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Review

Selenoproteins and maternal nutrition

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ABSTRACT

Selenium (Se) is an essential trace element of fundamental importance to health due to its antioxidant, anti-inflammatory and chemopreventive properties attributed to its presence within at least 25 selenoproteins (Sel). Sel include but not limited to glutathione peroxidases (GPx1–GPx6), thioredoxin reductases (TrxR1–TrxR3), iodothyronine deiodinases (ID1–ID3), selenophosphate synthetase 2 (SPS2), 15-kDa Sel (Sel15), SelH, SelI, SelK, SelM, SelN, SelO, SelP, SelR, SelS, SelT, SelV, SelW, as well as the 15-kDa Sel (Fep15), SelJ and SelU found in fish. In this review, we describe some of the recent progress in our understanding of the mechanisms of Sel synthesis. The impact of maternal Se intake on offspring is also discussed. The key regulatory point of Sel synthesis is Se itself, which acts predominantly at post-transcriptional levels, although recent findings indicate transcriptional and redox regulation. Maternal nutrition affects the performance and health of the progeny. Both maternal and offspring Se supplementations are essential for the antioxidant protection of the offspring. Prenatal Se supplementation provides an effective antioxidant system that is already in place at the time of birth while, postnatal Se supplementation becomes the main determinant of progeny Se status after the first few days of progeny life.

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1. Selenoproteins

Maternal nutrition affects performance and health of the progeny because all nutrients required by the developing offspring are transferred from the dam *via* either the placenta, the colostrum and the milk or the egg (Hamal et al., 2006). Environmental stress factors, such as undernourishment appearing prenatally in the dam can affect the developing fetus postnatally (Merlot et al., 2008). In this context, the hypothesis of "fetal programming" was described (Jones et al., 2007). This hypothesis asserts that disorders of adult life may originate in adaptations that the fetus makes when it is undernourished (Barker

Abbreviations: Se, Selenium; Sel, Selenoproteins; GPx, Glutathione peroxidase; TrxR, Thioredoxin reductase; DIO, Iodothyronine deiodinase family; ID, Type of Iodothyronine deiodinase; SPS2, Selenophosphate synthetase 2; Sel15, 15-kDa selenoprotein; Fep15, 15-kDa selenoprotein found in fish; ROS, Reactive oxygen species; Sec, Selenocysteine; H_2O_2, Hydrogen peroxide; dNTP, Deoxynucleotides; SeMet, Selenomethionine; H_2Se, Hydrogen selenide; SECIS, Selenocysteine insertion sequence; SBP2, Selenocysteine insertion sequence binding protein 2; EFSec, Selenocysteine specific elongation factor; ARE, Antioxidant response element; NMD, Nonsense-mediated decay pathway; eIF2, Global initiation factor 2; IRES, Internal ribosomal entry site.

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et al., 1993; Fowden and Forhead, 2004). This is the reason why maternal nutrition has received substantial attention in the recent years. In avian species, maternal nutrition is of importance because all the nutrients required by the developing embryo are pre-deposited inside the egg by the hen. Maternal nutrition affects the offspring short-termly during embryonic development and long-termly during development either postnatal (Dunstan et al., 2007) or posthatch (Pappas et al., 2006b).

The neonate is exposed to oxidative stress conditions because the extrauterine environment has much more oxygen than the intrauterine one (Przybylska et al., 2007). Similarly, in avian species, hatching is a time of stress because the bird is exposed in the oxygen of the air and the swift from the chorioallantoic respiration (respiration with the extraembryonic membranes) to pulmonary appears. Furthermore, the rate of aerobic metabolism accelerates dramatically to meet the needs of locomotion and endothermy (Hohtola and Visser, 1998). All the aforementioned stress conditions stimulate reactive oxygen species (ROS) generation by a decrease of coupling of oxidation and phosphorylation in the mitochondria that results in an increased electron leakage and overproduction of superoxide radicals. Living cells permanently balance the process of formation and inactivation of ROS and as a result ROS level remains low but still above zero. Once ROS production exceeds the ability of antioxidant system to neutralize them, lipid peroxidation develops and causes damage to unsaturated lipids in cell membrane and cell integrity is disrupted. Membrane damage of cells in gastrointestinal tract is associated with a decreased efficiency of absorption of different nutrients and leads to an imbalance of vitamins, amino acids, inorganic elements and other nutrients in the organism. All these events result in decreased productive and reproductive performance of animals. Free radical overproduction and oxidative stress are considered as a pathobiochemical mechanism involved in the initiation or progression phase of various diseases. The first postnatal hours are crucial for the neonate because if an insufficient colostrum intake appears or if there is a disturbance in the intestinal permeability then low concentration of maternal immunoglobulins may be transferred and this may lead to poor immunity (Przybylska et al., 2007). In other animal species, maternal exposure to stress conditions during the end of gestation may affect the active transplacental transfer of IgG (primates) or lower the IgG content of maternal colostrum (ungulates) or affect intestinal absorption in neonates (Merlot et al., 2008). In the newly hatched chick, the immune system is immature and not fully functional (Apanius, 1998; Hamal et al., 2006). Indeed, for the first days posthatch the chick is poorly protected from various infections, since the immune system is based mainly on maternal antibodies transferred from the parent bird *via* the egg. Maternal antibodies are comprised of many different types of immunoglobulins, but the three major classes are IgG (in avian species IgG is also called IgY), IgM and IgA (Lundqvist et al., 2006). Immunoglobulins are deposited mainly in the yolk and absorbed into the circulatory system by the chick. It has been reported that the amount of IgY transferred to the egg yolk is proportional to the maternal serum IgY concentration (Hamal et al., 2006).

Selenium (Se) is an essential trace mineral of fundamental importance to health. It is known primarily for its antioxidant activity

