Chapter 27
Polymorphisms in Selenoprotein Genes and Cancer

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Abstract Human selenoproteins comprise a diverse group of peptides whose role in cancer etiology might be presumed from what is currently known about their functions. For a subset of these, genetic data (1) demonstrating allelic loss during cancer development and/or (2) revealing an association between specific polymorphisms in selenoprotein genes and either cancer risk or survival have provided support for this association. Additional factors such as lifestyle, diet, gender, and interactions with polymorphisms in other genes may modify this level of risk. These data provide useful information that may eventually be used to identify individuals at increased risk of cancer and aid in the design and development of novel strategies to prevent and treat some of the more common cancer types.

27.1 Introduction

Interest in selenium as a means to reduce cancer risk has persisted for decades. Initial studies established that supplementation of the diets of animals with low, nontoxic doses of selenium could reduce tumor incidence, and these observations served as the foundation for hundreds of published papers showing that selenium was effective in most, if not all, organs tested in rodents. Focus on the anticancer benefits of selenium was further stimulated by a series of epidemiological studies showing an inverse association between dietary selenium intake and cancer risk. While the mechanism(s) underlying the likely benefits of dietary selenium intake have yet to be resolved, the identification of a class of proteins that include selenium in the form of the amino acid selenocysteine has led to speculation that one or more of these proteins are responsive to selenium availability and mediate selenium's

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Table 27.1 Cancer sites that have been linked to variants in selenoprotein genes

Gene	Linked cancer sites[a]
GPx-1	Bladder, breast, colon, head and neck, liver, lung, lymphomas, prostate
GPx-4	Breast (mortality), colorectal
SePP	Colorectal (advanced distal adenoma and cancer), prostate
Sep15	Breast, colorectal, head and neck, lung, prostate (mortality)
SepS	Colorectal, gastric

[a]See references in text

anticancer properties. Moreover, the antioxidant enzyme activity attributed to several of these selenoproteins offered a likely mechanistic appreciation as to how elevated levels of these proteins could be protective. Although proof of this speculation has yet to be realized, a role for a subset of selenoproteins in cancer etiology has been supported by human genetics.

The genomes of humans differ by approximately 0.1% or three million nucleotide positions. Many of these differences may not have functional consequences, while a subset can influence the activity and/or expression levels of the encoded gene products. This genetic diversity among members of our species has provided significant evidence that specific selenoproteins can affect both cancer risk and clinical outcome. In general, this has occurred in one of two ways. In the first, the ability to detect heterozygosity at selected genetic loci has facilitated the analysis of the loss of one of two gene copies during tumor development. Loss of heterozygosity (LOH) is typically indicative of the increased risk of cancer associated with the reduced dosage of a beneficial gene, or alternatively, the unmasking of a recessive mutation that promotes clonal cellular expansion. The second means by which human genetics supports a role for a gene in cancer etiology is by the identification of germline polymorphisms whose presence can be linked to a greater risk of developing or dying from cancer. In this chapter, the genetic evidence implicating several selenoproteins in cancer etiology is presented (see Table 27.1 for a summary), as is a comprehensive model for the interaction among several selenoprotein genes and additional modifying factors.

27.2 GPx1

GPx1 was the first selenoprotein characterized in detail and is an antioxidant enzyme located both in the mitochondria and the cytoplasm. This selenoprotein catalyzes the detoxification of reactive oxygen species (ROS) using glutathione as a source of reducing equivalents. GPx1 levels are responsive to selenium availability and it has long been considered a potential mediator of some of the consequences of selenium deficiency and perhaps also the benefits of its supplementation. In 1994, Moscow et al. reported the existence of two variants in the coding region of the human GPx1 gene: a codon 198 polymorphism resulting in either a leucine or proline at that

