Nutrigenomics and Selenium: Gene Expression Patterns, Physiological Targets, and Genetics

John Hesketh

Institute for Cell and Molecular Biosciences, The Medical School, Newcastle University, Newcastle-upon-Tyne, United Kingdom, NE1 4HH; email: J.E.Hesketh@newcastle.ac.uk

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Abstract

Dietary selenium intake is regarded as an important factor in determining optimal health and susceptibility to disease. Therefore, it is critical to understand the interaction between selenium intake and molecular events at the genetic and cellular level. This article addresses two facets of this interaction. The first facet is how genomics is contributing to understanding the molecular mechanisms by which selenium affects cell function through selenoproteins and downstream targets of Se supply in other metabolic pathways. The contribution of transgenic animals in this field is emphasized, and the more recent studies using transcriptomics are discussed. The second facet is the extent to which single nucleotide polymorphisms (SNPs) in genes encoding selenoproteins and components of the selenoprotein synthetic machinery affect individual dietary requirements for optimal health. The state of knowledge of known functional SNPs in selenoprotein genes is presented, and a strategy for future studies is discussed.

Contents

INTRODUCTION

Nutrigenomics is the study of nutrient-gene interactions and as such impinges on nutrition in two major ways. First, it allows the investigation of how genetic factors influence nutritional requirements. Traditionally, nutrition has dealt with requirements for populations, but the potential availability of genetic information from the Human Genome Project and subsequent single-nucleotide polymorphism (SNP) consortia projects is providing a basis for dissecting the extent to which genetic factors influence inter-individual variability in nutritional requirements. Nutrigenomics is bringing in a new era of research in which inter-individual variation is used to investigate nutritional mechanisms. Nutrigenomics also has implications for the delivery of nutritional advice and has led to much enthusiasm for so-called personalized nutrition: the tailoring of nutrition requirements to individuals or population subgroups based on genetic variations, gender, and life stage (62, 76). Second, nutrigenomics provides the tools (transcriptomics, proteomics, and metabolomics) to examine how alterations in nutritional status affect not simply one or two parameters but rather a whole range of biochemical pathways (19, 41, 104). Such approaches, in conjunction with gene knock-down and knock-out technologies, allow nutritionists to explore at the functional, mechanistic level how nutrients affect gene expression and cell function. Such knowledge is essential to complement data from intervention trials and epidemiology to develop better nutritional advice.

The aim of this article is to review the present state of knowledge about how intake of the micronutrient selenium (Se) affects gene expression and how genetic factors influence Se metabolism and thus potentially nutritional requirements for Se and optimal health (**Figure 1**). Low Se intake has been linked with a number of diseases, including colon and prostate cancer (86, 99), and thus the effects of Se at the molecular level and interaction of suboptimal Se intake with genetic factors are potentially important in increasing our understanding of the links between Se intake and susceptibility to disease. Se is incorporated into ~25 selenoproteins in humans (52, 63), and these proteins and their genes, as well as the factors involved in their synthesis, provide a focus for both mechanistic and genetic studies. This article addresses how genomics is contributing to studies of this biochemical unit that determines much of the functional activity of Se (herewith called the selenome) and then discusses how it is being used to identify downstream targets of Se supply in other metabolic pathways.

Selenium (Se) was first shown to be essential for human health in the 1970s when Keshan disease, an endemic cardiomyopathy in parts of China, was shown to be caused by a combination of severe Se deficiency and viral infection (see 9, 10). Since then, it has been suggested that Se plays a role in a number of physiological and pathological processes: in immune function, viral suppression (10, 20, 93), male fertility, thyroid function, and as an anticancer agent (86, 99). Human dietary Se intake varies throughout the world, and the very low intakes (<10 μg/day) that result in severe symptoms such as Keshan disease are rare. However,

SNP: single-nucleotide polymorphism

Selenome: the biochemical unit that determines much of the functional activity of Se; this includes proteins involved in synthesis of selenocysteine tRNA, in incorporation of selenocysteine during translation, and in transport of Se in the blood

suboptimal Se intake is more common. For example, in the United Kingdom and other parts of Europe, Se intake is estimated at about 30 μg/day, well below the current reference nutrient intake of 75 and 60 μg/day for men and women, respectively. Low Se intake has been linked to cancer susceptibility, and Se supplementation to above 200 μg/day has been reported to reduce cancer mortality (28). Thus, although Se intakes in many parts of the world are not low enough to cause overt deficiency, they may not be sufficient for optimal health. For example, a human supplementation trial has shown that an additional daily intake of 100 μg Se as sodium selenite above U.K. levels leads to changes in viral handling (20), which suggests that Se intake is suboptimal for response to viral infection. Recently, two prospective studies of aging populations have demonstrated an association between Se status, as assessed by plasma Se, and subsequent cancer mortality (2, 85). Two large Se supplementation trials (the Selenium and Vitamin E Cancer Prevention Trial and the Phase III Randomized Evaluation of Convection Enhanced Delivery of IL13-PE38QQR with Survival Endpoint trial) are now in progress to assess the extent to which Se supplementation has health benefits in cancer prevention. In addition, suboptimal Se intake may affect susceptibility or outcome of other clinical conditions, such as thyroid diseases and AIDS (10, 11, 86, 99).

SELENOPROTEINS

The physiological functions of Se are thought to result from its existence in a number of selenoproteins in which Se is present as the amino-acid selenocysteine (Sec). Se was first shown to be an essential component of glutathione peroxidase and subsequently has been found (or predicted to be found) in 25 mammalian selenoproteins (52, 63, 94). Sec is incorporated into the amino acid sequence of selenoproteins during translation, being coded for by a UGA codon in the coding region of the messenger ribonucleic acid (mRNA) (52). In most mRNAs, UGA codes for the stopping of translation, and this recoding of the UGA codon to incorporate Sec requires a specific stem-loop structure (Sec-insertion sequence, SECIS) within the mRNA; in bacteria, this occurs close to the UGA codon, but in eukaryotic mRNAs it is found at some distance from the UGA within the 3′untranslated region (3′UTR), as illustrated in **Figure 2**. The presence of one or more UGA-encoded Sec combined with a predicted SECIS structure is common to all selenoprotein mRNAs.

Sec: selenocysteine

SECIS: selenocysteine insertion sequence

3′UTR: 3′untranslated region

GPx: glutathione peroxidase

The absolute requirement for both a UGA codon and the SECIS for selenoprotein synthesis has provided the basis for bioinformatic searches of genome data in order to predict novel selenoproteins (52). Recently, such approaches have made a major contribution to our knowledge of selenoproteins; based on these predictions, a number of novel mammalian selenoproteins have been identified, and in some cases purified and assigned functional characteristics (35, 45, 52). In the majority of cases so far studied, the Sec is present at the active site of an enzyme with oxido-reductase activity.

The best characterized selenoproteins are the glutathione peroxidases (GPxs), the thioredoxin reductases (TRs) and deiodinases (IDIs), and selenoprotein P (SEPP). For example, five glutathione peroxidases are selenoproteins (18, 52): cytosolic glutathione peroxidase GPx1, gastrointestinal glutathione peroxidase GPx2, plasma glutathione peroxidase GPx3, phospholipid hydroperoxide glutathione peroxidase GPx4 and GPx6 (identified in silico). GPx1 and GPx2 have antioxidant functions, protecting cells from oxidative stress; knock-out mice lacking both GPx1 and 2 are more susceptible to an oxidative challenge (27). Responses of transgenic mice lacking or overexpressing GPx1 have suggested novel roles for GPx1 in relation to both reactive oxygen species and reactive nitrogen species as well as a link to insulin-mediated effects (64). GPx4 appears to have a complex range of functions in protection from oxidative stress, lipoxygenase metabolism, and sperm function (17, 82). TR1, 2, and 3 represent a second family of selenoproteins with redox functions: reduction of ribonucleotides

SEPP: selenoprotein P

to deoxyribonucleotides, maintenance of redox state, and regulation of transcription factor activity (8). The distinct cellular defense roles of GPx1, 2, and 4 reflect distinct regulatory effects on redox sensing and redox regulation of transcription factors (18). The iodothyronine deiodinases (IDII, IDIII, and IDIIII) are a family of selenoproteins involved in thyroid hormone metabolism (11).