Table 1
Selenoproteins and brief description of their functions

Selenoprotein	Abbreviation	Cellular distribution/tissues/species	Function
Cytosolic glutathione peroxidase	GPx1	Cytosol	Antioxidant protection
Gastrointestinal glutathione peroxidase	GPx2	Gastrointestinal tract	Antioxidant protection
Plasma glutathione peroxidase	GPx3	Extracellular space and plasma	Maintenance of cellular redox status
Phosholipid hydroperoxide glutathione peroxidase	GPx4	Cell membrane, many other tissues	Detoxification of lipid hydroperoxides
Epididymal glutathione peroxidase	GPx5	Restricted expression to epididymis	Antioxidant protection during spermiogenesis and sperm maturation
Olfactory glutathione peroxidase	GPx6	Olfactory epithelium, embryonic tissues	Antioxidant protection
Non-selenocysteine containing phospholipid glutathione peroxidase	GPx7 (NPGPx)	Many tissues	Unknown, possible role in alleviating oxidative stress in breast cancer cells
Thioredoxin reductase Type I	TRxR1	Cytosol, liver, kidney, heart	Part of the thioredoxin system. Antioxidant defense, redox regulation, cell signaling
Thioredoxin reductase Type II	TRxR2	Mitochondria, liver kidney	Part of the thioredoxin system. Antioxidant defense, redox regulation, cell signaling
Thioredoxin reductase Type III	TRxR3	Testes	Part of the thioredoxin system. Antioxidant defense, redox regulation, cell signaling
Iodothyronine deiodinase Type I	ID1	Many tissues like liver, kidney, thyroid	Conversion of T4 to T3 and T4 to reverse T3
Iodothyronine deiodinase Type II	ID2	Liver, kidney, thyroid, brown adipose tissue	Conversion of T4 to T3
Iodothyronine deiodinase Type III	ID3	Placenta, brain, skin, (not in pituitary, thyroid, adult liver)	Conversion T4 to reverse T3
Selenophosphate synthetase	SPS2	Testes, many other tissues	Synthesis of selenophosphate
15-kDa selenoprotein	Sel15	Endoplasmatic reticulum, T cells, many other tissues	Role in cell apoptosis and mediation of chemopreventive effects of Se
Selenoprotein H	SelH		Not fully known, possible upregulation of genes involved in glutathione synthesis
Selenoprotein I	SelI		Studies with *Escherichia coli* showed specific ethanolamine-phosphotransferase activity
Selenoprotein K	SelK	Cardiomyocytes	Possible antioxidant protection in cardiomyocytes
Selenoprotein M	SelM	Brain and other tissues	Distantly related to Sel15. May be involved in cancer etiology
Selenoprotein N	SelN	Endoplasmatic reticulum	It is linked with rigid spine syndrome
Selenoprotein O	SelO	Widely distributed	Unknown
Selenoprotein P	SelP	Plasma, other tissues	Involved in Se transport, antioxidant defense
Selenoprotein R	SelR	Cytosol, nucleus	Reduction of oxidized methionine residues in damaged proteins
Selenoprotein S	SelS	Endoplasmatic reticulum	Cellular redox balance. Possible influence of inflammatory response
Selenoprotein T	SelT	Ubiquitous	Role in regulation of Ca^{2+} homeostasis and neuroendocrine secretion
Selenoprotein V	SelV	Testes	Unknown, possible role in redox regulation
Selenoprotein W	SelW	Heart and other tissues	Antioxidant protection
Fish 15-kDa Selenoprotein	Fep 15	Endoplasmatic reticulum	Fish homologue of Sep15
Selenoprotein J	SelJ	Restricted to actinopterygian fishes and sea urchin	Structural role
Selenoprotein U	SelU	Fish and chicken but not higher eukaryotes	Unknown

and for its anti-inflammatory, chemopreventive and antiviral properties (Rayman, 2000). Unlike metals that interact with proteins in form of cofactors, Se as metalloid becomes cotranslationally incorporated into the polypeptide chain as part of the amino acid selenocysteine (Sec). Proteins that contain Sec as an integral part of their polypeptide chain are defined as selenoproteins (Sel) (Table 1). Sel are present in all lineages of life (*i.e.*, bacteria, archaea and eukarya). Much of Se beneficial influence on health is attributed to its presence within at least 25 Sel (Kryukov et al., 2003; Kryukov and Gladyshev, 2004; Castellano et al., 2005; Zhang et al., 2005).

In recent years, several families of mammalian and human Sel have been cloned and partially characterized with respect to their function (Gladyshev and Hatfield, 1999; Köhrle et al., 2000; Birringer et al., 2002; Kryukov et al., 2003). In detail, glutathione peroxidase family (GPx) which is comprised of at least 6 members (GPx1–GPx6) has a strong antioxidant role in cell cytosol (GPx1), gastrointestinal tract (GPx2), extracellular space and plasma (GPx3) and in cell membrane and sperm (GPx4). The latter one is also known as phosholipid hydroperoxide GPx due to its role in detoxification of lipid peroxides inside the membrane of the cell. GPx5 is called epididymal GPx due to its restricted expression in the epididymis (Surai, 2006). The newly discovered GPx6 is located in olfactory epithelium and embryonic tissues with unknown function (Vaishnav et al., 2008). Recently, the expression of the non-Sec (no selenocysteine) containing phospholipids hydroperoxide glutathione peroxidase (NPGPx or GPx7) in breast cancer cells has been reported (Utomo et al., 2004). The major function of these peroxidases is considered to be the removal and detoxification of hydrogen peroxide (H_2O_2) and lipid hydroperoxides. Maintenance of cellular redox state is another important function. In addition, GPx are involved in such physiological events as differentiation, signal transduction and regulation of pro-inflammatory cytokine production (Moghadaszadeh and Beggs, 2006). Another role of these enzymes is the antioxidant defense during spermiogenesis, maturation of spermatozoa and embryonic development (Ursini, 2000). The thioredoxin reductase (TrxR) family has at least 3 members (TrxR1, TrxR2 and TrxR3). All of them are involved in the thioredoxin system, which also involves other non-Sec containing proteins like thioredoxin and thioredoxin peroxidase. The biological role of the system is to provide antioxidant defense, regulate other antioxidant enzymes, modulate several transcription factors, regulate apoptosis and modulate protein phosphorylation (Surai, 2006). Iodothyronine deiodinase (DIO) family is comprised of 3 types, namely the ID1, ID2 and ID3 with several defined roles in thyroid metabolism. Types ID1 and ID2 convert thyroxin (T4) to bioactive 3,5,3′-tri-iodothyronine (T3) while types ID1 and ID3 convert T4 to 3′,3′,5′ reverse T3, which is a less bioactive form than T3.

Other Sel that may not be part of a family have been annotated in alphabetic order and include, but not limited to, the selenophosphate synthetase 2 (SPS2), 15-kDa selenoprotein (Sel15), SelH, SelI, SelK, SelM, SelN, SelO, SelP, SelR, SelS, SelT, SelV, and SelW. Furthermore, in fish the 15-kDa selenoprotein (Fep15), SelJ and SelU have been identified. While the role of them is largely unknown, SPS2 is involved in the synthesis of selenophosphate for Sel synthesis (Beckett and Arthur, 2005). Sel15 seems to play a role in cell apoptosis and mediation of chemopreventive effects of Se (Papp et al., 2007). SelH regulates the expression levels of genes involved in *de novo* glutathione synthesis and phase II detoxification in response to redox status (Panee et al., 2007). SelI function is still elusive with current research pointing that its expression in *Escherichia coli* shows cytidine diphosphate ethanolamine-specific phosphatidyltransferase activity (Horibata and Hirabayashi, 2007). SelK is a newly identified Sel with potent antioxidant properties in cardiomyocytes (Lu et al., 2006). SelM is distantly related to Sel15. It may be involved in the early-onset of Alzheimer's disease and play a role in cancer etiology (Kumaraswamy et al., 2000; Korotkov et al., 2002). SelN is a glycoprotein localized within the endoplasmic reticulum. It is directly linked to the rigid spine muscular dystrophy and the classical form of multiminicore disease (Petit et al., 2003). SelO is a widely distributed protein that has homologs in animals, bacteria, yeast and plants, but its function is unknown (Gladyshev, 2006). SelP is an abundant extracellular glycoprotein that is rich in Sec. It is involved in Se transport and antioxidant actions on endothelium. Evidence supports functions of the protein in Se homeostasis, antioxidant defense and transport and delivery of Se to remote tissues (Burk and Hill, 2005). Furthermore, plasma SelP seems to be a better indicator of Se nutritional status than the previously used GPx3 (Papp et al., 2007) because full expression of SelP requires a greater Se intake than does full expression of GPx3 (Xia et al., 2005). SelR contains also zinc and catalyzes the stereospecific reduction of oxidized methionine residues in damaged proteins with thioredoxin as reductant showing antiaging and neurologic properties (Kryukov et al., 2002; Kim and Gladyshev, 2004). SelS may be implicated in the retrotranslocation of misfolded proteins from the endoplasmic reticulum of mammalian cells to the cytosol where these proteins are further degraded. SelS is related to the regulation of cellular redox balance and may be implicated in the control of inflammation response (Kryukov et al., 2003; Curran et al., 2005). SelT has recently been found to play a role in the regulation of Ca^{2+} homeostasis and neuroendocrine secretion in response to a cAMP-stimulating trophic factor (Köhrle et al., 2005; Grumolato et al., 2008). SelV has a homology to SelW. It is expressed exclusively in testes. The protein contains specific amino acid sequence motives that predict a role in redox regulation. Its function is still unknown (Kryukov et al., 2003). Finally, SelW seems to be implicated in antioxidant protection of cardiac and skeletal muscle (Whanger, 2000).

