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REGULATION OF SELENOPROTEINS

Raymond F. Burk and Kristina E. Hill
Division of Gastroenterology, Department of Medicine and Center in Molecular Toxicology, Vanderbilt University School of Medicine, Nashville, Tennessee 37232

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INTRODUCTION

Nearly all the selenium in animal tissues is associated with protein. Several protein-bound forms have been identified, but only one, selenocysteine encoded by a UGA in mRNA, has been shown to be specific for the element and to be regulated physiologically. Proteins containing this form of selenium are referred to as selenoproteins in this review. Other types of protein binding

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of selenium are recognized, but they lack specificity and are frequently related to the chemical similarities between selenium and sulfur. The less specific terms "selenium-containing protein" and "selenium-binding protein" are suggested to refer to them.

This review focuses on selenoprotein synthesis and its regulation. Related reviews have appeared in recent years (14, 17, 58, 59, 61).

FORMS OF SELENIUM IN PROTEIN

Selenocysteine

All proteins that have been shown to incorporate selenium stoichiometrically contain it in the form of selenocysteine. This form was first identified in 1976 in protein A of the glycine reductase complex of *Clostridium sticklandii* (25). Since then it has been found in several other proteins, and a specific mechanism for its synthesis and incorporation has been characterized (see below). Proteins containing selenocysteine are selenium dependent. That is, they are present in diminished concentration when selenium supply is restricted. This review focuses on proteins containing selenium as selenocysteine and refers to them as selenoproteins.

Selenomethionine

Plants and bacteria synthesize selenium-containing amino acids, including selenomethionine. Most evidence suggests that animals do not distinguish this amino acid from methionine. Thus it appears to be incorporated into protein in place of methionine and to have no selenium-related function. Incorporation of selenium administered as selenomethionine into animal proteins is directly correlated with selenomethionine intake and inversely correlated with methionine intake (69). Under appropriate conditions, most of the selenium in animal tissues can be in this form. This selenium is released and utilized in specific selenium pathways when selenomethionine is catabolized.

Selenomethionine can be metabolized to selenocysteine by the transsulfuration pathway. However, the resultant selenocysteine is catabolized by selenocysteine β-lyase (27) and does not serve as a form of selenocysteine for specific incorporation into proteins. There is evidence that selenocysteine can be incorporated into protein in place of cysteine by some bacteria (60). Such incorporation should be prevented by selenocysteine β-lyase activity in cells containing this enzyme.

Selenotrisulfides

The reaction of selenite with thiol compounds leads to the formation of selenotrisulfides such as selenodiglutathione (33). Selenotrisulfide formation in a protein was induced by adding selenite to reduced pancreatic ribonuclease (34). This nonspecific incorporation of selenium appears to be largely an in vitro phenomenon and is not likely to be of physiological importance.

Selenium-Heavy Metal Complexes

There is evidence that selenium occurs in proteins in complexes with heavy metals, especially mercury (18). Binding to selenium may reduce the toxicity of the heavy metals, but this also reduces the bioavailability of the selenium.

Other Forms

Recently a group investigating anticarcinogenic properties of selenium has shown that injected selenium associates with several proteins in rodent tissues that do not contain the element as selenocysteine (5). Selenium deficiency does not cause a decrease in the concentrations of these proteins, and the form and stoichiometry of selenium in them is not known. Thus, it is uncertain whether selenium association with these proteins has biological significance.

IMPORTANCE OF SELENOPROTEINS

Under physiological conditions selenium has several metabolic fates. A major one in a quantitative sense is incorporation into selenoproteins. A five-month equilibration study, in which selenite labeled with ^{75}Se was administered in the drinking water to rats fed a selenium-deficient diet, revealed that over 80% of the ^{75}Se in the rat was present as selenocysteine in protein (38). Two other fates of the element are known. Methylated forms of selenium are synthesized for excretion (15), and selenium has been shown to be incorporated into certain tRNAs in cultured cells (23). The physiological significance of these tRNAs has not been established.

