *GPx1* Pro¹⁹⁸Leu genotypes differentially affected the Se status and GPx activity. Similarly, a later study by Donadio *et al.*⁽¹³⁸⁾ showed that Brazil nut supplementation significantly increased *GPx1* mRNA expression only in subjects with the CC genotype. Crosley *et al.*⁽¹³⁹⁾ have demonstrated elevated adhesion levels in human umbilical vein endothelial cells (HUVEC) and monocytes in individuals homozygous for the T-variant of functional *GPx4* (c718t) as compared with carriers of the C-variant. This effect was modified by Se and PUFA. Méplan *et al.*⁽¹⁴⁰⁾ showed that following clinical intervention with Se supplementation for 6 weeks in non-smokers, both lymphocyte GPx1 protein concentrations and plasma GPx3 activity increased significantly in homozygote CC individuals in the *GPx4* 718 T/C (rs713041) SNP but not in homozygote TT participants. After Se withdrawal, there was a significant fall in both lymphocyte GPx4 protein concentration and activity in the homozygote TT, but not in homozygote CC participants⁽¹⁴⁰⁾.

Several studies, although scarce, show suggestive interaction between *GPx1* polymorphisms and other dietary components: Hu & Diamond⁽¹³⁰⁾ have shown that the *GPx1* Pro¹⁹⁸Leu variant allele results in lesser response to the stimulation of GPx1 enzyme activity during Se supplementation compared with the common allele. Significant gene–diet interactions were found in the prospective Diet, Cancer and Health Study, where homozygotes for the variant allele had higher colorectal cancer risk with alcohol consumption and homozygotes for the common allele with higher dietary vitamin C intake had reduced risk of colorectal cancer⁽¹⁴¹⁾.

In summary, most of the published data regarding *GPx* polymorphisms and dietary components are related to Se, both in cancer and in viral infection. Although scarce data exist regarding other nutritional factors, it is quite clear from the publications so far that GPx are affected by dietary components, especially by Se, and that *GPx* polymorphisms can alter the need for dietary components and vice versa. This is particularly relevant to cancer and to viral infections.

Glutathione peroxidase 1 polymorphisms and viral infection

Se deficiency, which is a major regulator of selenoprotein expression, has been associated with the pathogenicity of several viruses. Moreover, several selenoprotein family members, including GPx, suggestively have an important role in different models of viral replication⁽⁹⁾. For instance, in Epstein–Barr virus infection, GPx activity reduction is associated with elevation in viral load⁽¹⁴²⁾. Supplementing herpes simplex virus-2 patients with selenium aspartate and multi-supplementation results in faster recovery, reduction in viral load and elevation in antiviral cytokines⁽¹⁴³⁾. The effect of GPx on inhibiting HIV activation is well documented. Correspondingly, Se can alter mutagenesis rates, both in viral genomes and in the DNA of mammalian cells exposed to carcinogens⁽⁹⁾. Similar to *CAT*, most published literature regarding *GPx1* polymorphisms and viral infection is regarding chronic hepatitis C. Sousa *et al.*⁽¹¹⁹⁾ found that homozygosity to the common *GPx1* Pro¹⁹⁸Leu (rs1050450) allele was significantly associated with severity of liver fibrosis and chronic

hepatitis C. Thus, they concluded that *GPx1* polymorphisms may be implicated in the severity of liver fibrosis and HCC caused by HCV⁽¹¹⁸⁾. Farawela *et al.*⁽⁷⁶⁾ found that HCV infection and *GPx1* gene polymorphisms had a synergetic effect on non-Hodgkin lymphoma risk (OR 15; 95 % CI 2.2, 69.6; *P*<0.0001) in Egyptians.

Conclusion and future directions

Antioxidant enzymes have common functional polymorphisms, with world population MAF ranging from 0.5 to 50 %. These polymorphisms result in altered enzymic function, requiring scientific and clinical attention to whether the intake of specific micronutrients, that serve as cofactors of antioxidant enzymes, should be adjusted to enable carriers of the polymorphisms to better cope with oxidative stress. One of the major hallmarks of viral infections is oxidative stress, which contributes significantly both to the host pathophysiology and to viral function and replication. In relevance both to cancer and to viral infections, including the COVID-19 pandemic, good nutritional status should be monitored and implemented to reduce disease risk and to better cope with health challenges. In fact, many studies have shown that viral infection simultaneously increases the demand for micronutrients and causes their loss, which leads to antioxidant deficiencies that should be monitored and addressed as an essential part of treatment of viral infections in the general population and with special attention in individuals carrying functional polymorphisms in relevant genes.

Intriguing studies show a significant world prevalence of functional polymorphisms in antioxidant enzymes, with initial studies demonstrating gene–nutrient interactions (between antioxidant enzymes and micronutrient cofactors); these findings warrant special attention in future scientific and clinical studies to interactions of genetic polymorphisms in antioxidant enzymes with nutritional factors. Thus, future clinical and scientific studies should give special attention to the incorporation of sub-populations with common functional polymorphisms of antioxidant enzymes, in order to understand and possibly implement personalised nutrition in the future. Indeed, further studies (especially randomised controlled trials) are needed to unravel the optimal requirements of dietary micronutrients during viral infections in sub-populations with common functional polymorphisms of antioxidant enzymes. Such trials, beyond assessing the therapeutic benefits to different sub-groups, are needed to assess the secondary effects and to analyse whether these effects vary for different viral infections. Furthermore, analysing the antioxidant enzymes' functional genetic polymorphisms in *in vitro* and *in vivo* models could serve as a tool for both elucidating the much needed mechanism related to genetic background–nutrient interactions and serve as an experimental model for the study of developing 'cell-based' anti-viral nutritional agents.

Acknowledgements

The present review received no specific grant from any funding agency, commercial or not-for-profit sectors.

There are no conflicts of interest.

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