Recent research has revealed the existence of few more proteins that share the features of Sel namely, SelX, SelZf1, SelZf2 (Lescure et al., 1999) 18 kDa Sel (Kyriakopoulos et al., 2002) and several other Sel of low molecular weight ranging from 3 to 7 kDa (Kyriakopoulos et al., 2000). The physiological function of the aforementioned ones has not yet been identified. Regarding the Sel found in fish, the Fep15 is homologous to the mammalian Sel15 and is present in the endoplasmic reticulum and possibly in Golgi. Its role is still elusive (Gladyshev, 2006). SelJ has unknown functional role but has structural role in contrast to the majority of known selenoenzymes (Castellano et al., 2005) SelU is found in fish, chickens, sea urchins, a green alga and a diatom but not in higher eukaryotes. Its function is not known (Castellano et al., 2004). It seems that most of these Sel exhibit redox functions like biosynthesis of desoxynucleotides (dNTP) for nucleic acids, removal of damaging or signaling peroxides, reduction of oxidized proteins and membranes, regulation of redox signaling, thyroid hormone metabolism, selenium transport and storage and potentially protein folding.

2. Synthesis of selenoproteins from dietary Se

Selenomethionine (SeMet) and the 21st amino acid, Sec, are identical to methionine and cysteine except that the sulphur (S) atom is replaced by Se (Combs and Combs, 1984; Whanger, 2000). SeMet is an essential amino acid synthesized only by plants, yeast and some bacteria. Plants absorb Se from the soil in the form of selenite or selenate and synthesize SeMet (Rayman, 2004). That means that Se in natural feed ingredients is mainly in the form of SeMet (Combs, 2001). Vertebrates receive dietary Se in the forms of SeMet and other Se-amino acids including Se-cysteine and its methylated forms depending on their contents in feed/food components. In addition, currently the feeds for farm animals are widely supplemented with inorganic Se sources like sodium selenite and sodium selenate as well as with organic form of Se, e.g. selenized yeast. There are principal differences in absorption and metabolism of these forms of selenium. Sodium selenite is passively absorbed in the intestine and more efficiently in the ileum segment of the intestine (Pesti and Combs, 1976; Wolffram

et al., 1985; Shennan, 1988; Würmli et al., 1989; Huang et al., 1994; Park and Whanger, 1995). SeMet is the primary organic Se in plant material and it is actively absorbed *via* methionine transport mechanisms (Vendeland et al., 1994). Since it is actively absorbed in the intestine, it requires a transport mechanism to actually move the molecules through the enterocyte cell membrane, by all segments of the intestine (Wolffram, 1999). In the chicken jejunum, L-methionine is transported by four transport systems, the two of them are specific for neutral amino acids (L- and B-like) and the other two systems can also transport cationic amino acids (y^+m and $b^{0,+}$-like) (Soriano-García et al., 1998, 1999). Regarding the SeMet synthesis, Se may compete with S for methionine. Increasing consumption of Se leads to higher S replacement by Se thus higher SeMet content could be expected (Köhrle et al., 2005). However, it is not clear whether there is a saturation of this process. Köhrle et al. (2005) reported that there is no evidence for either saturation or a significant altered function of metabolism of SeMet containing proteins compared to the Met ones. On the contrary, an excessive substitution of S by Se in amino acid residues may lead to a progressive inactivation of proteins/enzymes (Mikkelsen et al., 1989).

The oxidized forms of inorganic Se (selenite or selenate) undergo reductive metabolism yielding hydrogen selenide (H_2Se) which is converted to Sel. Organic sources of Se can also be used for the production of H_2Se. SeMet can be trans-selenated into SeCys, similarly to the trans-sulfuration pathway for methionine to cysteine, before lysis by β-lyase to H_2Se. In order for H_2Se to be converted to Sel, it has first to be transformed to Sec. This means that H_2Se has to be metabolized into selenophosphate which then reacts with the tRNA specific for serine ($tRNA^{Ser(Sec)}$) *via* the enzyme Sec tRNA synthase to give Sec bound tRNA from which Sec is inserted into Sel by the codon specific to Sec the UGA (Böck, 2000; Combs, 2001; Lacourciere and Stadtmanm, 2001; Rayman, 2004). The unique feature of the Sec incorporation into proteins is that it uses the UGA codon for translation. This was originally believed to function as a stop codon, a codon that terminates the process of translation. This incorporation occurs when the mRNA contains a distinct hairpin mRNA sequence downstream of the UGA codon in its 3′-untranslated region (3′-UTR) called Sec insertion sequence (SECIS) or Sec translation element. SECIS prevents termination of the translation by competing for release factors that would otherwise lead to disassembly of the mRNA-ribosomal complex (Chambers et al., 1986; Böck et al., 1991; Shen et al., 1995; Low and Berry, 1996). The high regulation of this process is further achieved by the binding of several specific proteins by SECIS. Namely, SECIS recruits SECIS-binding protein 2 (SBP2) (Copeland and Driscoll, 1999) and binds the Sec-specific elongation factor (EFSec) loaded with its $tRNA^{Sec}$. Several other proteins that bind to SECIS are currently being investigated (Fujiwara et al., 1999; Copeland et al., 2000; Copeland and Driscoll, 2001; Schomburg et al., 2004). As reported recently by Dumitrescu et al. (2005) mutations in SBP2 lead to impaired Se status and reduced expression of several Sel, including GPx3, ID2 and SelP, resulting in abnormal thyroid hormone metabolism.