Selenoproteins with known enzymatic activity are redox enzymes and contain selenocysteine in their active sites. Replacing selenium with sulfur causes a sharp decline in activity (4, 11, 52). Thus, effective function of these enzymes depends on their selenium.

Studies utilizing polyacrylamide gel electrophoresis of tissue extracts from rats which were administered ^{75}Se point to the presence of 10 to 15 high-abundance selenoproteins (7). Based on this figure, and the inference from the number of genes present in the genome that ten nonabundant proteins are present for every abundant one, it seems reasonable to speculate that as many as 100 selenoproteins exist in animals. Five selenoproteins have been characterized to the extent of cloning their cDNA and determining their sequences.

Cellular Glutathione Peroxidase (cGSH-Px)

This enzyme was discovered 36 years ago (48) and was noted to be dependent on selenium 20 years ago (53). It represented the only known biochemical role of selenium for many years and has been used extensively to assess selenium nutritional status. cGSH-Px is found in virtually all cells, but its

specific activity varies greatly between species and tissues. In the rat, cGSH-Px contains more selenium than any other selenoprotein (38). Approximately 25% of rat total body selenium is present in liver cGSH-Px (9).

The active enzyme comprises four identical 22-kDa subunits. Each subunit contains one selenocysteine residue. Glutathione is required as the reducing substrate. Hydrogen peroxide and free organic hydroperoxides, including free fatty acid hydroperoxides, can be reduced by cGSH-Px. Fatty acid hydroperoxides esterified in phospholipids cannot serve as substrates (36).

cGSH-Px is thought to regulate intracellular hydroperoxide concentrations. Its importance has been questioned, however, because deficiency of selenium resulting in a fall in cGSH-Px activity to less than 1% of control in liver has no obvious effect on the health of the rat. Moreover, direct evidence that it affects levels of hydrogen peroxide or other free hydroperoxides under physiological conditions has not been presented. Because cGSH-Px contains a large fraction of the total body selenium and its loss appears to be well tolerated, researchers have proposed that it represents a reserve of selenium that can be mobilized for other uses (19, 61, 70). A family of cGSH-Px proteins appears to exist because related cDNAs have been cloned and sequenced (1, 28). This observation indicates that a great deal remains to be learned about cGSH-Px function.

Extracellular Glutathione Peroxidase (eGSH-Px)

Plasma glutathione peroxidase was recognized as a different enzyme from cGSH-Px in 1986 (63). Since then, its presence has been demonstrated in milk, and it has been referred to as eGSH-Px. Its activity in plasma is a convenient index of selenium nutritional status.

eGSH-Px shares some sequence identity with cGSH-Px but is clearly a separate gene product (62). It consists of four identical 23-kDa subunits, each of which contains one selenocysteine. Recent work indicates that it is synthesized in the kidney and in the lung (24).

The function of eGSH-Px is not known. The fact that its reducing substrate, glutathione, is present at very low concentrations in extracellular fluids has led to suggestions that the enzyme might have a function other than as a glutathione peroxidase.

Phospholipid Hydroperoxide Glutathione Peroxidase (phGSH-Px)

This third glutathione peroxidase has been characterized in recent years (57). It is a monomer of 20 kDa and is similar to one subunit of the other two glutathione peroxidases. It contains one selenocysteine. Thiol compounds other than glutathione can serve as its reducing substrate. It is capable of reducing fatty acid hydroperoxides esterified to phospholipids (66).

phGSH-Px is found in several tissues but has a distribution different from that of cGSH-Px. Relatively little is present in rat liver while it is quite abundant in the testis (54). It has been suggested that this enzyme plays a role in eicosanoid metabolism (67) and that it protects against lipid peroxidation (65).

Type I Iodothyronine 5'-deiodinase (5'DI)

Thyroid function depends on the conversion of thyroxine to triiodothyronine. Several deiodinase enzymes can perform this conversion and one of them is a selenoprotein (2, 8, 11). The enzyme is a homodimer and each 27-kDa subunit contains one selenocysteine (11). The enzyme is present in the endoplasmic reticulum of liver and kidney (13).