SEPP is an extracellular protein that is unique in containing up to 10 Secys residues, 9 of which reside in a Sec-rich C-terminal domain. SEPP accounts for more than 50% of the total plasma Se content, and the generation of transgenic mice lacking SEPP has shown that the protein has a key function in delivery of Se to extrahepatic tissues. It has also been suggested to have a second function in antioxidant defense (21, 22, 87–89). This transport function appears to be due to both liver-derived SEPP and locally synthesized protein (87). Transgenic mice with the Sec-rich region after the serine at codon 239 of SEPP deleted have a similar, but less severe, phenotype to that of the full-SEPP knock-out mice with low brain and testis Se content (53), indicating the importance of the Sec-rich region in transport of Se to the brain and testis.

Less-comprehensively studied and more-novel selenoproteins include selenoproteins H, L, N, S, and W (SelH, Sel L, SelN, SelS, and SelW) and the 15 kDa selenoprotein. Several of these proteins appear to be members of a novel redox protein family. SelW was suggested to have an antioxidant function because overexpression in CHO and H1299 cells resulted in lower sensitivity to an oxidative challenge from hydrogen peroxide (60), and structural studies have recently revealed a thioredoxin-like fold with a CxxSec redox fold (1). SelH is a redox-sensing DNA-binding protein (79), and together with SelW, SelL, SelM, SelT, and the 15 kDa selenoprotein, it seems to be a member of a family of selenoproteins that contain such a thioredoxin-like redox fold (35, 45, 92). SelS has recently been found to be a membrane protein of the endoplasmic reticulum that is possibly involved in redox balance and protein folding (49). SelN and SelM are also present in the endoplasmic reticulum where SelM appears to have a redox function (45).

As illustrated schematically in **Figure 2**, Se incorporation requires not only an in-frame UGA codon and a SECIS structure but also a specific selenocysteyl-tRNA (tRNA-Sec). The tRNA-Sec contains both a highly modified adenosine (N6-isopentyladenosine) at position 37 within the anticodon loop and a methylated ribose grouping on the uridine at position 34 (Um34). Sec is synthesized directly on the tRNA from selenide, ATP, and seryl-tRNA. Synthesis of this tRNA-Sec requires both a selenophosphate synthetase to synthesize selenophosphate from selenide and a selenocysteine synthetase to convert selenophosphate to the tRNA-Sec (102). Two selenophosphate synthetases have been identified by homology to the bacterial enzyme, one of which is a selenoprotein itself (SPS2) and one that is not a selenoprotein (SPS1). RNA interference and in vitro studies indicate SPS2, but not SPS1, is essential for selenoprotein synthesis (101, 102). In addition, a number of specific RNA-binding proteins are required as part of the machinery necessary for UGA recoding and Sec incorporation. The SECIS-binding protein 2 (SBP2) is essential for selenoprotein synthesis: It binds to the SECIS structure within the 3′UTR and is a limiting factor in selenoprotein synthesis (29). SBP2 itself binds to a specific elongation factor, EF-Sec, that is also essential for Sec incorporation (43) and competes for SECIS binding with ribosomal protein L30 (26).

It is now clear that the overall pathway from dietary Se to a functional selenoprotein thus consists of several key interrelated steps, illustrated schematically in **Figure 3**: (*a*) synthesis of tRNA-Sec from selenide; (*b*) transport of Se from liver to the target tissues; and (*c*) SECIS-dependent incorporation of Sec into active selenoproteins. The enzyme SPS2, the selenoprotein SEPP, 3′UTR sequences and proteins of the Sec incorporation machinery all form a "unit" that coordinates selenoprotein synthesis. The pattern of selenoproteins and their downstream targets are the functional outcome of

dietary Se intake. Potentially both nutrition (Se intake) and genetic factors (SNPs in the selenome) can influence this pattern, as illustrated schematically in **Figure 4**.

REGULATION OF THE PATTERN OF SELENOPROTEIN EXPRESSION

A large body of evidence shows that low Se intake in animals or modulation of cell culture Se content influence both the level of activity of several selenoproteins and in some cases also cause changes in mRNA levels for selenoprotein genes. Thus, for example, in Se-deficient rats there is a dramatic fall in GPx1 activity and mRNA levels in liver and other tissues (12, 13, 42, 65). Effects on other selenoproteins are also observed in the liver, and there are falls in activity of both GPx4 and IDI (13), but to a lesser extent than was observed for GPx1. Similarly, although falls in both thioredoxin reductase isoenzymes were observed in the liver, TR1 was more sensitive to Se depletion than was TR2 (33). In colonic cell lines, Se depletion leads to dramatic falls in GPx1 expression, but not GPx2 expression (75, 100). Thus, selenoprotein synthesis is sensitive to the availability of Se, but not all selenoproteins are affected to the same extent. Therefore, a hierarchy of effects exists such that synthesis of some proteins is maintained more than that of others (12, 13, 67, 75, 100).

The 3′UTRs of the different selenoprotein mRNAs, central to Secys incorporation in eukaryotes (52), appear to play a role in determining the hierarchy. Selenoprotein mRNAs show considerable variation in 3′UTR length and in the position of the Sec-encoding UGA within the coding region and, as a result, in the number of nucleotides between UGA and SECIS (66, 71). Thus, SECIS-based Secys incorporation functions over a range of UGA-SECIS distances (200–1700 nt with a minimum distance of 50–111 nt) and it has proved possible to produce chimeric gene constructs with various coding region–UTR combinations that are active in driving UGA read-through or synthesis of an active selenoprotein reporter. Such gene constructs express transcripts in which the 3′UTR from a selenoprotein is linked either to a UGA-containing coding region such as the selenoprotein deiodinase (15), to two reporters separated by an in-frame UGA (57, 100), or to part of a glutathione peroxidas coding region (up to and including the UGA) joined to luciferase (33). Data from such studies indicate that the 3′UTR can be influential in determining the response to Se. Investigators using the deiodinase reporter found that synthesis of active enzyme by transfected hepatoma cells was affected less by Se depletion when the reporter was linked to the GPx4 3′UTR than when linked to the GPx1 3′UTR (15). In addition, read-through at a UGA between B-galactosidase and luciferase reporters linked to GPx2 3′UTR was less sensitive to Se depletion than when the reporters were linked to the GPx1 3′UTR (75, 100).

The precise mechanism behind such effects is not known, but it is likely to be related to the ability of the different transcripts to bind the proteins necessary to form the Sec incorporation complex. Indeed, fibroblasts derived from individuals who carry a mutation in SBP2 show differential down-regulation of selenoprotein expression, with a greater effect on iodothyronine deiodinase than GPx1 (39). However, factors other than the 3′UTR seem to be involved because in the case of TR1 and TR2, reporter transcripts with the two 3′UTRs failed to demonstrate any differences in read-through, although there were differences in response to Se deficiency in vivo (33). One possible additional factor is methylation of Um34, a step in maturation of the tRNA-Sec (25). Mutation of tRNA-Sec at codon 37 inhibits modification of Um34, and transgenic mice carrying this mutation show a protein- and tissue-specific lowering of selenoprotein synthesis (25, 74), which suggests that the extent of Um34 modification influences Sec incorporation into some selenoproteins more than into others: GPx1, GPx3, and SelT are more sensitive to the mutation than are TR1 and GPx4 (25).