position and a variable number of nucleotide triplet repeats resulting in either 5, 6 or 7 alanines in the amino terminus of the GPx1 protein [1]. Differences in the *GPx1* allele frequency were observed between DNA obtained from lung tumors as compared to DNA obtained from individuals without evidence of cancer with significantly fewer *GPx1* heterozygotes noted in tumors from lung cancer patients [1]. Similar results were obtained many years later by establishing that LOH at the *GPx1* locus occurred frequently in the DNA obtained from two other tumor types, breast cancer [2] and cancers of the head and neck [3]. These results could be explained by either the loss of one *GPx1* allele during malignant progression (as would occur if, for example, GPx1 had tumor suppressor activity) or if certain genotypes predisposed an individual to cancer development. Evidence in support of the former possibility comes from studies indicating that there was a loss of one of two *GPx-1* alleles in colon tumor DNA [4] and cancers of the head and neck [3] as compared to noncancerous tissues obtained from the same individuals.

While LOH may be indicative of the loss of a genetically linked gene with beneficial properties and not GPx1, epidemiological and functional data support a role for GPx1 genetic variants in cancer risk and outcome. Some studies have indicated that the number of alanine repeats is associated with increased cancer risk, but there does not appear to be a consistent pattern for a particular number of repeats [5–7]. In contrast, there is significant literature indicating that the identity of the amino acid encoded by codon 198 contributes to cancer risk with the majority of these studies identifying the *leu*-encoding allele as the one associated with increased risk (recently reviewed in [8, 9]). The types of malignancies whose risk increases with the presence of the *GPx1 leu* allele include cancers of the lung, breast, bladder, liver, and lymphomas, and these associations have been found in populations from Finland, USA, Korea, Denmark, Japan, the United Kingdom and France [10–18]. Of note were the results of a recent meta-analysis indicating an association between the *leu* allele and breast cancer risk, but only among African American women [19]. In contrast, three studies investigating the association between *GPx1* alleles and cancer risk reported an increased risk of cancers of the lung and prostate among carriers of the *pro* allele [11, 20, 21]. These apparently conflicting results, as well as those showing that *GPx1* genotype has no effect on cancer risk [22–29], may be explained by other variables, some of which are discussed below.

27.2.1 Interaction Between GPx1 Genotype and Selenium Status

The functionality of the leu/pro variant in GPx1 has been investigated using both cells in culture and in humans. Taking advantage of the observation that human MCF-7 breast carcinoma cells produce negligible quantities of GPx1, derivative cell lines were generated that exclusively produce the *leu* or *pro GPx1* allele and it was shown that there was a differential response to the amount of the selenium available in the culture media with cells expressing the *leu* allele requiring more selenium to achieve the same level of GPx1 activity as compared to those expressing the *pro*

allele [2]. These results were expanded to show that the difference in response to selenium availability occurred only when the *leu* polymorphism was associated with 5 alanine repeats, indicating an interaction between the amino terminus and carboxy terminus of the protein [30]. Less clear is whether the GPx1 genotype affects the corresponding enzyme activity *in vivo*. Several studies have reported lower GPx activity associated with the *leu* allele [13, 31–33]; there was one report of this relationship existing only among women [34] and two studies failed to find any genotype–phenotype association at all [21, 35]. Jablonski et al. were only able to detect an association between plasma selenium levels and GPx activity among individuals who were *leu* homozygotes [36]. While most of these studies reported a reduced GPx1 enzyme activity associated with the same *leu* allele most frequently linked to increased cancer risk, all GPx1 assays reported in these manuscripts examined activity in erythrocytes, which may not reflect the consequences of genotype in the particular organs where the cancers investigated arise. It is of interest to note that the urine of individuals that were either heterozygous or homozygous for the *leu* allele contained higher levels of the DNA oxidation product 8-OHdG than those who were homozygous for the *GPx1 pro* allele [12].

In addition to selenium status, there may be other effect modifiers of associations between *GPx1* genotype and cancer risk. For example, it has been shown that the nature of this relationship depends on smoking habits, alcohol intake, age, gender, and vitamin use, although the emerging patterns can be complicated to discern [20, 24, 33]. One example of this comes from a study of 237 lung cancer patients and 234 community-based controls enrolled at the Mayo Clinic. An interaction was observed between the *GPx1* Pro198Leu polymorphism and smoking status among older individuals (>80 years): among smokers, the homozygous *pro*/*pro* genotype was associated with a threefold increased risk of lung cancer (relative risk (RR) = 3.3, 95% confidence interval (CI): 1.3–8.4), whereas among never smokers, this genotype was linked with more than an eightfold lower risk of disease (RR = 0.12, 95% CI: 0.02–0.7) [11].