3. Selenoproteins and health

Se is essential for life and adequate amounts of this element are required for optimal animal and human health. Se content of plant is affected by the Se content of the soil and its availability for the plants (e.g. acidic soils contain Se in elemental form, which is not available for plants). Furthermore, the Se content of animal products reflects the Se content and availability in the diet consumed by the animal (Barclay et al., 1995). The Se content of foods that comprise the diet varies geographically and this variation is reflected in the dietary intake of Se in each country. Se bioavailability is affected by its chemical form (part of organic molecule vs. inorganic) and other dietary factors such as total protein, fat and the presence of heavy metals content (Surai, 2006). According to recent studies, human population of many countries in Europe and other parts of the world still have a dietary Se intake below of that of 55 μg/day recommended by health regulatory bodies such as the Institute of Medicine in USA (Combs, 2001; Rayman, 2005). Most notably, in the UK the daily Se intake is 34 μg/day (Barclay et al., 1995), in Austria is 48 μg/day (Wilplinger et al., 1998), in Switzerland is 70 μg/day (Foster and Sumar, 1997), in the Netherlands is 67 μg/day (Foster and Sumar, 1997) and in Greece is 39.3 μg/day (Pappa et al., 2006). In the UK, the recommended dose is 75 μg/day for men and 60 μg/day for women (Committee on Medical Aspects of Food Policy, 1991). These recommendations were based on the GPx3 optimal enzyme activity (Thomson et al., 1993; Duffield et al., 1999). A recent study indicated that higher Se intake is required to obtain full expression of SelP. It was suggested that SelP may be a better indicator of Se nutritional status than GPx3 and that the recommended dietary intake may need to be revised (Xia et al., 2005).

The precise molecular mechanisms behind the effects of Se in physiologic and in pathologic conditions remain unknown. Many of its physiologic roles are directly attributed to its presence within Sel. Moderate Se deficiency has been linked to many conditions, such as increased cancer and infection risk, male infertility, decrease in immune and thyroid function, and several neurologic conditions, including Alzheimer's and Parkinson's disease (Rayman, 2000). For some of these conditions, the evidence is rather scant, lacks consensus and must be further demonstrated. Keshan disease is a potentially fatal form of cardiomyopathy, prevalent in children and endemic in parts of China with extremely low levels of Se in the soil (intake, ≤10 μg/day). Infection by Coxsackie B virus is believed to trigger the onset of this disease (Li et al., 1985; Levander and Beck, 1997). Remarkably, the condition is preventable or completely reversible by Se supplementation (Reeves et al., 1989; Xia et al., 2005). The actual mechanism for this protective effect is currently unknown. Furthermore, myxedematous cretinism, which is a condition, characterized by mental and growth retardation is attributed to a combined Se and iodine deficiency (Vanderpas et al., 1990). It is believed that Se deficiency causes a reduction in GPx and DIO enzymes activity resulting in accumulation of H_2O_2 causing damage to the thyroid gland, and impaired thyroid hormone metabolism (Contempre et al., 1995; Zimmermann and Köhrle, 2002). Se supplementation during this condition must be administered after iodide levels have been restored, as Se increases the activity of DIO, leading to a further loss of iodide from the damaged thyroid (Zimmermann and Köhrle, 2002).

At times of low-Se intake, the reserves built up in the tissues start to diminish. The rate of depletion is different among different tissues. Brain, endocrine and reproductive organs maintain the Se levels for longer period compared to liver, muscle and skin that rapidly lose their Se content (Behne et al., 1988). The hierarchy of Se retention during Se depletion exists not only among organs but also among Sel. During depletion, Se is rapidly mobilized from GPx1 stores, whereas expression of other Sel such as GPx4, GPx2, ID2, ID3 and TrxR is hardly affected or may even be increased, like in case of ID1. This hierarchy is reflected and in the level of mRNA with some mRNAs to be preferentially translated into Sel (Grundner-Culeman et al., 1999; Low et al., 2000). It should be mentioned that those proteins residing high in the hierarchy of Se retention during Se depletion also appear to lead in the priority for repletion (Hill et al., 1992; Bermano et al., 1995; Gross et al., 1995; Lei et al., 1995; Mitchell et al., 1998; Driscoll and Copeland, 2003).

4. Selenoproteins and lactation

The lactating mammary gland is an essential source of trace elements for the suckling newborn. Se is present in breast milk at concentrations, which depend on the concentration and form of Se in dam's food. In turn, the Se concentrations in natural foods consumed by the dam reflect the Se content of the soils where these plants are grown. In humans, the median Se concentration from studies at

different parts of the world is 26 μg/l in colostrum (0–5 days), 18 μg/l in transitional milk (6–21 days), 15 μg/l in mature milk (1–3 months) and 17 μg/l in late lactation milk (5 months) (Dorea, 2002). Se is incorporated in milk proteins as a component of specific selenoamino acids such as selenocystamine, Sec, selenocystine and SeMet (Milner et al., 1987). The mammary gland regulates the synthesis and secretion of selenocompounds throughout lactation. Dorea (2002) reported that the Se level in the colostrum is initially high and decreases as lactation progresses. The same author attributed this decline to the reduction of milk protein content, which is higher in the colostrum compared to the late lactation milk.

Although the Se content of breast milk is influenced by maternal Se intake, mechanisms of Se complexation with S-containing amino acids modulate Se incorporation into milk proteins (Dorea, 2002). Organic Se will be incorporated into milk proteins while inorganic will not do so until incorporated into Sec. In dairy animals and sows, selenite and selenate supplements were only as half as effective as Se yeast in raising total colostrum and milk Se content (Ortman and Pehrson, 1999; Surai, 2006). Se supplementation of cows feed during the last 60 days of gestation not only greatly increased endogenous Se reserves of newborn calves but also resulted in an improved Se status that still was present in calves at 42 days of age. The mechanisms that control nutrient utilization during pregnancy are not well defined.

Mammalian milk is fundamental for an infant's optimum Se status (Ortman and Pehrson, 1999). Maternal Se deficiency induces oxidative stress in the fetus, as measured by increased generation of lipid peroxides in the fetal liver, and impairs the development of the neonatal immune system. It has been shown that formula-fed human babies may exhibit lower Se and GPx blood levels compared to breast fed ones (Fraga et al., 1988; Trafikowska et al., 1998). Mothers deficient in selenium, even if they were breast feeding could improve milk Se status if they were to eat foods rich in Se. Fish and meat products are considered as good sources of Se although its bioavailability can vary (Pappa et al., 2006). Premature babies and extremely low-birth weight infants exhibit Se and GPx blood level deficiencies that were not associated with specific deficits such as hypothyroidism (Klinger et al., 1999; Sievers et al., 2001).

Not only Se but iodine as well is present in milk and actively concentrated and secreted by the mammary gland (Thomson et al., 2001). There is indication of cell-, proliferation- and differentiation-specific distribution of the Sel ID1 and ID2 in the lactating mammary gland of rats. During lactation, ID1 expression is increased in the lactating gland and decreased in liver (Valverde and Aceves, 1989). Expression of ID1 is restricted to the differentiated alveolar epithelium in the gland and stimulated by suckling (Aceves et al., 1995, 1999). GH and oxytocin have no effect on ID1 expression levels whereas norepinephrine enhances both mRNA levels and enzyme activity. In addition, prolactin increases ID1 activity but not transcript levels (Aceves et al., 1999). Constitutive expression of ID2 is confined to the nonepithelial cells, fibroblasts and fat pads in the mammary gland. Breast ID2 activity varies along the estrous cycle, with the lowest activity in diestrus (Capuco et al., 1989; Fujimoto et al., 1998).