As illustrated in **Figure 5** an important feature of the hierarchy in selenoprotein synthesis is the tissue specificity. For example, in the Se-deficient rat, IDI activity falls by >90% in the liver but increases in the thyroid, expression of the TR1 is affected more in the liver than kidney, and GPx4 activity falls in the heart and liver but not in the thyroid (15, 33). Thus, determination of the selenoprotein hierarchy is complex, involving differences in both 3′UTR sequences, the RNA-binding protein SBP2, and potential other factors such as modification of Um34, some of which must be tissue specific. Notably, the effects of tRNA-Sec modification on selenoprotein synthesis appear to be tissue specific (25, 59). Although it is now well substantiated that a tissue-specific hierarchy exists in selenoprotein synthesis, our knowledge is limited to only a few selenoproteins, and much less—or in some cases, nothing—is known about the responses of the other selenoproteins, such as SelS, X, H, W, relative to effects on the GPx, TR, and IDI families. Because the overall physiological and functional effects of changes in Se intake effects will be determined by the modification of the pattern of selenoprotein expression, it is important to obtain a clear picture of how a much wider range, or preferably all, of the selenoproteins respond to altered Se intake.

In theory, genomic techniques such as transcriptomics and proteomics offer the potential to assess how the overall pattern of selenoprotein expression changes in response to selenium supply. Since Se is incorporated into the selenoproteins during translation, it is arguable to how great an extent transcriptomics, which measure mRNA levels, can be used to assess expression patterns of the selenoproteins. Such techniques will not pick up differences in protein expression regulated by mRNA translation, but they will be able to show changes in expression that reflect altered mRNA stability or promoter activity. However, the use of focused gene arrays covering all the selenoprotein genes to investigate the effects of Se depletion on the intestinal epithelial cell line Caco-2 has proved useful in showing that SelW mRNA levels were particularly sensitive to lower Se supply (77) and in confirming that GPx2 expression in these cells was unchanged by Se depletion, whereas GPx1 expression was highly sensitive; this effect on SelW was confirmed in the rat colon. In this case, the gene array approach was able to identify SelW expression as being potentially highly sensitive to nutritional modulation by Se, at least in the colonic epithelium. This may be due to the instability of SelW mRNA when Se supply is low (50), as found also for GPx1 mRNA (14, 64).

Transgenic mouse models are proving useful in investigating the selenoprotein hierarchy. As mentioned above, generation of mice lacking modification of tRNA-Sec has clearly demonstrated a protein- and tissue-specific hierarchy in selenoprotein synthesis (25, 59, 74). Investigators using reverse transcription and polymerization chain reaction to measure transcript levels for 26 selenoprotein or Se-associated genes in a range of mouse tissues have shown differential effects of SEPP gene knock-out between different selenoproteins and different tissues (54). The use of proteomics to examine the pattern of selenoproteins rather than their transcript levels could provide more information about the response of the selenoproteome to nutritional modulation. The potential of such an approach is illustrated by the recent observations, using proteomics, that GPx1 and TR1 levels are regulated by dietary fatty acid intake (6).

DOWNSTREAM TARGETS OF Se

In order to fully understand the physiological effects of altered Se intake, it is important to assess not only the effects of Se nutrition on selenoproteins but also the effects on changes secondary to altered selenoprotein function (downstream targets) that contribute the full physiological consequences of marginally low Se intake or Se supplementation. DNA microarrays that allow assessment of either the genome-wide or the pathway-specific pattern of gene expression provide tools to identify such targets.

To date, gene-array studies of Se in a nutritional context have been limited in number. However, several studies have been carried out in transformed cell lines, for example, prostate cell lines treated with either methylseleninic acid (37, 38, 105) or Se-methionine (105). After treatment with methylseleninic acid, 951 genes were reported to change in expression level. Particularly significant changes were seen in clusters of cell cycle regulated genes as well as in genes that exhibit altered expression associated with changes in cell proliferation, androgen-regulated genes including the androgen receptor, and genes encoding phase 2 detoxification enzymes. Following supplementation of cell culture medium of these prostate cancer cells with selenomethionine, a larger number of genes showed evidence of altered expression, but again there were significant changes in clusters of genes associated with cell cycle regulation and induced cell cycle arrest, and androgen signaling. Thus, there was similarity in the pathways affected by administration of either selenomethionine or methylseleninic acid. In another study, expression of 154 genes was found to change in both rat and human prostate cancer cell lines (90), and data mining identified genes encoding IGF binding protein 3 and retinoid receptor alpha as showing the largest changes.

In a study of methylseleninic acid treatment of breast cancer cell lines using cell cycle and apoptosis targeted arrays, major changes in expression of 30 genes were seen in cell cycle checkpoint controllers, regulators of apoptosis, and signaling pathways (37). Array analysis of the HTC116 colonic cell line after supplementation of the culture medium with selenomethionine led to changes in expression of 50 cell cycle and apoptosis genes; similarly, treatment of acute promyelocytic leukemia-derived NB4 cells with 10 μM sodium selenite led to changes in the expression profile of apoptosis and cell cycle–related genes (24). Thus, consistent data are emerging from gene array studies of a variety of transformed cell lines following treatment with high concentrations (10–30 μM) of methylseleninic acid, selenomethionine, or selenite; in all cases, there is evidence for changes in genes involved in cell cycle regulation. This is consistent with known cell growth inhibition that results from treatment of cells with methylseleninic acid and selenomethionine at micromolar concentrations (collated in 40). It is not clear either to what extent these effects are the result of pharmacological effects on tumor cells or whether the effects are secondary to changes in cell growth; they may be of little relevance to the effects of marginally low Se intake or Se supplementation in humans.

Data on effects of nutritional modulation of patterns of global gene expression by Se in vivo are sparse. In the rat, Se deficiency has been shown to lead to changes in expression of genes encoding enzymes of xenobiotic metabolism (46) in the liver. Muscle global gene expression has been assessed in mice fed either an Se-depleted or control diet for three generations (55). The major changes were increases in expression of prostaglandin E2 receptor, the T-cell receptor beta, and the T-cell transcription factor Tcf-7, as well as a decrease in the Vav2 oncogene. Selenomethionine supplementation for 10 months to patients with esophageal dysplasia failed to reveal any more changes in esophageal biopsy gene expression than expected by chance despite the chemoprevention trial reporting beneficial effects (61). Thus, microarray studies to date have not provided much insight into downstream targets of marginally suboptimal Se intake or Se supplementation in humans to a level associated with improved health outcomes. However, recently a study has been carried out in which lymphocyte gene expression was assessed by microarray analysis in healthy volunteers following Se supplementation (78). The European volunteers were supplemented with 100 μg/day sodium selenite for six weeks, a supplementation regime that is sufficient to raise plasma Se from approximately 1.15 to 1.38 μmol/l and to raise plasma SEPP to a level comparable to that in the United States (69). Not surprisingly, such a small modification of Se intake was associated with relatively subtle changes in gene expression. However, 250 genes were found to show consistent changes in

expression, and pathway analysis allowed identification of an up-regulation of genes associated with protein biosynthesis. These changes are consistent with an up-regulation of selenoprotein synthesis or increased lymphocyte activity following Se supplementation, but their further significance remains to be explored. Importantly, this study shows the potential of transcriptomics, combined with pathway analysis of the data, to describe the overall effects of changes of Se intake at suboptimal rather than severe deficiency levels. Pathway analysis has been reported to be critical for identification of expression pattern changes following nutritional interventions (96).

In summary, studies on cancer cell lines have identified cell cycle genes as downstream targets of high Se concentrations in cell culture. However, it remains to be seen whether these genes are targets of nutritionally relevant changes in Se intake in non-neoplastic tissue. Investigators who have combined transcriptomics with pathway analysis have been able to detect changes in patterns of lymphocyte gene expression in humans following small changes in dietary intake, including Se supplementation (78, 96). Information on expression changes in other tissues is needed, and one way to obtain this may be to carry out comparisons of changes in gene expression patterns across species: human supplementation versus animal and cell-line studies and comparison within animals/cells of responses of different tissues to nutritionally relevant levels of Se.