27.3 GPx4

Another member of the GPx family of antioxidant selenoproteins is GPx4 – the only member that is associated with membranes where it functions in the detoxification of lipid hydroperoxides [37, 38]. There is an abundance of evidence indicating that enhanced expression of GPx4 can protect against oxidative stresses and also against carcinogenesis (reviewed in [8]). A single nucleotide polymorphism (SNP) in the 3′-untranslated region of the *GPx4* gene at position 718, which results in either a C or T, has been identified and implicated in the regulation of lipoxygenase metabolism [39]. The functionality of this SNP was substantiated by both *in vivo* and *in vitro* studies, which indicated that the SNP influenced the ability of the 3′-UTR to function as a SECIS element required for the proper insertion of selenocysteine into

the growing peptide in response to the in-frame UGA codon present in the *GPx4* coding sequence [40]. The identity of the position 718 SNP also influenced the amount of GPx4 present in individuals following selenium withdrawal and this effect was modified by gender [40, 41]. This same polymorphism has been shown to be associated with the risk of colorectal cancer in two separate populations, one Czech and one English, although the results of these studies were inconsistent as to which allele was associated with increased cancer risk. [41, 42]. While these studies showed an association between the *GPx4* SNP and risk of colon cancer, others have examined this variant in relation to clinical outcome. For example, data obtained from the Studies of Epidemiology and Risk Factors in Cancer Heredity (SEARCH) breast cancer study demonstrated that the *GPx4* 3-UTR 718C polymorphism was associated with increased risk of death from breast cancer among women previously diagnosed with this disease [29].

27.4 SePP

If the levels of GPx's impact cancer risk and progression and the levels of these proteins are affected by selenium availability, then it follows that factors that influence the levels of selenium in organs would also have an effect on cancer risk. Selenium levels in the body are regulated in the liver where selenium is designated either for excretion or for further processing for use in selenoproteins, which includes the major transport selenium-containing protein, SePP [43]. SePP is an extracellular protein containing ten selenocysteines in humans comprising the major form of selenium in plasma. SePP accounts for approximately 44% of the selenium in plasma [44]. SePP enters the tissue where the protein is catabolized by Sec-β-lyase and the products are funneled into selenium metabolism [45].

Several polymorphisms in the *SePP* gene have been identified two of which are common in multiple ethnicities and have been shown to influence SePP levels in the blood and/or SePP levels in response to selenium supplementation [46–48]. A SNP that causes an amino acid change at codon 234 was recently found to increase the risk of sporadic colorectal cancer by 39% in females, although this association was only of borderline significance [42]. The other SNP is located in the 3′ UTR of the mRNA, yielding a G-to-A base change. Individuals with the variant *AA* genotype have been shown to have increased risks of prostate [48] and colorectal [42] cancers, with the latter association limited to females. Other, less commonly studied polymorphisms and haplotypes have also been characterized and linked with advanced distal colorectal adenoma [28] and overt colorectal cancer [42]. Of note is the finding by Méplan et al. that carriage of at least one variant *T* allele of rs2972994 (a polymorphism located in the promoter region) conferred an increased risk of colorectal cancer in males but a significantly decreased risk of this disease in females [42]. Furthermore, results from this study indicated that several SNPs in *SePP* interact with polymorphisms in either *Sep15* or *GPx4* to affect disease.