Expression of proteins that reversibly bind Se and do not contain Sec, in contrast to Sel, has been linked to inhibition of mammary tumor cell growth (Morrison et al., 1988; Hwang and Milner, 1996). Such kind of proteins include, but not limited to, the 56-kDa and 58-kDa proteins (Morrison and Medina, 1989; Bansal et al., 1991; Bansal and Medina, 1993). In mice, an inhibition of mammary tumor cell growth has been linked to the expression of 56-, 58-kDa protein (Morrison et al., 1988). The 56-kDa protein, also present in human tissues, was found to exert prostate tumor cell growth inhibitory properties; this may be of importance regarding the antiproliferative actions of Se compounds (Yang and Sytkowski, 1998). Regulation of normal and tumor cell growth has been linked to TrxR, which has recently been identified in mammary tumor cell line. TrxR expression is stimulated (37-fold) by selenite treatment (Gallegos et al., 1997). The functional relevance of these findings for tumor cell growth and gene expression is of interest firstly because not all tumor cells express TrxR and secondly because Se-dependent apoptosis, cell and tumor growth, and stimulation of TrxR activity differ significantly between cell lines and among various tumors. Recent studies found inhibitory effects of both low (<0.1 ppm) and high (2.25 ppm) selenite supply on tumor development (Novoselov et al., 2005). Expression of several Sel was altered, and 3β-hydroxysteroid dehydrogenase as well as other enzymes involved in detoxification reactions were expressed at higher levels. These observations warn against indiscriminate Se administration for prevention or treatment of all tumor forms.

5. Selenoproteins in female reproduction

Se is transported with the action of SelP which contains Se in the form of Sec and is the major Se transporting protein (Burk and Hill, 2005; Surai, 2006). Placental transfer is bi-directional and this may affect the net retention of Se in maternal, fetal and neonatal tissues (Lee et al., 1995). It is still elusive whether Se rapidly passes the human placenta or is actually concentrated in placental tissues (Eisenmann and Miller, 1994). Both inorganic and organic Se regulate the expression of SelP. Feeding sodium selenite to sows did not change total Se reserves of newly born piglet indicating that Se supplemented in this form, although undergoes reductive metabolism yielding hydrogen selenide, is not efficiently transferred *via* placenta. On the other hand, inclusion into the sow's diet organic selenium in the form of Se-yeast doubled total Se reserves in the piglet showing Se transfer *via* placenta (Surai, 2006). It seems that the transport process may be a more complex action than a simple passive transport mechanism (Korpela et al., 1984).

Rat placental Se content and expression of Sel concomitantly increase during gestation. Uterus is a tissue where many Sel such as SelP, ID3 and TrxR are expressed (Bou-Resli et al., 2001). SelP expression in mouse uterus and placenta alters as gestation progresses with elevated expression levels appearing 4 days before birth and maximal expression levels at term. Preterm SelP expression is also observed in fetal mouse liver (Kasik and Rice, 1995). The uterus of the rat, where the embryo is embedded, expresses extremely high levels of ID3 mRNA. The ID3 expression is time (by gestational day 9) and region (epithelial lining cells of the uterine lumen) specific, which suggests an important role in the control of thyroid hormone availability to the embryo (Galton et al., 1999). This high expression of ID3 at the implantation site is assumed to prevent exposure of the developing fetus to excess thyromimetic T3. Similarly, in human placental cell, ID3 activity increases with gestational age (Koopdonk Kool et al., 1996).

There are a lot of factors that are in play in the placenta and the uterus. In human and rodent placenta, Trx and TrxR have region specific expression. In detail, they are localized histochemically in cytotrophoblasts, decidua and stromal cells in the stem villi. Their role is protective for the placental tissues during inflammation (Ejima et al., 1999a,b). There are interactions between Sel and hormonal events. In the uterus, but not in the liver, of ovariectomized rats, expression of Trx mRNA is stimulated by estradiol, androgen and 5α-dihydrotestosterone, but not progesterone. The combined treatment by estradiol and the antiestrogen (ICI 182780) or by testosterone together with the antiandrogen flutamid attenuated the stimulatory effect of the hormones alone (Sahlin et al., 1999; Yin et al., 1999). These findings indicate that Trx regulation is mediated *via* steroid hormone receptors possibly coupled to growth-promoting effects of steroids in this tissue. In human endometrial stromal cells, rapid Trx expression at the mRNA and protein level is induced by estradiol, augmented by progesterone and inhibited by tamoxifen. Although Trx itself did not promote endometrial cell growth, it enhanced the epidermal growth factor induced mitogenic effect (Maruyama et al., 1999). Se not only stimulates proliferation of bovine granulosa cells from small follicles,

but also potentiates the stimulatory action of gonadotropins on estradiol secretion. Bovine FSH stimulates estradiol production in cells from large follicles in the absence of Se. Its action on cells from small follicles requires addition of Se. In rat cultured ovarian follicles, GPx mimics the ability of FSH to suppress apoptosis (Tilly and Tilly, 1995).

6. Se levels and regulation of mammalian Sel expression

Se has a narrow window between deficiency and excess and its essentiality and toxicity are well described. Highly controlled mechanisms must be in place to sustain optimal concentrations of Se within cells. Sel expression is regulated by Se itself. It is not surprising the finding that Se is a key regulator of its incorporation into Sel and acts predominantly at post-transcriptional levels, with recent findings indicating that Se may also act at transcriptional levels (Brigelius-Flohe and Banning, 2006).

Several experimental data denote that the expression of certain Sel depends on the level of Se. For example, using a polarized pig thyrocyte culture-system, the role of Se-dependent expression of GPx activity for thyrocyte integrity and protein iodination was demonstrated. H_2O_2 exposure of Se-depleted thyrocytes with low GPx activity presented cytoplasmatic iodination of proteins whereas, in Se-adequate thyrocytes with sufficient GPx activity iodination of proteins was restricted to the apical surface irrespective of exogenous H_2O_2 (Ekholm and Björkman, 1997). This finding indicates that Se-depleted cells, devoid of sufficient antioxidative defense capacity, may experience aberrant intracellular iodination of proteins, leading to deleterious events such as apoptosis, exposure of unusual epitopes, misrecognition by the immune system, or aberrant targeting and processing of iodinated proteins. Se also has a protective role against cytotoxic H_2O_2 effects mediated by caspase-3-dependent apoptosis in primary culture pig thyrocytes (Demelash et al., 2004). These observations may provide an experimental biochemical basis for the pathogenesis of myxedematous endemic cretinism and a rationale for beneficial effects of Se supplementation reported in studies with patients suffering from Hashimoto's autoimmune thyroid disease (Gartner et al., 2002; Duntas et al., 2003).