NUTRIGENETICS OF SELENIUM AND SELENOPROTEINS GENES

Se, through the selenoproteins, has a range of important biochemical functions, and genetic variation in components of the selenome therefore would be expected to have some phenotypic consequences. Mutations in two genes related to Se metabolism, namely selenoprotein N and SBP2, have been found to give rise to disease. First, a missense mutation in SBP2 has been found cause a defective SECIS-driven Secys incorporation characterized by defective thyroid function (39). Second, mutations in selenoprotein N gene within the predicted SECIS region of the 3′UTR lead to a congenital muscular dystrophy (5, 72). This mutation is associated with lower levels of both mRNA and protein and gives rise to lower binding of SBP2 to the SECIS. Both demonstrate the importance of SBP2-SECIS interactions in selenoprotein synthesis. However, these mutations are rare, and their phenotype is independent of Se intake. In contrast, when considering the role of dietary Se and genetic factors in determination of susceptibility to multifactorial disease, the major questions are whether there are common genetic variations in the selenome that have functional consequences and whether they have phenotypic effects alone or only in combination with dietary factors (see **Figure 4**).

As with all genes, selenoprotein and Se-related genes contain stable allelic variations at single nucleotides (SNP). Sequencing data show that the human genome contains a huge number of such allelic variations within gene sequences, with SNPs occurring every 100–300 bases throughout the genome. By definition, in SNPs the minor allele occurs in at least 1% of the population; it has been estimated that there are approximately 3 million SNPs. This is a huge source of subtle genetic variation, and crucially the allelic variants of these SNPs occur at frequencies that are stable in the population and alone do not necessarily give rise to any major phenotype. In order to affect the phenotype, diet, environmental factors, or even additional genetic variations may need to come into play. Furthermore, much of this variation may not have functional consequences because the SNPs are in an intron, because they do not cause any amino acid change, or because the amino acid change has essentially no effect on function. Therefore, when considering Se and selenoprotein genes, the first challenge is to identify SNPs that alone or in conjunction with other SNPs or nutritional factors affect metabolism and selenoprotein function.

An SNP may cause an amino acid change that alters protein function or it may occur in a gene regulatory region so that it alters the

regulation of expression of the gene. The gene regulatory region could be the promoter. Since the SECIS region within the 3′UTR is vital for Se incorporation, SNPs in the 3′UTR also have the potential to alter Sec incorporation and selenoprotein expression and are of particular interest in the selenoprotein genes. Selenoprotein expression and activity, and thus functional Se metabolism, could be influenced by SNPs within the coding region or 3′UTR of selenoprotein genes, the coding region of proteins involved in the Se incorporation mechanism (e.g., SBP2, EF-Sec), or in tRNA-Sec and its modification, or Se transport. Thus, research on SNPs in relation to Se intake, Se metabolism, and disease should focus on the whole selenome, and indeed several SNPs in regulatory regions have been described.

Selenoprotein synthesis and functional activity will result from the combined influences of the genetic information in the genes encoding the selenome and dietary Se intake (**Figure 4**). SNPs in these genes could potentially influence the Se intake required to achieve a particular level of functional activity and thus individual requirements for Se. Any functional effect of a single nucleotide change is likely to be relatively small, and therefore detectable physiological changes are likely to be due to a combination of different SNP(s) in selenoprotein-related gene(s), possibly also in combination with dietary Se intake. When Se intake is suboptimal, such an interaction may give rise to differences in the ability of selenoproteins to function at optimal capacity; thus, selenoprotein function in protection of cells from oxidative stress, thyroid hormone, Se metabolism, fertility, or inflammation could be compromised. This could be relevant in parts of the world (e.g., Europe, China, Zaire) where Se intake is low (86). To date, the number of SNPs identified in selenoprotein genes and shown to be functional is limited (see **Table 1**). This information has largely accrued through studies of single SNPs; very little information is available on the combined effects of SNPs in multiple genes coding for different components of the Sec incorporation machinery and selenoproteins.

The glutathione peroxidases are thought to function, at least in part, as protective antioxidant enzymes that react with damaging oxidative free radicals (17, 18, 94). Thus, SNPs in the genes encoding the glutathione peroxidases could potentially influence antioxidant defense. A T/C variation in the protein-coding region of the *GPx1* gene (rs1050450) was first identified by loss of heterozygosity and bioinformatics (73) and was confirmed in a Scandinavian population (47). The C variant encodes Pro at codon 198, and the alternative T variant causes an amino acid change to Leu. Both variants have been reported in Afro-Caribbean, Caucasian, and Japanese populations (47, 51, 56, 83), and a recent gene-screening study has confirmed the SNP in these ethnic groups (48). The alternative homozygous T occurs at a frequency of only 7%–11% in healthy Caucasians (47) but at higher frequency (~15%) in healthy Afro-Caribbeans (48, 56, 83). The amino acid change caused by this SNP has been shown to lead to functional changes, with the Leu variant of the protein having lower activity in transfected cell lysates. No data are available on whether this SNP affects either GPx1 function in vivo or the Se intake required to maintain GPx1 activity, but several studies suggest an association of the Leu variant of this SNP with disease susceptibility. The Leu allele has been reported to show increased association with lung, breast, and bladder cancer (56, 58, 83). The association with higher risk of breast cancer has been confirmed in some further studies (84) but not in others (30). Of course, the disease consequences of this SNP might be evident only when combined with other factors such as other SNPs or diet, and in this regard it is interesting to note that the impact of the Leu allele on susceptibility to either bladder cancer (58) or breast cancer (31) has been reported to be influenced by a second SNP—one within the gene that codes for another antioxidant defense protein, manganese superoxide dismutase (58). Furthermore, a stronger association between alcohol intake and smoking with lung cancer risk has been reported in the homozygous Leu carriers than in carriers of the other variants (81).

Table 1 SNPs in selenoprotein genes reported to have functional consequences

Gene and SNP identification	Polymorphism and predicted change	Presence confirmed/ethnic groups	Functional effect in cell culture	Functional effect in vivo	References
GPx1 rs 1050450	C/T in coding region giving Pro->Leu at codon 198	7%–11% in Caucasian, Afro-American, Japanese	Leu has lower activity	Small-medium disease association studies. Several but not all suggest T (Leu) increases susceptibility	30, 31, 47, 48, 56, 58, 83, 84
GPx3	8 variants in promoter	—	Reporter gene studies of 2 haplotype groups	??	98
GPx4 rs 713041	C/T in 3′UTR	~25% TT in Caucasian, South Asian, Chinese	Reporter gene and RNA-protein binding studies. C has stronger activity	Affects lymphocyte GPx4 and GPx1 activity, lipoxygenase levels. Two studies (one large) suggest that C increases cancer susceptibility	16, 48, 70, 95, 97
15 kDa rsrs5845 rs5859	 C/T G/A Both in 3′UTR	 Caucasian, Afro-American	Reporter gene study. TA combination has lower response to Se	One report: CG has increased association with breast cancer	57
SEPP rs 387789	G/A in coding region, Ala->Thr codon 234	Caucasian, South Asian	??	Affects plasma Se and plasma SEPP	4, 48, 71
rs 7579	G/A in 3′UTR	Caucasian, South Asian, Chinese	??	Affects response of plasma SEPP to Se supplementation	48, 71
	TC repeat in promoter	—- Caucasian	Reporter gene study: (TC_5) stronger than (TC_3)	??	3
SelS rs34713741	G/A in promoter	Caucasian	Reporter gene study: G variant gives higher promoter activity	Affects inflammation markers	32, 91

Other SNPs in the *GPx1* gene have recently been described in the promoter region (rs3811699) and in the coding region at codons 75 and 91 where they are predicted to lead to an amino acid change (48); however, there are no data on their functional significance. Although screening of the *GPx2* gene found no SNPs within the coding region of the *GPx2* gene (48), a previous study has reported an SNP within the *GPX2* coding region that is predicted to lead

to a Pro-to-Leu change at codon 103 (4). A recent study of 123 individuals has identified up to eight strongly linked variants in the promoter region of the *GPx3* gene that fell into two haplotype groups (98); reporter studies indicated a lower activity in the haplotype that was also over-represented in children and young adults with arterial ischemic stroke.