The function of 5'DI is to deiodinate thyroxine, thus producing triiodothyronine. A reducing substrate is required which, in vivo, is probably glutathione. In selenium deficiency, thyroxine levels in plasma rise as a consequence of the decrease in 5'DI activity (6). Triiodothyronine levels are depressed slightly by selenium deficiency (6), but selenium-deficient animals remain euthyroid (16).

Selenoprotein P (Se-P)

The existence of a plasma selenoprotein other than eGSH-Px has been known for over 15 years, but the purification and characterization of Se-P has been accomplished only in the last five years. In the rat, Se-P contains 65% of the plasma selenium (50).

A cDNA for Se-P has been cloned and sequenced (41). There are ten TGAs (UGAs in mRNA) in the open reading frame (ORF), indicating that the protein contains ten selenocysteine residues in its primary structure. It is the only selenoprotein characterized so far that contains more than one selenocysteine per polypeptide chain. The protein is a glycosylated single polypeptide chain of 41 kDa (50).

The function of Se-P is not known. Its appearance in plasma correlates with protection against free radical injury of the liver by diquat (20, 21). Thus, it may be a free radical scavanger. Another hypothesis is that it transports selenium from the liver to other tissues. However, Se-P mRNA has been detected in several tissues, thus indicating that it is synthesized in sites other than the liver (40). Also the half-life of its selenium is not affected by the selenium status of the animal (20). These observations make a transport role unlikely.

EVIDENCE THAT SELENOPROTEINS ARE REGULATED

Selenium availability regulates selenoproteins. Although it is likely that there are other modifiers that are specific for individual proteins, deficiency of selenium causes a fall in the concentration of all selenoproteins that have been

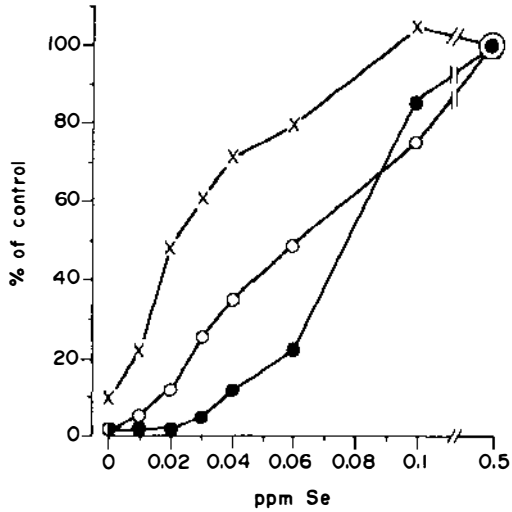

Figure 1 Effect of dietary selenium supplementation on selenoproteins in the rat. cGSH-Px in liver (•), eGSH-Px in plasma (*o*), and Se-P in plasma (*x*) were measured in animals fed varying levels of selenium in the diet for 8 weeks. Values are means of 6 animals. See Reference 70 for experimental details. The dietary requirement of the rat for selenium is 0.1 ppm. The control group was fed a diet supplemented with 0.5 ppm selenium (0.5 mg selenium per kg). As selenium was introduced into the diet, Se-P increased first and was followed by eGSH-Px. Liver cGSH-Px was the last to increase in response to dietary selenium.

studied. This finding suggests that synthesis of selenoproteins is decreased by selenium deficiency.

Figure 1 compares the effect of dietary selenium level on cGSH-Px in liver, eGSH-Px, and Se-P. All three measures of these selenoproteins are sharply decreased when no selenium is added to the deficient diet. As small amounts of selenium are provided, Se-P and then eGSH-Px increase before liver cGSH-Px begins to rise. This demonstrates that selenoproteins are regulated by the supply of selenium and that regulation of individual proteins occurs at different levels of the element. Evidence also indicates that 5′DI is better preserved than cGSH-Px in selenium deficiency (3).