Both excess and deficiency of Se supply lead to impaired growth. Most notably, Se intake (5.0 mg/kg feed) in the form of sodium selenite causes growth retardation, accumulation of Se in somatotrophs, lack of growth hormone response to GHRH and an 80% reduction in serum IGF-I (somatomedin C) in infant rats. In addition, it induces a slight reduction in serum albumin and occasionally slight centrolobular liver necrosis (Thorlacius-Ussing et al., 1988a). The exact mechanisms involved are not fully elucidated, but inhibition of GH secretion might be caused by Se accumulation in secretory vesicles (Thorlacius-Ussing et al., 1987). In rats, three weeks after withdrawal of selenite excess the growth was restored and GH response to GHRH was normalized, but IGF-I production remained decreased, and signs of liver damage also persisted, including elevated serum alanine aminotransferase and albumin (Thorlacius-Ussing et al., 1988b). High doses of GH administered to rats during excess selenite exposure also restored growth, indicating that circulating levels of IGF-I do not reflect local events at the growth plates and suggesting direct action of GH or paracrine GH-dependent mechanisms (Thorlacius-Ussing et al., 1988a). Long-term treatment of rats with sodium selenite in drinking water (3.3 mg/L water) decreased serum GH, IGF-I, and IGF binding protein-1, -2, and -3 levels and resulted in growth retardation (Thorlacius-Ussing et al., 1988a; Gronbaek et al., 1995). However, recent studies with ruminants fed at least 10 times the maximum permitted European Union (EU) Se dietary inclusion rate in the form of Se-enriched yeast derived from a specific strain of *Saccharomyces cerevisiae* revealed no adverse effects on animal health, performance, and feed intake (Juniper et al., 2008). In EU, the maximum authorized total Se contents in feeds, background Se plus supplemented one, for farm animals is 0.5 mg/kg of complete feeding stuffs with a moisture content of 12% (European Union Commission, 2004). It seems that the form of Se added to the diet (*i.e.* sodium selenite or organo-Se compounds) plays an important role on the appearance or not of adverse toxicological effects on animal growth and that is well documented in several recent reviews (Letavayová et al., 2006; Schrauzer, 2000).

Regulation of deiodinase enzymes and conversion of thyroid hormones is affected by Se levels. Iodine deficiency increases the activity of ID2, whereas it is decreased by selenium deficiency. The stimulation of ID2 activity under iodine-deficient conditions is a compensatory mechanism that maintains local T3 homeostasis to some extent (Moreno-Reyes et al., 2006). Se deficiency inhibits growth response in animals and Se deficiency can result in elevated T4 levels and decreased T3 levels. In experiments with Se-deficient rats T4 increased T4 by 67% compared to control treatment and T3 decreased by 23% compared to control treatment (Thompson et al., 1995). In the same study, repletion of Se in second-generation Se-deficient male and female weanling rats normalized serum thyroid hormones, liver Se content and GPx activity. Injection of T3 to these animals restored normal thyroid hormone levels but did not restore growth. The fact that selenium supplementation improved growth in selenium-deficient rats, whereas T3 infusion did not, indicates that restoration of ID2 activity may have a greater effect on bone metabolism than increased circulating T3 (Moreno-Reyes et al., 2006).

7. Transcriptional regulation

Transcriptional regulation provides another regulatory point of Sel expression. The Nrf2/Keap1 system is one of the major cellular defense mechanisms against oxidative stress (Motohashi and Yamamoto, 2004). NF-E2-related factor 2 (Nrf2) is the most effective transcription factor that acts through "antioxidant response element" (ARE), a member of the NF-E2 family of basic leucine zipper transcription factors (Itoh et al., 1997). Kelch-like ECH-associated protein-1 (Keap1) is a cysteine-rich actin associated protein that keeps Nrf2 complexed in the cytosol (Kang et al., 2004). Nrf2/Keap1 regulates the expression of phase 2 detoxification enzymes and redox active proteins, including TrxR1 (Motohashi and Yamamoto, 2004). It was recently demonstrated that GPx2 is a target of this transcriptional system and may be up-regulated (Banning et al., 2005). The Nrf2/Keap1 system is important due to its activation by electrophilic compounds, metals, thiol modifiers, and other potential anticarcinogenic compounds derived from dietary sources (Brigelius-Flohe and Banning, 2006). Whether Se or Se metabolites also act as an activator of this system, thus controlling global or specific Sel synthesis at a transcriptional level remains an exciting area for future investigation. Transcriptional regulation of additional GPx family members extends beyond the Nrf2/Keap1 system and has been recently reviewed (Brigelius-Flohe, 2006). A complex transcriptional regulation pattern involving interplay between several transcription factors, such as Oct-1, Sp1, Sp3 and multiple transcription start sites in a cell has been reported for the TrxR1 gene (Rundlof and Arner, 2004). Characterization of the promoter region and transcriptional regulation of the GPx4 gene also has been reported (Maiorino et al., 2003; Imai et al., 2006). An interesting, speculative question is whether all or some Sel genes contain potential Se-response elements. Such Se-response elements may allow a more efficient regulation of their synthesis at the transcriptional level in response to alterations in Se supplies.

8. Post-transcriptional regulation

Recent reviews have indicated that Sel synthesis is regulated at post-transcriptional level (Behne and Kyriakopoulos, 2001; Hatfield and Gladyshev, 2002; Driscoll and Copeland, 2003; Schomburg et al., 2004; Caban and Copeland, 2006). Behne and Kyriakopoulos (2001) working with cell-culture models found a hierarchy in Sel expression

during Se deprivation and repletion. The same authors showed that some tissues and organs are more efficient in maintaining Se levels and the production of certain Sel during Se deprivation compared to other ones. This is indicative of differences in the requirements and biologic roles of Sel in different tissues (Brigelius-Flohe, 1999; Behne and Kyriakopoulos, 2001).

Se exerts its regulatory action on mRNA stability since in cases of Se deficiency an increased susceptibility to the nonsense-mediated decay pathway (NMD) and consequently decay of mRNA have been noted (Moriarty et al., 1998; Maquat, 2001; Weiss Sachdev and Sunde, 2001). Efficiency control of UGA-Sec codon translation (Fletcher et al., 2000; Martin and Berry, 2001), regulation of total Sec $tRNA^{Ser(Sec)}$ levels and regulation of the ratio between the methylated and unmethylated Sec $tRNA^{Ser(Sec)}$ isoforms are influenced by Se (Hatfield et al., 1991; Chittum et al., 1997; Jameson et al., 2002; Carlson et al., 2005). Recent data demonstrated that the methylated isoform of $tRNA^{[Ser]Sec}$ is translationally active and that Se-induced tRNA methylation is a mechanism of regulation of the synthesis of Sel (Jameson and Diamond, 2004). Evidence demonstrating that the two Sec $tRNA^{[Ser]Sec}$ isoforms control the expression of distinct Sel was provided in transgenic mice rescued with either a wild-type *trsp*, or a methylation mutant *trsp* transgene (Carlson et al., 2005). It was discovered that the methylated isoform controls the synthesis of Sel involved in the oxidative stress response such as GPx1 and GPx3, whereas the unmethylated form governs synthesis of housekeeping Sel such as TrxR1 and TrxR3. Another regulatory point of Sel synthesis is provided through availability of essential *trans*-acting factors (Driscoll and Copeland, 2003). In HEK293T cells, endogenous SBP2 levels appear to be sufficient for maximal Sel synthesis whereas, in human embryonic kidney cells (HEK293), SBP2 overexression is necessary for a significant increase of Sel synthesis (de Jesus et al., 2006). Papp et al. (2006), using (small interfering) siRNA technology demonstrated that depletion of SBP2 leads to a general decrease in Sel synthesis indicating that *trans*-acting factors are necessary for Sel synthesis regulation.