27.5 Sep15

A 15-kDa selenoprotein was identified in human T cells by virtue of its ability to be labeled with ^{75}Se and was shown to be encoded by a gene on chromosome 1; the highest levels of this gene's product are found in the thyroid, parathyroid, and prostate [49]. This selenoprotein was subsequently shown to reside in the lumen of the endoplasmic reticulum (ER) where it associated with UDP-glucose:glycoprotein glucosyltransferase [50] – a protein with an established role in maintaining the quality of folded proteins – and likely functions in the response to unfolded proteins and ER stresses [51]. The *Sep15* gene includes two polymorphisms in the 3′-UTR at positions 811 (C/T) and 1125 (G/A) that result in only two observed haplotypes: either a 811C/1125G or 811T/1125A with the haplotype shown to be functional in determining the amount of the Sep15 protein produced for a given level of available selenium [52, 53]. In addition, the 811T/1125A is relatively uncommon in Caucasians where only 7% are homozygous, as compared to African Americans where 31% are homozygous [53].

A role for Sep15 in cancer etiology is supported by recent data indicating that reducing its levels in colon cancer cells could attenuate the tumorigenic and metastatic potential of CT26 colon cancer cells in BALB/c mice [54]. In humans, the *Sep15* allele frequency was shown to be different in breast cancer cases and cancer-free individuals, and LOH was demonstrated in both breast cancers and cancers of the head and neck [53, 55]. Evidence that *Sep15* genotype can specifically influence cancer risk in humans was provided by a Polish study designed to investigate the relationship between the *Sep15* allelic identity, selenium status, and risk of lung cancer [56]. In this study, there was a reduced risk of lung cancer among individuals with higher plasma selenium levels; however, there was an increased risk of lung cancer for those who carried at least one copy of the Sep15 variant G allele at position 1125 [56]. A more recent study in a Korean population demonstrated an increased risk of colorectal cancer among male (but not female) carriers of the *Sep15* 811T/1125A haplotype [57]. In contrast, a search for an association among SNPs in a region of DNA including 5 kb upstream and downstream of *Sep15* failed to identify any association of these SNPs with the risk of prostate cancer [58]. In the same study, however, a haplotype consisting of five SNPs (including the 1125 variant) was significantly associated with higher prostate cancer mortality and the presence of one of these SNPs abrogated the observed protection against prostate cancer mortality seen with high levels of plasma selenium [58].

27.6 SEPS

Selenoprotein S (SEPS), also referred to as SELS or VIMP, is an ER-associated protein that functions in the removal of misfolded proteins from the ER to the cytoplasm [59]. It is also involved in the regulation of the inflammatory response and

stimulating the production of proinflammatory cytokines [60]. Allelic variation at *SEPS* has been investigated with regard to a variety of conditions, including cardiovascular disease and preeclampsia, the latter of which is a condition in which there is pregnancy-associated excessive inflammation (reviewed in [9]). One particular polymorphism located in the promoter region at position −105 (yielding either a G or A) has received considerable attention. The A-containing allele is associated with reduced levels of mRNA [60, 61]. Promoter polymorphisms in SEPS have been associated with risk of gastric cancer in a Japanese population [62] and increased colorectal cancer [42], although one recent study revealed the latter relationship only among women [57].

27.7 The Interaction Among Selenium and the Genotypes of Selenoproteins and MnSOD

MnSOD is a major protective mitochondrial enzyme that detoxifies superoxide radicals produced during electron transport to the less toxic hydrogen peroxide. A variant *MnSOD* allele containing an alanine (A) rather than a valine (V) at codon 16 has been described, and in several reports, has been associated with an elevated risk of several cancer types, including prostate cancer, in human epidemiological studies [17, 63–65]. As a consequence of alanine being at this position in the mitochondrial import signal peptide, there is increased transport of MnSOD into the mitochondria [66]. While it might be counterintuitive that elevated levels of an antioxidant enzyme would increase risk, several studies have shed light on the likely explanation. Li et al. reported an impressive tenfold swing in the risk of prostate cancer among men who expressed the *AA* genotype (those being homozygous for the allele encoding alanine at codon 16) between the lowest quartile of total antioxidant consumption and the highest with those consuming the lowest levels of dietary antioxidants being at greatest risk [64]. A separate analysis also showed that there was a threefold increase risk of prostate cancer for *AA* men with low carotenoid status [$P = 0.02$, confidence interval 1.37–7.02] [65]. As originally proposed by Li, it is therefore likely that increased mitochondrial transport of MnSOD as a consequence of a codon 16 alanine is beneficial when antioxidant activity is high and the MnSOD dismutation product, H_2O_2, can be reduced to water [64]. A low antioxidant status, defined either by individual genetics and/or dietary intake, would facilitate the cycling of H_2O_2 to more ROS that are potentially mutagenic and therefore carcinogenic.