GPx4 has a role in the sperm midpiece and therefore attempts have been made to relate several genetic variants to male infertility or sperm viability (34, 68); however, no clear relationship has been found. An SNP within the region of the *GPx4* gene corresponding to the 3′UTR at position 718 (rs713041) is found in Caucasians, and both allelic variants occur at common frequencies (48, 97). A second variant at position 738 was reported as a rare variant in individuals of African American/African heritage (48) and was not found in Caucasians (97). In contrast, several lines of evidence suggest that rs713041 has functional significance. First, homozygous CC individuals were found to differ from the TT homozygotes in the level of lymphocyte 5′ lipoxygenase metabolites (97). Subsequently, reporter gene studies were carried out in which the two variants of the 3′UTR were linked to the iodothyronine deiodinase coding region and transfected into Caco-2 cells (16); under both Se-adequate and Se-deficient conditions, the C variant produced a higher level of deiodinase reporter activity. Furthermore, RNA-protein binding studies in vitro using electromobility shift assays indicate that the single-nucleotide change from T to C leads to altered protein binding (70), and computer prediction suggests that this may be the result of altered RNA structure within the 3′UTR (16). Recently, a human supplementation trial showed that this T/C variation in the *GPx4* 3′UTR led to differences in responses of GPx4, GPx1, and GPx3 protein expression or activity in response to Se supplementation or withdrawal (70). In vitro studies indicate that transcripts containing the T/C allelic variants differ in their ability to form RNA-protein complexes: The C variant competes better with *GPx1* transcripts than does the T variant. These in vivo and in vitro data are compatible with this SNP altering the position of GPx4 in the hierarchy of selenoprotein synthesis. Interestingly, in two association studies the T variant has been reported to be associated with a lower risk of ulcerative colitis (80) and colon cancer (16). In addition, a large association study in the United Kingdom has reported a link between genotype at this SNP and susceptibility to breast cancer (95). Thus, several sources of data suggest that rs713041, the SNP at position 718 in the 3′UTR of GPx4, has functional consequences and is linked to changes in glutathione peroxidase 1 and 4 expression as well as possibly inflammatory changes and cancer susceptibility. Further work is required to confirm its relation to disease and to explore whether its influence is compounded by other SNPs or nutritional Se status.

Thirteen SNPs have been described in the selenoprotein S gene, and of these, one (rs34713741) has been reported to be functionally associated with alterations in markers of inflammation such as tumor necrosis factor-alpha and interleukin-1 beta (32). This functional SNP is a G-to-A variation at position 105 in the promoter, and functional assays show it modulates response to stress agents that affect the endoplasmic reticulum. However, a recent disease association study failed to link the SNP to risk of ulcerative colitis (91).

Two polymorphic variants, a C/T substitution at position 811 (rs5845) and a G/A at position 1125 (rs5859), have been identified in the region of the *Sep15* gene that corresponds to the 3′UTR of the mRNA (57). The SNP at position 1125 is located close to the SECIS structure. Assessment of read-through at a UGA codon using a reporter gene assay indicated that the combination of C811 and T1125 made SECIS function more sensitive to Se supply, which suggests that these two SNPs would affect Se incorporation during Sep15 synthesis. Furthermore, malignant mesothelioma cells expressing the A variant at position 1125 were less responsive to growth inhibition by increased Se supply (7). There is also one report of an association of the combined variants with breast cancer (57).

Strong evidence now exists to implicate SEPP in having a central and critical role in the transport of Se in the bloodstream. This extraordinary protein, which contains multiple Sec and has two SECIS in its mRNA (illustrated schematically in **Figure 6**), is found in plasma, where it contributes the bulk of functionally available Se. The central role of SePP in Se transport makes it likely that variants in the *SePP* gene could have significant functional consequences. A functionally relevant SNP has been identified in the promoter region of the *SePP* gene (3): this is a variant in a TC repeat sequence that reduces basal promoter activity in reporter gene constructs expressed in hepatoma cells. Screening for transcript heterozygosity by denaturing high-performance liquid chromatography has identified two variants within the coding region and 3′UTR of the *SePP* gene (69): both G-to-A variations, one resulting in an alanine-to-threonine amino acid change at codon 234 (rs3877899) and the other close to the SECIS within the 3′UTR at position 25191 (rs7579). The predicted Ala to Thr change at codon 234 is close to the beginning of the Sec-rich region in the protein (**Figure 6**). The frequencies of the allelic variants in rs3877899 in a cohort of Caucasians were 46% for the GG, 47% for the heterozygotes, and 7% for the rare AA homozygous allele. Interestingly, the SNP was not detected in a population of Chinese ethnic origin. One homozygote (GG) and the GA heterozygote for the 25191 g/a also occur at high frequency (47% and 46%, respectively) with a rare (7%) AA homozygote, but in this case the frequency was similar in Caucasian, South Asian, and Chinese groups (69). Thus, within one gene we see one SNP with different allele frequencies in different ethnic groups and one with similar frequencies. This illustrates the importance of considering ethnicity in studies of nutrient-gene interactions.

Data from a human Se supplementation trial in which prospectively genotyped individuals were supplemented with Se provided evidence that both rs3877899 and rs7579 influenced a number of biomarkers of Se status (69). Plasma Se at baseline depended on both these SNPs as well as body mass index (BMI), baseline plasma SePP levels depended on rs24731, and plasma SePP postsupplementation depended on the rs25191 SNP. Both SNPs also had effects on plasma and lymphocyte glutathione peroxidase activities. Thus, both these variants appear to have functional consequences, but the mechanistic basis of each needs further investigation. The SNP within the 3′UTR (G/A at nt 25191) occurs at positions close to, but not within, the region predicted from the two SECIS structures. However, unlike for the rs713041 in the GPx4 gene, no data are available from in vitro experiments to show whether it affects functionality of the 3′UTR in reporter or protein-binding assays. Initial studies suggest that neither the TC promoter polymorphism nor the Ala-Thr SNP show altered allele frequencies in colon cancer patients (3, 4).

It is clear from the above-mentioned studies that a number of SNPs in selenoprotein genes demonstrate functional differences between the allelic variants. These have been mostly identified in studies of individual SNPs in single genes. However, when assessing the impact of such variants on Se metabolism, it is important to take a wider view and consider two critical aspects. First, as when considering genetic variants in genes involved in any nutrient metabolism and function, one should take into account variation in all the metabolic events in which the nutrient is involved (see sidebar The Effect of Genetic Variation on Nutrient Metabolism) (**Figure 7**). Thus, in the case of Se, since there is a known hierarchy and competition in the use of Se for selenoprotein synthesis (12, 13, 66, 75), changes in synthesis of one selenoprotein owing to an SNP may alter another selenoprotein. Second, it is important to consider the effect of genetic variation over the whole functional pathway because the consequences of one SNP may be magnified or counterbalanced by variants in other genes; this net pathway effect is likely to determine the overall physiological interaction between genetics and

nutrition. For example, an SNP in the *SBP2* gene might affect Se incorporation but without consequences unless combined with an SNP in the 3′UTR of the *GPx4* gene; or the effect of the SNP in *GPx1* might be magnified by an SNP in the *SePP* gene that affects Se delivery to target tissues. However, to date the research on nutrient-gene interactions in relation to Se metabolism has been limited to studies of individual SNPs in relation to measurements of physiological parameters, so as yet such effects of multiple SNPs are largely unknown. Interestingly, one haplotype study reported that the association of the Leu allele for the *GPx1* Leu198Ala SNP with bladder cancer is influenced by an SNP within the manganese superoxide dismutase gene that codes for another antioxidant defense protein (58). Similarly, a recent nested case-control study of breast cancer showed increased disease risk in individuals who carried both the Ala16Ala genotype for the manganese dismutase and the Leu198Leu genotype for *GPx1* at codon 198 (33). These data illustrate that it is important to consider combined effects of multiple genetic variants (see **Figure 6**) and that when considering such combined effects, it is necessary to take into account a wide view of the functional pathway in which the nutrient and its associated genes function. The functional pathway would be different depending on the tissue and functional outcome under consideration.