9. Redox regulation

Redox regulation has emerged as an essential regulatory process of many pathways in cell biology (Linke and Jakob, 2003; Ghezzi, 2005). Disruption of the intracellular redox balance leads to a state of oxidative stress, during which proteins, nucleic acids, lipids, and other macromolecules can suffer severe damage (Surai, 2006). Oxidative stress appears to be a major factor in aging. It has been implicated in numerous diseases such as Alzheimer's, diabetes and cancer (Berlett and Stadtman, 1997; Kovacic and Jacintho, 2001; Aliev et al., 2002).

TrxRs and GPxs, through the action of Sec within their catalytic sites, serve housekeeping redox functions. This is mediated by controlling the activity of cellular proteins and scavenging free radicals. These antioxidant enzymes respond to oxidative stress by inducing gene expression and by changing their activity and subcellular localization (Hirota et al., 1997; Karimpour et al., 2002; Hattori et al., 2005). The enzyme conformational changes result in activation or deactivation of gene expression and changes in activity (Nordberg and Arnér, 2001; Xia et al., 2003). Comparison of the conformational similarities and differences of Sec and other amino acids involved in enzymatic activity (selenocysteine, cysteine and serine), reveals that Se atom is larger than both the S and the O atoms and has longer bond lengths. As a result, the Se atom has greater polarizability, and is therefore a better nucleophile (Hegedus et al., 2005).

In response to cellular stress conditions, protein translation is reduced allowing the cells to conserve resources in order to initiate a reconfiguration of gene expression (Holcik and Sonenberg, 2005). This response is regulated by inhibitory phosphorylation of the global initiation factor 2 (eIF2) (Fernandez et al., 2001; Dunand-Sauthier et al., 2005; Wek et al., 2006) and by a simultaneous switch to the cap-independent, internal ribosomal entry site (IRES)-mediated translation. This kind of response allows production of a selected set of proteins required for cell survival, proliferation or apoptosis depending on the severity of the stress (Fernandez et al., 2001; Nevins et al., 2003). It can be concluded that regulation of Sel synthesis is a complicated process involving redox regulation of SBP2 through the thioredoxin and glutaredoxin systems.

10. Impact of maternal Se intake on offspring

Biological mechanisms regulating normal postnatal growth and nutrient utilization are programmed during fetal development (Godfrey and Barker, 2000). Maternal undernutrition from early to mid gestation leads to growth retardation, cardiac ventricular hypertrophy and increased liver weight in the fetal sheep (Vonnahme et al., 2003). The impact of maternal intake on fetal body weight at 90th and 130th day of gestation was investigated and was reported that ewes restricted to 60% of controls had reduced fetal body weight at 130th day (Scheaffer et al., 2004). Furthermore, Reed et al. (2007) factorialized supranutritional levels of Se (3 ppm) with nutrient restriction (60% of controls) and reported that in ewes the supranutritional levels of Se can increase fetal body weight. In fact, the increase in fetal body weight was greater in restricted animals than it was in controls, suggesting that Se in this study may have provided a sparing effect on fetal body weight (Godfrey and Barker, 2000).

Undernourishment of specific nutrients during gestation can negatively affect progeny. The amount of Se received by cows during grazing can fluctuate due to different available Se soil concentrations (Hintze et al., 2001, 2002). Dylewski et al. (2002) evaluated the impact of dietary Se intake on rat neonatal immune cell differentiation and function. A low-Se intake during pregnancy and lactation produced reductions in the Se content of maternal plasma, milk and neonatal plasma. Thymocytes from neonates receiving low-Se milk showed an impaired activation in vitro. The percentages of CD8 cytotoxic T cells, CD2 T cells, panB cells and natural killer cells were all decreased in neonates nursed by mothers fed a low-Se diet. The results indicate that maternal Se intake impacts neonatal Se status which in turn influences the neonatal immune system development.

There is increasing evidence that Se supplementation of the maternal diet may be important for the development of the progeny. In mammals, Se is transferred *via* the placenta and the mammary gland. Se in the colostrum is part of selenoamino acids that are well tolerated by the progeny (Przybylska et al., 2007). In avian species, Se is deposited in the yolk and the albumen as well as the shell and the shell membranes of the egg (Pappas et al., 2005b). In chicken, inclusion of Se in the maternal diet could have an effect on embryo viability, hatchability and growth of the progeny (Pappas et al., 2005a, 2006a,b). These authors investigated the persistence of the effects of maternal nutrition on the progeny by examining prepeak (23 weeks) and peak (27 weeks) production breeders that were fed 1 of 4 diets: a wheat-based commercial breeder diet with 55 g/kg of either soybean oil (SO) or fish oil (FO), but no added Se (only that originating from feed ingredients) and each diet with added Se in the organic form as Se yeast (SO+Se, FO+Se). The diets were designed to contain <0.1 mg/kg of Se and about 0.5 mg/kg of Se for the non supplemented (no added Se) and the supplemented diets, respectively. The effects of maternal nutrition on the concentration of DHA of the progeny persisted for 14 days post hatch because for up to 14 days posthatch, chicks from hens fed diets high in PUFA (FO, FO+Se) had higher concentrations of DHA in the brain and liver compared with chicks hatched from hens fed diets low in PUFA (SO, SO+Se). Similarly chicks hatched from hens fed diet rich in Se (FO+Se, SO+Se) had higher concentration of Se in the tissues than the progeny originating from breeders fed diets low in Se (FO, SO). All the differences noted for up to 14 days posthatch are attributable to the differences of maternal diets. Furthermore, Se had a strong antioxidant role because the DHA content of the tissues of chicks from breeders fed diets supplemented with Se

was higher than that in chicks from breeders fed unsupplemented diets. This indicates that supplementation of the maternal diet of chicks with organo-Se appears to enhance the DHA concentration of the chick brain, which may improve brain function.

To investigate the effects of maternal nutrition on antioxidant enzyme activity, Hostetler and Kincaid (2004) fed a low-Se diet in pigs during gestation and noted an increased fetal oxidative stress, as measured by fetal liver H_2O_2 and MDA. Hostetler et al. (2006) examined if levels of mRNA encoding GPx1 change during porcine fetal development, and if maternal Se intake during gestation (unsupplemented and supplemented with 0.15 ppm Se as sodium selenite) affects the mRNA levels of this protein. They noted that during late gestation fetal liver mRNA levels of GPx1 decreased regardless of the sow's dietary treatment. Comparison of fetal and maternal porcine liver with real time PCR showed that mRNA levels of GPx1 were about 3.5 times lower in fetal liver during compared to maternal ones. These results indicate that neonatal pigs are born with reduced GPx1 activity corresponding to reduced GPx1 mRNA levels supporting the hypothesis expressed by other authors (Mahan and Kim, 1996; Hostetler and Kincaid, 2004) that newborn pigs, regardless of maternal Se intake, have lower GPx activity in serum and liver compared with the dam.