As described above, the at-risk *GPx1 leu* allele encodes a protein that is less responsive to selenium as compared to the protein with a proline at the same position [2, 30]. Cox et al. initially reported that there was no association between the at-risk *leu* allele of *GPx1* and breast cancer risk among participants in the Nurse's Health Study [22]. However, a follow-up study from the same authors indicated that there was indeed a significant risk for breast cancer among participants of the same cohort when the *MnSOD* genotypes were also considered; carriers of both the *AA* and

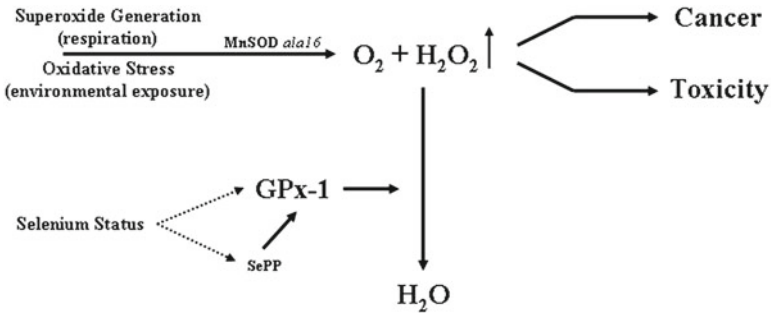

Fig. 27.1 Model for the interaction among endogenous and environmental sources of oxidative stress, individual genotype and risk of cancer and other degenerative disease. Elevated expression and/or activity of MnSOD will generate an additional load of H_2O_2, which if detoxified, will be beneficial. In contrast, reduced levels of GPx-1, as a result of result of polymorphisms in GPx1 or SePP1, or reduced selenium/antioxidant levels, will increase the levels of H_2O_2 and contribute to cancer and degenerative disease risk

leu/leu genotype were at increased risk of breast cancer with an odds ratio of 1.87 [95% CI, 1.09–3.19] [14]. These human data indicate a direct interaction between MnSOD and GPx1 in influencing cancer risk. GPx1 may be a particularly important H_2O_2-detoxifying enzyme because of its cellular location in the mitochondria as well as in the cytoplasm. Further support for this concept comes from human data indicating that polymorphisms in the gene for the selenium transport protein SePP that result in less SePP in the plasma and reduced levels of GPx1 are associated with a significant risk of prostate cancer only in men also expressing the *ala16 MnSOD* allele [67]. Furthermore, the observed gene–gene interaction was strongest in current and former smokers, a group with higher levels of oxidative stress due to exposure to free radicals in tobacco smoke and poor antioxidant nutrient intake. A diagrammatic representation of the dietary and genetic factors that interactively influence the risk of cancer and perhaps other degenerative diseases due to the expression of the *ala16 MnSOD* allele is presented in Fig. 27.1.

27.8 Concluding Remarks

Animal studies, in vitro data and human epidemiology have supported a role for selenium in cancer risk and survivability, and selenoproteins such as those described in this chapter are likely to be important mediators of at least some of these effects. While this seems likely given the functions of selenoproteins in processes such as selenium delivery to tissues, antioxidant defenses, and the maintenance of correct protein folding, this concept is directly supported by human genetic data indicating allelic loss of selenoprotein genes during cancer development or the presence of polymorphisms that predispose to cancer or predict clinical outcome. The impact of allelic variants in selenoprotein genes and/or the loss of one of two gene copies

during carcinogenesis may be influenced by a number of factors, such as genetics, gender, and a host of modifiable behaviors. Future studies that clarify these relations and establish the mechanisms by which they occur offer the potential to develop new strategies to predict, diagnose, prevent, and treat a wide variety of cancer types.

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