MECHANISMS OF SELENOPROTEIN SYNTHESIS

The synthesis of selenocysteine and the incorporation of it into protein are components of a complex process. Studies by Böck and coworkers utilizing *E. coli* mutants have characterized the process in prokaryotes (14). Figure 2 shows the major steps. A UGA codon in the open reading frame of the mRNA corresponds to selenocysteine in the protein. Four unique gene products are

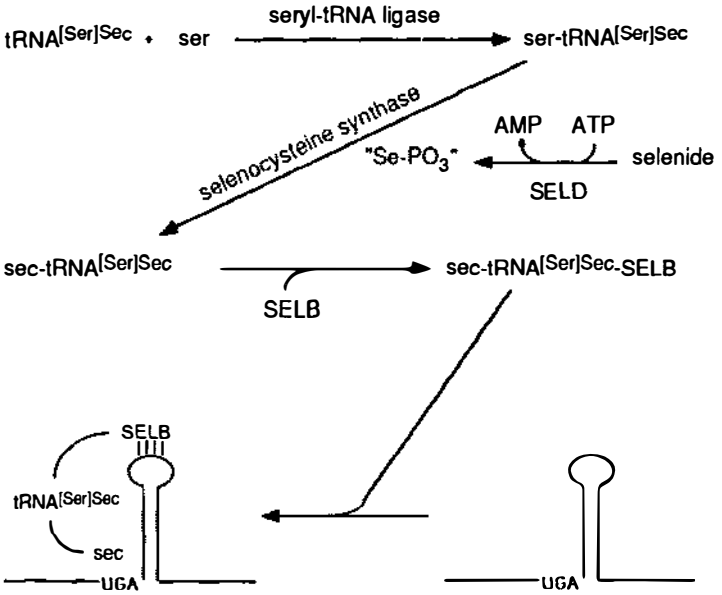

Figure 2 Synthesis of selenocysteine and incorporation of it into selenoproteins by prokaryotes. $tRNA^{[Ser]Sec}$ contains the anticodon for UGA. Unique structural features of $tRNA^{[Ser]Sec}$ allow it to bind to selenocysteine synthase (formerly known as SELA) after charging with serine (31). Selenocysteine synthase, a pyridoxyl 5-phosphate enzyme, catalyzes the replacement of the side-chain oxygen in serine by selenium, yielding selenocysteine (29). A selenophosphate compound is required for this reaction (68). It is produced from selenide and ATP by an enzyme known as SELD (29, 44). The sec-$tRNA^{[Ser]Sec}$ is released from selenocysteine synthase and is bound by a unique elongation factor, SELB. SELB has a 43-kDa region similar to EF-Tu, the elongation factor that serves for all other amino acid-tRNAs (32). The additional 25 kDa of SELB allows it to recognize the sec-tRNA[Ser]Sec (30) and presumably to bind to the stem-loop structure of the selenoprotein mRNA. This sec-$tRNA^{[Ser]Sec}$-SELB complex attached to the stem loop facilitates incorporation of selenocysteine into the protein. It might function by bringing the sec-$tRNA^{[Ser]Sec}$ into the vicinity of the UGA codon. Additionally, it might block access of release factor 2 to the A site on the ribosome where it acts to terminate translation.

required: In addition to $tRNA^{[Ser]Sec}$ which carries the anticodon for UGA, two enzymes, selenocysteine synthase and SELD, and an elongation factor, SELB, are needed. A stem-loop structure with a specific sequence on the loop is required in the mRNA immediately downstream from the UGA. This structure is necessary for the UGA to specify selenocysteine incorporation instead of termination. It binds the elongation factor-$tRNA^{[Ser]Sec}$-selenocysteine complex and facilitates its interaction with the UGA (39). Thus, the location of the stem loop in proximity with the UGA is necessary for this mechanism.