When one considers Se intake and genetic factors, the picture that is emerging is a complex one of multiple, possibly interacting, functional SNPs, the influence of which (in public health terms) may be modulated by ethnicity, gender, BMI, lifestyle, and dietary factors. For example the influence of two SNPs in *SePP* (Ala234 Thr and 25191 g/a) on plasma Se are both modulated by BMI (69), whereas the effect of rs713041 in *GPx4* on lymphocyte GPx4 levels following withdrawal of Se supplementation was observed in females but not males (70). Data on several SNPs in selenoprotein genes highlight differences in frequency distribution in populations of different ethnic origins (48, 57, 69).

THE EFFECT OF GENETIC VARIATION ON NUTRIENT METABOLISM

Approaches to analyzing how multiple genetic variations contribute to nutrient requirements are also relevant to folate acid intake, where there is a question of linking data from SNP association studies and biomarkers of status with regard to B vitamin intake, folate metabolism, and disease susceptibility (see Haggarty 2007 in Related Resources). This problem has distinct similarities to the question of how variation in selenoprotein genes and other genes associated with Se metabolism affect Se requirements. In both cases, in order to understand how genetic variation affects nutrient metabolism, it is necessary to consider data from several sources: mechanistic studies giving knowledge of nutrient function, SNP-disease association studies, and nutritional intervention and biomarker studies on genotyped individuals. One investigator (see Haggarty 2007 in Related Resources) advocates combining such data in a "causal-pathway" approach to assess how multiple genetic variants contribute to overall nutrient-gene interactions. This approach considers how genetic variation across a broad functional nutrient-related pathway influences metabolism and is potentially applicable to a number of nutrient-gene interactions, including those discussed in this review in relation to selenium.

CONCLUSIONS AND FUTURE PERSPECTIVES

The Physiological Effects of Suboptimal Se Intake

Transcriptomic approaches have provided interesting data on the responses of certain selenoprotein genes, for example, SelW, to modulation of Se supply, but in general, the data are limited by the major regulation of selenoprotein synthesis at the level of translation. Proteomic methods, perhaps in combination with inductively coupled plasma mass spectroscopy to detect selenoproteins, need to be developed. In contrast, gene array studies have identified downstream targets of Se. However, to date these have been largely limited to cell culture studies with high concentrations of Se that induce apoptosis. Further studies are needed in which nutritionally relevant concentrations of Se are used in cell culture, animal, and human

studies. Recent studies of lymphocyte gene expression patterns in humans show that pathway analysis is very useful in allowing detection of subtle changes in gene expression following nutritional interventions (41, 69, 96).

Metabolomics has not been used to any significant extent to explore the downstream targets of Se intake. However, studies in cell culture indicate that metabolomics combined with transcriptomics may allow annotation of metabolic networks by gene regulation and gene regulatory networks by metabolites. This approach was used to identify changes in metabolic pathways in A549 lung carcinoma cells in response to 0.2–0.5 ppm sodium selenite (44), at which concentrations there is growth inhibition and induction of apoptosis. This combined approach does detect differences between treatment with selenite and selenomethionine. Such an approach, combined with inductively coupled plasma mass spectroscopy to detect Se species, may prove useful in identifying regulated pathways in humans that respond to Se and in dissecting the different metabolic responses to different selenium-containing compounds. Interestingly, studies of ^{75}Se metabolism in transgenic mice expressing a mutated tRNA-Sec have allowed exploration of the relative roles of selenoproteins and low-molecular-weight selenocompounds in the colon (59).

In general, the development of transgenic mice with selenoprotein genes knocked out or modified has proved highly useful not only in elucidating mechanisms of Sec incorporation and selenoprotein function but also in providing more details of the selenoprotein hierarchy (25, 27, 53, 59, 64). Further investigation of such models (for example, in conjunction with microarray analysis) is likely to assist in defining the downstream targets of altered selenoprotein function. In addition, further breeding of such mice with other transgenic animals with increased cancer susceptibility, as is done to examine prostate cancer (36), may provide novel tools to investigate the links between selenoproteins and disease. Likewise, the recent report of a technique to combine knock-down and knock-in (103) may prove useful in assessing selenoprotein function and downstream targets. Se function may also be explored using transgenic mice in which non-selenoprotein genes have been modified. For example, Se feeding experiments in mice lacking apolipoprotein E receptor 2 show that this receptor is required for maintenance of brain Se (23).

Gene-Se Interactions and Disease Susceptibility

Several SNPs have been identified in the glutathione peroxidases and other selenoprotein genes, some within the coding region and others within regulatory regions that correspond to the promoter or the 3′UTRs. There is evidence that some of these are functional and that they may be associated with susceptibility to a range of diseases (see **Table 1**). Our level of knowledge is limited, however: SNPs with apparent functional consequences have been identified in only a few selenoprotein genes but not in others, and we have essentially no picture of how these SNPs combine together, and with Se intake, to influence Se metabolism and cell physiology. A major challenge is to obtain a view of how genetic variation in the selenome as a whole, combined with Se intake, influences selenoprotein function, its downstream targets, and susceptibility to disease (see **Figure 7**).

One approach to this challenge would be to use modern genotyping technology to carry out large-scale human studies measuring many SNPs (even genome-wide scans) in combination with measures of Se status and dietary and lifestyle characterization. To date, nutritional data in such studies have usually been sparse, and to adopt this approach would require obtaining detailed biochemical and dietary data in large population cohorts. A second limitation to this approach is that in general it does not test, but rather generates, a hypothesis. An advantage is that it does not depend on our existing knowledge or preconceptions.

An alternative is to use our knowledge of Se metabolism to focus on the selenome genes and genes encoding proteins that function in

Se-related metabolic pathways (see **Figures 3**, **4**, and **7**). In this way, the number of SNPs to be tested is limited, so a lower number of individuals participate in the study while the problems of loss of statistical power are minimized. Such an approach has several advantages. It allows hypothesis testing; lowering the number of individuals in the study improves the quality of nutritional and phenotypic data; multiple effects of different SNPs from genes within a pathway may magnify effects; and one can assess the effects of genetic variation in a pathway as a whole. This approach, focused on one biochemical "unit," would screen the selenome genes for SNPs, identify the SNPs in these genes that are critical in terms of their functional effects, and then define how these interact with each other and with nutritional factors such as Se intake to influence physiological processes, optimal health status, and susceptibility to disease. It would require a demonstration of SNP functionality at the molecular (protein or RNA), cellular, and physiological levels (preferably at more than one) for each individual SNP to build up the full list of SNPs that affect Se-related cell processes. Finally, case-control association studies would be needed to define if the individual SNPs and/or combinations of SNPs influence disease risk.

Until now, very few intervention studies have been carried out to assess the functionality of SNPs in vivo. There is a need to assess SNPs in human intervention studies using prospectively genotyped cohorts and appropriate biomarkers in order to show causality in the relationship between Se, SNPs, and the biomarkers of health status. There is also a need to carry out further disease association studies involving analysis of larger, repeat cohorts and to combine genotyping with studies of nutritional intake, or status, to assess the importance on nutrient-gene interactions in determining susceptibility. A wide range of SNPs should be studied, initially based on a selenome approach to include genes encoding products involved in Se incorporation mechanisms and Se transport. Since effects of individual SNPs in isolation are expected to be relatively small, it will be necessary to assess how these individual genetic factors fit into the complex picture: How do the groups of SNPs interact with each other or with other factors such as Se intake, ethnicity, and gender to contribute to biomarkers of health and nutrient requirements? Finally, mathematical modeling is needed to define which SNPs are the major determinants of individual responses to dietary Se and consequently individual Se requirements, and thus the extent of their role, in conjunction with Se intake, in determination of risk of diseases such as prostate and colon cancer. Our ultimate aim should be to define the extent of the contribution from these different SNPs and other factors. There are major challenges to develop statistical approaches needed both to analyze the data from large human studies on multiple SNPs and nutritional factors likely to influence the biological outcomes and then to model mathematically the multiple effects in terms of the different factors that influence Se metabolism and optimal health or disease. However, rising to these challenges is worthwhile because the associations between suboptimal Se status and disease in large population groups worldwide and in animal models identify Se intake as a potential public health concern. Nutrigenomics, both in terms of mechanistic studies and detailed SNP studies, provides exciting approaches with which to tackle this important issue.