Much less is known about the process in eukaryotic systems (Figure 3). A

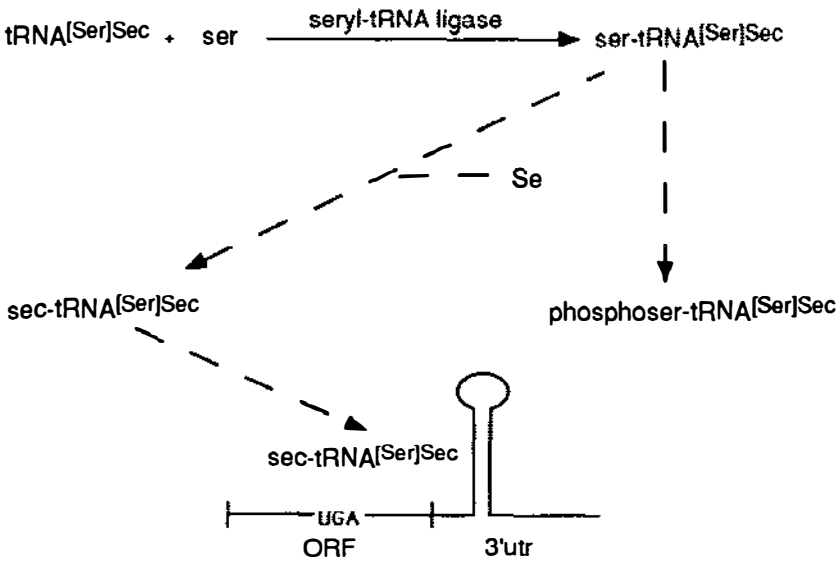

Figure 3 Synthesis of selenocysteine and incorporation of it into selenoproteins by eukaryotes. The compounds named in the figure have been identified in animal cells. The *solid line* indicates a characterized reaction. Eukaryotes contain $tRNA^{[Ser]Sec}$, which is charged with serine (46). *Broken lines* indicate pathways for which evidence has been presented but which have not been characterized in detail. $tRNA^{[Ser]Sec}$ has been isolated in three amino acid-acylated forms—with serine, phosphoserine, and selenocysteine attached (46). Details of the conversion of serine to selenocysteine in eukaryotes have not been firmly established, but a recent report (49) presents evidence for the existence of enzymes analogous to selenocysteine synthase and SELD in prokaryotes. Phosphoser-$tRNA^{[Ser]Sec}$ did not appear to be a precursor of sec-$tRNA^{[Ser]Sec}$, and its formation was speculated to compete with the selenocysteine synthase reaction (49). As yet, no elongation factor has been identified but, by analogy with the prokaryotic system, one is likely to be involved in the association of sec-$tRNA^{[Ser]Sec}$ with the mRNA. A UGA in the ORF of the selenoprotein mRNA corresponds to selenocysteine in the protein. Essential stem-loop structures are present in the 3′utr instead of in the ORF as in prokaryotes. The interaction of the three elements known to be essential for insertion of selenocysteine into protein (sec-$tRNA^{[Ser]Sec}$, the stem loop, and UGA) has not been characterized. Thus, only partial characterization of the eukaryotic system has been achieved. However, facts that have been established indicate that it differs from the prokaryotic mechanism in at least one major way—the location of the stem-loop structure in mRNA, which is essential to the decoding of UGA as selenocysteine.

unique $tRNA^{[Ser]Sec}$ has been described and, like the bacterial $tRNA^{[Ser]Sec}$, it has the anticodon for UGA. Two forms of this tRNA exist, and both differ in sequence from that predicted by the genomic DNA sequence (26). This finding indicates that the forms of $tRNA^{[Ser]Sec}$ isolated from the cell are both edited versions of the original transcript. $tRNA^{[Ser]Sec}$ is charged with serine in a manner similar to the bacterial tRNA. $tRNA^{[Ser]Sec}$ has been recovered in three

forms—with serine, phosphorylated serine, or selenocysteine attached (46). The mechanism of conversion of the serine to selenocysteine has not been characterized in detail. There has been speculation that the phosphorylated compound is an intermediate, but recent evidence suggests that a selenocysteine synthase converts ser-tRNA$^{[Ser]Sec}$ directly to sec-tRNA$^{[Ser]Sec}$ (49).