SUMMARY POINTS

1. Both dietary Se intake and genetic factors can potentially influence the pattern of selenoprotein synthesis.
2. There is a hierarchy in the response of selenoprotein synthesis to Se supply. The hierarchy determines the pattern of selenoprotein expression and functional effects of Se. It is

important to determine how the pattern of synthesis of all selenoproteins is affected by Se supply and genetic factors.

3. Conversion of Se into functioning selenoproteins requires synthesis of selenocysteine tRNA, incorporation of selenocysteine during translation by a mechanism involving the 3′UTR and specific RNA-binding proteins, and transport of Se in the blood by SEPP. SNPs in genes that code for proteins that are involved in these processes may influence selenoprotein synthesis and nutrient requirements.
4. Functional SNPs have been identified in some selenoprotein genes, and some have been linked to disease susceptibility in small association studies. However, our knowledge is limited, and much further work is needed to identify and assess the effects of SNPs that influence Se metabolism, nutritional requirements for Se, and disease susceptibility.
5. It is important to consider how multiple SNPs interact to affect Se metabolism.
6. Transcriptomic studies (gene microarrays) on transformed cells in culture have shown relatively high concentrations of Se to alter expression of genes involved in apoptosis and cell cycle control.
7. Combining transcriptomics and pathway analysis may allow identification of novel targets of dietary Se, even in human studies.
8. Proteomic and metabolomic approaches to Se metabolism should be explored.

FUTURE ISSUES

1. What are the molecular mechanisms behind tissue-specific hierarchy in selenoprotein synthesis?
2. What downstream (i.e., nonselenoprotein) pathways are affected by dietary Se intake, and what can this tell us about the physiological effects of Se?
3. Can transcriptomics, proteomics, or metabolomics provide novel, improved biomarkers of Se status?
4. To what extent does genetic variation in Se metabolism genes affect which SNPs have the most influence on nutritional requirements for Se and susceptibility to multifactorial diseases?

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The author is not aware of any biases that might be perceived as affecting the objectivity of this review.

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RELATED RESOURCES

Bleys J, Navas-Acien A, Guallar E. 2008. Serum selenium levels and all-cause, cancer, and cardiovascular mortality among US adults. *Arch. Intern. Med.* 168:404–10. Suggests that the optimal Se intake is one that gives a serum Se of ~130 ng/ml

Haggarty P. 2007. B-vitamins, genotype and disease causality. *Proc. Nutr. Soc.* 66:539–47. Discusses approaches to study of nutrient-gene interactions

Jablonska E, Gromadzinska J, Sobala W, Reszka E, Wasowicz W. 2008. Lung cancer risk associated with selenium status is modified in smoking individuals by Sep15 polymorphism. *Eur. J. Nutr.* 47:47–54. Suggests that in smokers, SNPs in the selenoprotein 15 gene influence lung cancer risk

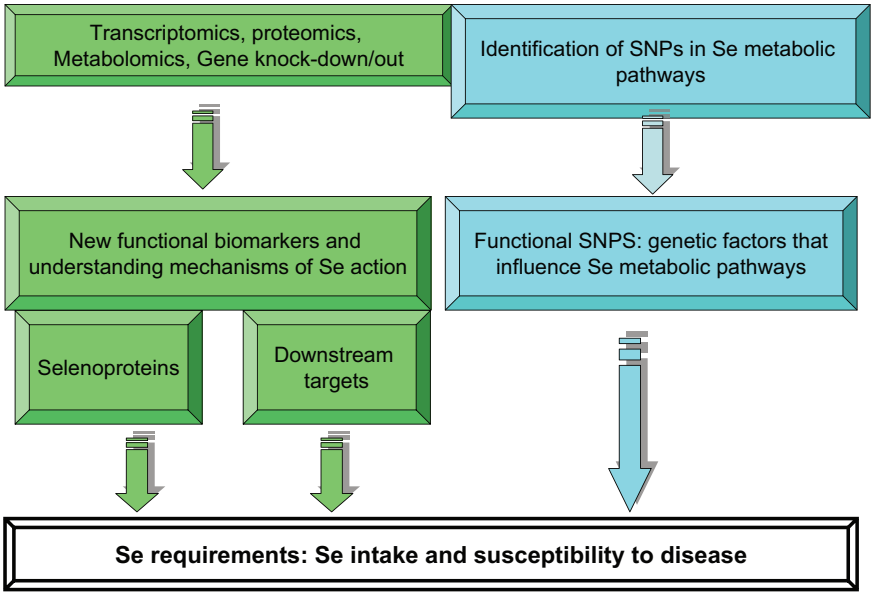

Figure 1

The contribution of genomics to understanding the nutritional science of selenium (Se). Two aspects are emphasized: (*a*) the genetics of selenoprotein and other genes relating to Se metabolism, and (*b*) the potential of functional genomic approaches to elucidate novel aspects of physiological targets of altered Se supply. SNPs, single-nucleotide polymorphisms.

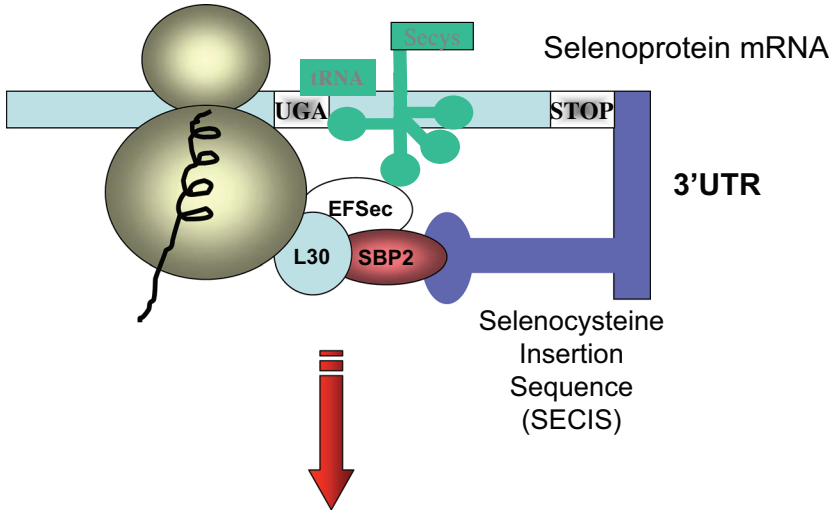

Figure 2

Selenocysteine incorporation. The scheme illustrates the key factors in Sec incorporation: (*a*) the in-frame UGA, (*b*) Sec-tRNA, (*c*) the selenocysteine insertion sequence (SECIS) element in the 3' untranslated region (UTR), and (*d*) RNA-binding proteins SECIS-binding protein 2, EF-Sec, and ribosomal protein L30. RNA, ribonucleic acid; mRNA, messenger RNA; tRNA, transfer RNA.

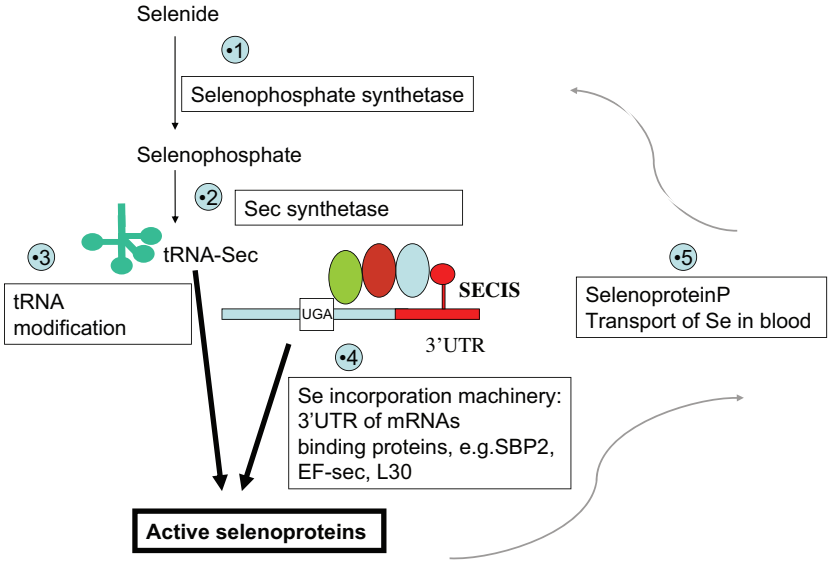

Figure 3

The selenome encompassing the key features in synthesis of active selenoproteins. *1* and *2* illustrate synthesis of Sec-tRNA; *3*, modification of Sec-tRNA; *4*, SECIS-dependent Sec incorporation during translation; and *5*, transport of Se in plasma as selenoprotein P. EF, elongation factor; RNA, ribonucleic acid; mRNA, messenger RNA; SBP, SECIS-binding protein; Se, selenium; SECIS, selenocysteine insertion sequence; tRNA, transfer RNA; UTR, untranslated region.

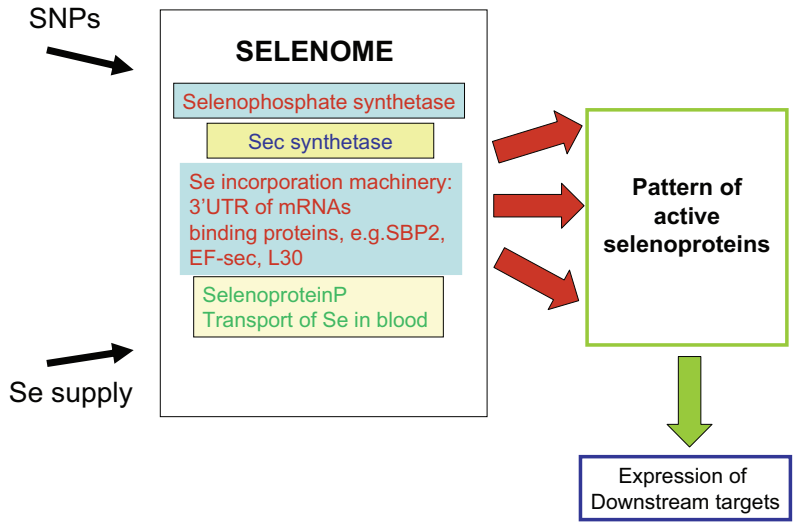

Figure 4

Single-nucleotide protein (SNP)-diet interactions determine response to dietary Se. The scheme illustrates how theoretically selenoprotein activity and physiological effects on downstream targets of Se are caused by an interaction between dietary Se supply and genetic variation (SNPs) in genes encoding components of the selenome. EF, elongation factor; mRNA, messenger ribonucleic acid; SBP, SECIS-binding protein; Se, selenium; Sec, selenocysteine; SECIS, selenocysteine insertion sequence; UTR, untranslated region.

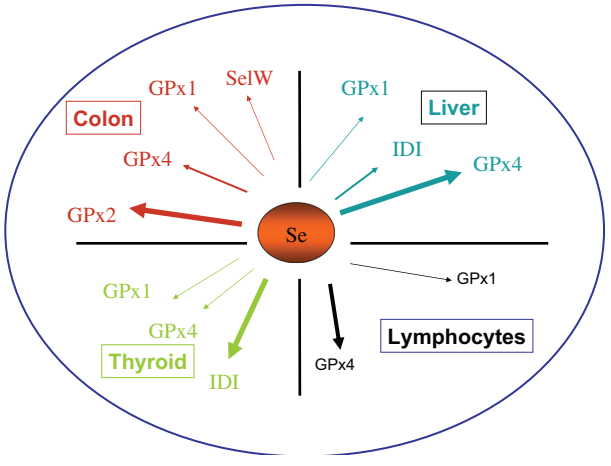

Figure 5

The hierarchy in selenoprotein synthesis. The sensitivity of expression to lower selenium (Se) supply is shown for four different cell types/tissues based on data from various studies on rats (colon, liver, thyroid), human cells in culture (colon, liver), and human supplementation trials (lymphocytes). Sensitivity is illustrated schematically by the thickness of the arrows. Note that some selenoproteins are more sensitive than are others to Se depletion and that this sensitivity is tissue dependent. GPx, glutathione peroxidase; IDI, deiodinase; SelW, selenoprotein W.

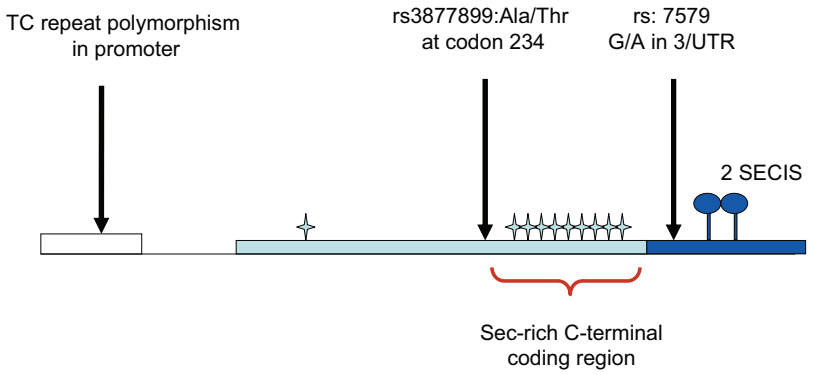

Figure 6

Single-nucleotide polymorphisms in the human selenoprotein P (SEPP) gene. The exons of the SEPP gene are illustrated schematically together with the Sec-rich C-terminal region of the coding region and the two SECIS in the 3'UTR. The positions of three known genetic variations in the SEPP gene are highlighted by arrows. Sec are denoted by stars. Sec, selenocysteine; SECIS, selenocysteine insertion sequence; UTR, untranslated region.

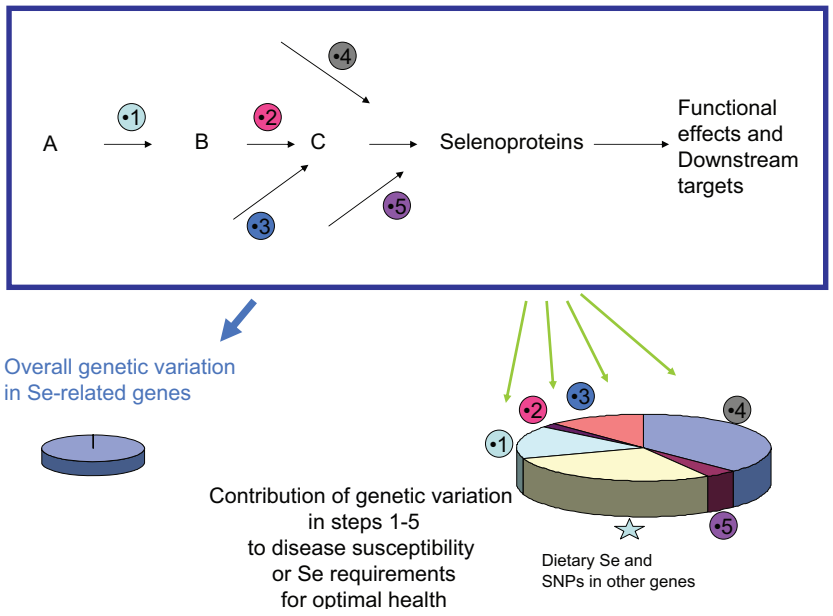

Figure 7

The theoretical impact of multiple single-nucleotide polymorphisms (SNPs) in the genes encoding components of the selenome and selenium (Se)-related pathways. SNPs can occur in genes encoding different steps in the selenome (e.g., steps 1–5 in **Figure 4**) as well as in associated pathways leading to downstream targets. Two aspects should be considered when assessing the interaction between these SNPs and dietary Se supply and their contribution to determining individual Se requirements for optimal health. First, genetic variation across this overall metabolic unit (schematically illustrated by the blue-bordered box) may theoretically influence Se requirements. Second, the different SNPs in the individual steps and individual genes within the selenome, as well as dietary Se, may make quantitatively different contributions to the determination of Se requirements (illustrated by the pie chart).

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Errata

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