mRNA context plays a role in eukaryotic, as well as in prokaryotic, systems. Essential stem-loop structures have been described in eukaryotic selenoprotein mRNAs. Berry and coworkers studied requirements for expression of transfected 5′DI in cultured animal cell lines and determined that a segment of the 3′ untranslated region (3′utr) of about 200 bases was necessary for readthrough of the message with incorporation of selenocysteine at the UGA codon (10). They named this segment a selenocysteine-insertion sequence (SECIS) motif (Figure 4*A*). None of the 3′utr was needed for readthrough when the UGA was mutated to a codon for cysteine. A stem-loop structure was found in the 200-base 3′utr segment by computer analysis. Analysis of the 3′utr of cGSH-Px mRNA revealed a similar stem loop. These structures contained only a small amount of sequence identity, but the segment from cGSH-Px could nevertheless replace that from 5′DI in supporting expression of 5′DI in the cultured cell lines (10). Thus eukaryotic systems utilize stem loops in mRNA to specify UGA coding for selenocysteine. A major difference from prokaryotic systems is that the stem loops in eukaryotes are not adjacent to the UGA but are separated from it by hundreds of bases.

Recently the mRNA of Se-P has been analyzed for stem loops (40). Two were predicted (Figure 4*B*) and both contained elements of the SECIS motif, proposed by Berry et al (10), in the form of some common sequence in unpaired regions. Se-P mRNA contains ten UGAs in the open reading frame, so there is no strict stoichiometry of stem loops to UGAs. This raises the possibility that the stem loops in eukaryotic mRNAs function differently from those in bacterial mRNAs. It would seem unlikely that two stem loops are enough to bind complexes containing tRNA$^{[Ser]Sec}$-selenocysteine and deliver them to the ribosome rapidly enough to serve the ten UGAs in Se-P mRNA. Another function the stem loops might subserve is to prevent the release factor from interacting with the ribosome at the UGA codons and terminating translation. This would suppress the termination function of UGA and allow the UGAs to specify selenocysteine incorporation. Expression of Se-P has not yet been achieved. Once it has, these possibilities can be examined.

Figure 3 shows the elements of selenocysteine synthesis and incorporation that are known in eukaryotic systems. Major gaps in this scheme still remain, but at least one important difference between it and the prokaryotic scheme (Figure 2) is evident. That is the location of the essential stem loop in the mRNA. This difference is sufficient to account for the failure of attempts to express eukaryotic selenoprotein messages in prokaryotic systems (51). In fact,

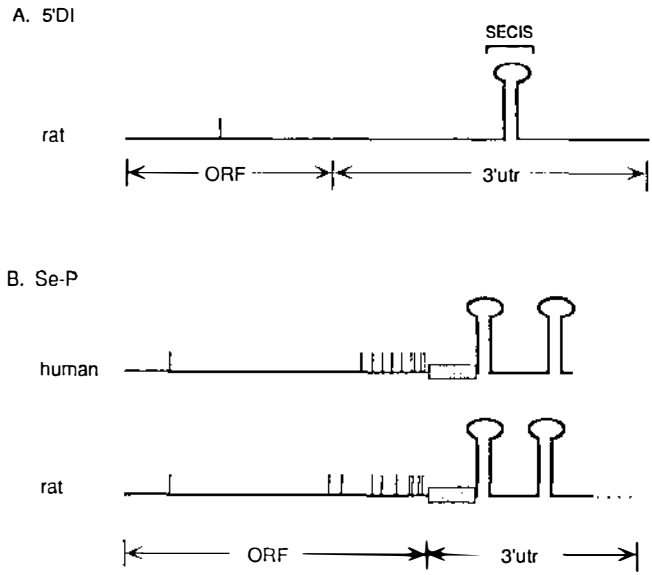

Figure 4 Features of the mRNAs of 5′DI (*A*) and Se-P (*B*). The mRNAs are shown as a *line* with the ORF and the 3′utr indicated by the *arrows* below. The positions of UGA codons, corresponding to selenocysteine residues in protein, are marked by *vertical lines* arising from the ORF. 5′DI contains one (11) and Se-P contains ten (41). The SECIS motif is indicated in the 3′utr of the 5′DI (10). It contains a stem-loop structure necessary for readthrough of the UGA as selenocysteine (see text). Comparison of rat and human Se-P mRNAs reveals two conserved stem loops, which appear to be SECIS motifs (40). In addition, the first 261 bases of the 3′utr (shown as a *shaded box*) are highly conserved. The function of this segment is unknown.

it is even possible that different eukaryotic systems might be incompatible with one another. A better understanding of the process of selenocysteine synthesis and incorporation into protein by eukaryotes will be required before all potential sites of regulation of selenoprotein synthesis can be identified.

SELENOPROTEIN SYNTHESIS IN SELENIUM DEFICIENCY

Posttranslational Effects

cGSH-Px has been studied in selenium deficiency more than any other selenoprotein. A fall in the activity of the enzyme uniformly accompanies the development of deficiency. An early hypothesis of selenoprotein synthesis proposed posttranslational modification of a serine or a cysteine in the primary structure of the protein. Replacement of serine oxygen or cysteine sulfur by

selenium posttranslationally was supposed to yield selenocysteine in the primary structure of the protein. In selenium deficiency, the precursor protein would have been expected to accumulate. Several studies sought such a precursor protein by comparing cGSH-Px activity with protein levels measured using antibodies. No evidence of an inactive precursor protein was found (45, 71). Even though the posttranslational modification hypothesis is now known to be incorrect, these experiments provided useful information. They indicate that no protein recognizable by the polyclonal antibody preparation accumulates in selenium deficiency. This includes the polypeptide terminating at the UGA codon for selenocysteine. Thus, these experiments suggest that regulation of cGSH-Px synthesis by selenium deficiency occurs at the level of translation initiation or before.

Limited information is available on turnover of selenoproteins in selenium deficiency. The half-life in rat plasma of ^{75}Se administered intravenously as eGSH-Px was approximately 12 h and the half-life of ^{75}Se administered as Se-P was 3–4 h. Neither was affected by selenium deficiency (20). Thus, there is no evidence that selenium deficiency affects turnover of selenoproteins.

Levels of mRNA

The synthesis rates of many proteins are regulated by changes in the concentration of their mRNAs. The effect of selenium deficiency on cGSH-Px mRNA has been examined. Most groups have noted a fall in this mRNA in rodent liver as a consequence of selenium deficiency (42, 55, 64, 72), although one group did not (47). Transcription rate can determine mRNA levels, so nuclear run-on studies were performed to assess the effect of selenium deficiency on the synthesis of cGSH-Px mRNA. No effect was found (47, 64), even when mRNA levels were very low. This implies that regulation of mRNA by selenium status resides at a posttranscriptional site.

No studies that examine mRNA degradation or activation in selenium deficiency have been reported. Such processes are likely to underlie the mRNA regulation related to selenium status. Comparison of 3′ utr of human and rat Se-P mRNAs reveals two segments of highly conserved sequence (Figure 4*B*). Part of the first segment and all of the second one consist of predicted stem-loop structures thought to facilitate decoding of the UGAs. However, no function is known for the portion of the first conserved segment between the open reading frame and the stem-loop structure. Possibly this segment is involved in regulation of the mRNA.

Regulation of mRNAs of individual selenoproteins could serve as a means of using limited amounts of selenium in the most efficient manner. Thus selenoproteins of greatest importance to survival of the organism could be preserved by decreasing mRNA (and thus synthesis) of less essential

selenoproteins. Evidence of such a differential regulation of selenoprotein mRNAs has been presented (42). Rats were fed a selenium-deficient diet for 14.5 weeks and liver mRNA levels were compared with levels in control livers. cGSH-Px mRNA levels were 3% of control while those of Se-P were 19% of control. This finding provides an explanation for the observation that selenium supplied to selenium-deficient rats led to a rapid rise in Se-P concentration but that cGSH-Px activity appearance was delayed (20). These results strongly suggest that the synthesis of individual selenoproteins can be controlled by regulation of mRNA level.

Supply of Selenium

Regulation of mRNA is not the only mechanism by which selenium status affects selenoprotein synthesis. Cultured cells deprived of selenium exhibit a fall in cGSH-Px activity without a concomitant fall in its mRNA (22). In the study discussed above in which mRNAs of cGSH-Px and Se-P fell to 3% and 19% of control, respectively, cGSH-Px activity was 0.8% of control and Se-P concentration was 4.3% of control (42). Thus, there was an additional effect beyond that of mRNA decrease, and it was approximately the same for both selenoproteins. This suggests that supply of selenium in the form needed for incorporation into protein can limit selenoprotein synthesis.

Figures 2 and 3 illustrate that the supply of selenium to the ribosome is a complex process and involves many gene products that might be affected by selenium status. Studies in bacteria involving expression of selenoproteins indicate that individual gene products can limit selenoprotein synthesis under these conditions (56). A preliminary report indicates that selenium status affects the editing of the $tRNA^{[Ser]Sec}$ in animal tissues (37). The function of these two forms of the $tRNA^{[Ser]Sec}$ is not known, but possibly each form favors a different mRNA population and thus changes in the forms would regulate selenoprotein synthesis. That is speculation and will require study. Other steps in the scheme for eukaryotes will have to be characterized and studied in selenium deficiency. At present, results indicate that the selenium supply affects selenoprotein synthesis. No direct evidence indicates that this effect varies from one selenoprotein to another, but so little is known about this process in eukaryotes that further work will be needed before a conclusion can be reached.

OTHER FACTORS INFLUENCING SELENOPROTEIN LEVELS

Selenoprotein expression varies by species and by tissue. The activity of cGSH-Px is very low in guinea pig liver and kidney in comparison to the activity in the same rat tissues, but the activity in red cells is comparable in

the two species. A recent report studied cGSH-Px mRNA levels and transcription rates in guinea pig tissues (43). mRNA levels and transcription rates were very low in liver and kidney, thus accounting for the low enzyme activity. Values were higher in reticulocytes and erythroblast-enriched bone marrow. Thus, tissue differences in this enzyme would appear to be determined by transcriptional regulation.

Clinical circumstances other than selenium deficiency can influence the activities of cGSH-Px (35) and 5′DI (12). Little is known about the mechanisms of these effects and whether selenium is involved.

CONCLUSIONS

1. The synthesis of selenoproteins is a complex process that has been characterized in detail in prokaryotic systems. Several steps of the process have not been characterized in eukaryotic systems, and a full understanding of its regulation in them will be possible only after the process has been completely characterized.
2. Levels of selenoproteins fall in selenium deficiency as a result of decreased synthesis.
3. The supply of selenium appears to have a general effect on synthesis of selenoproteins. When selenium supply is limiting, synthesis of all selenoproteins is depressed.
4. Selenoproteins are also regulated individually through changes in their mRNA levels. This allows maintenance of some selenoproteins at the expense of others when selenium supply is limiting.
5. Expression of selenoproteins varies between species and tissues. Limited evidence suggests that transcriptional regulation accounts for this variation of expression.

SUMMARY

Selenium exerts its biological activity largely through selenoproteins, which contain the element in the form of selenocysteine. Five selenoproteins have been characterized in animal tissues and there is evidence that a number of others exist. Selenoprotein synthesis is a complex process that has been well characterized in prokaryotic systems but incompletely characterized in eukaryotic systems.

Selenium deficiency causes a decrease in selenoproteins, but the decrease is not uniform and some selenoproteins are maintained better than others. The selenoprotein most sensitive to selenium deficiency is liver cGSH-Px. It contains a significant fraction of the selenium in the body, and decreased synthesis of it under deficiency conditions might serve to increase the selenium

available for synthesis of selenoproteins that are more important to the survival of the animal than is cGSH-Px.

The regulation of individual selenoproteins in selenium deficiency appears to be at the mRNA level. Factors that affect mRNA levels have not been completely characterized, but the fall in cGSH-Px mRNA in rat liver is not accompanied by decreased transcription, which suggests that it is regulated through changes in degradation.

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