In chicken, it was demonstrated that the effects of maternal nutrition in the activity of GPx in the liver of the progeny persisted for 5 days posthatch (Surai et al., 1999). This was concluded because chicks originating from breeders fed diets supplemented with 0.4 mg/kg Se in the form of Se yeast had higher activity of GPx in the liver for at least 5 days posthatch compared to chicks hatched from breeders fed diets that were not supplemented with Se and contained 0.044 mg/kg Se. In a study with cross over design, hens and progeny were fed with either a diet unsupplemented in Se (only that originating from the feed ingredients) or a diet supplemented with organic Se (Pappas et al., 2005b). This resulted in 4 progeny treatments designated as follows: LL (parents and offspring fed low-Se diets), LH (parents fed low-Se, offspring fed high-Se diets), HL (parents fed high-Se, offspring fed low-Se diets), and HH (parents and offspring fed high-Se diets). When the offspring from the two parental groups were both maintained on the low-Se progeny diet, (HL and LL treatments) the tissue Se concentrations in chicks originating from the high-Se hens (HL) remained significantly higher for 3 (in liver) to 4 weeks (in breast muscle) after hatching, compared with the values in chicks from the low-Se hens (LL). Effects of maternal nutrition persist for up to 4 weeks post hatch. Taking into account and the 3 weeks required for embryonic development maternal effects can persist for up to 7 weeks. Regarding the action of antioxidant enzymes, the same authors reported that tissue glutathione peroxidase activity remained significantly higher in chicks from the high-Se hens (HL) for 2–4 weeks posthatch compared to the activity found in the tissues of the chicks of the LL treatment. Thus, selenium concentration can elevate GPx activity during the early postnatal development and provide the necessary protection to the developing chick. In the same study it was noted that when chicks hatching from low-Se eggs were placed on a high-Se diet (LH), their tissue Se concentrations at 7 days of age were as high as the values in chicks from high-Se eggs placed on the low-Se diet (HL). This means that after the first week, progeny nutrition can elevate the Se status of the progeny to a concentration equal with that achieved by maternal nutrition at hatch (Pappas et al., 2005b). These results reveal the cruciality of the first week of posthatch development. Recently, it was reported that Se stored in tissues could be utilized to maintain plasma GPx activity during period of low-Se intake (Payne and Southern, 2005) and this might be true for the other selenoproteins as well. During development of the chick embryo, the activity of GPx in the liver increases (Gaal et al., 1995). GPx is expressed in the day-old chicken in a tissue-specific manner with the liver and kidney having the highest GPx activity (Surai et al., 1999).

The effect of the source of Se to the GPx activity is not so clear. In detail, Mahmoud and Edens (2003) demonstrated that GPx activity in both blood and liver of broilers fed diets supplemented with organo-selenium compounds was higher than the activity of broilers fed diets with sodium selenite. However, no different effects of sodium selenite and selenized yeast on plasma or blood GPx activities have been demonstrated in experiments with pigs (Mahan and Parret, 1996) and poultry (Kuricová et al., 2003).

In order to understand the role of maternal nutrition we should avail ourselves findings from studies that reveal the role of trace elements and gene expression. Rao et al. (2001) reported that SeMet could influence gene expression in the intestine of the mouse. These authors reported that low intake of a SeMet (Se level of diet was less than 0.01 mg/kg) can have broad effects on gene expression patterns. In detail, they reported that the low-Se status can up regulate genes involved in DNA damage and oxidative stress and decrease the expression (down-regulate) of genes involved in detoxification. The results of the aforementioned study indicate that suboptimal intake of a single trace element can influence gene expression. Under this context, it was found that maternal diet can influence gene expression in the intestine of the progeny and in that way affect the functionality of the intestine, which in turn can affect the intestinal health (Rebel et al., 2006). In detail, these authors noted prenatal nutrition can affect metabolic pathways in the offspring and influence the number of proliferating cells in the villus thus influence the intestinal development (Rebel et al., 2006). Both prenatal and postnatal Se supplementations are essential for the offspring antioxidant system. Prenatal Se supplementation provides an effective antioxidant system that is already in place at the time of birth and postnatal Se supplementation becomes the main determinant of progeny Se status after the first few days of progeny life.

References

Aceves, C., Rodon, C., Ramirez-C, I., Wilson, S., Pineda, O., Lopez, L., Mancilla, R., Valverde-R, C., 1995. Mammary 5′-deiodinase (5′D) during breeding cycle of the rat: indirect evidence that 5′D type I is specific to the alveolar epithelium. Endocrine 3, 95–99.

Aceves, C., Pineda, O., Ramirez, I., de la Luz Navarro, M., Valverde, C., 1999. Mammary type I deiodinase is dependent on the suckling stimulus: differential role of norepinephrine and prolactin. Endocrinology 140, 2948–2953.

Aliev, G., Smith, M.A., Seyidov, D., Neal, M.L., Lamb, B.T., Nunomura, A., Gasimov, E.K., Vinters, H.V., Perry, G., LaManna, J.C., Friedland, R.P., 2002. The role of oxidative stress in the pathophysiology of cerebrovascular lesions in Alzheimer's disease. Brain Pathol. 12, 21–35.

Apanius, V., 1998. Ontogeny of immune function. In: Starck, M.J., Ricklets, R.E. (Eds.), Avian Growth and Development: Evolution Within the Altricial–Precocial Spectrum. Oxford University Press, Oxford, UK, pp. 203–222.

Banning, A., Deubel, S., Kluth, D., Zhou, Z., Brigelius-Flohe, R., 2005. The GI-GPx gene is a target for Nrf2. Mol. Cell Biol. 25, 4914–4923.

Bansal, M.P., Medina, D., 1993. Expression of fatty acid-binding proteins in the developing mouse mammary gland. Biochem. Biophys. Res. Commun. 191, 61–69.

Bansal, M.P., Ip, C., Medina, D., 1991. Levels and 75-Se-labeling of specific proteins as a consequence of dietary selenium concentration in mice and rats. Proc. Soc. Exp. Biol. Med. 196, 147–154.

Barclay, M.N.I., MacPherson, A., Dixon, J., 1995. Selenium content of a range of UK foods. J. Food Compos. Anal. 8, 307–318.

Barker, D.J.P., Godfreyn, K.M., Gluckman, P.D., Harding, J.E., Owens, J.A., Robinson, J.S., 1993. Fetal nutrition and cardiovascular disease in adult life. Lancet 341, 938–941.

Beckett, G.J., Arthur, J.R., 2005. Selenium and endocrine systems. J. Endocrinol. 184, 455–465.

Behne, D., Kyriakopoulos, A., 2001. Mammalian selenium-containing proteins. Annu. Rev. Nutr. 21, 453–473.

Behne, D., Hilmert, H., Scheid, S., Gessner, H., Elger, W., 1988. Evidence for specific selenium target tissues and new biologically important selenoproteins. Biochim. Biophys. Acta 966, 12–21.

Berlett, B.S., Stadtman, E.R., 1997. Protein oxidation in aging, disease and oxidative stress. J. Biol. Chem. 272, 20313–20316.

Bermano, G., Nicol, F., Dyer, J.A., Sunde, R.A., Beckett, G.J., Arthur, J.R., Hesketh, J.E., 1995. Tissue-specific regulation of selenoenzyme gene expression during selenium deficiency in rats. Biochem. J. 311, 425–430.

Birringer, M., Pilawa, S., Flohe, L., 2002. Trends in selenium biochemistry. Nat. Prod. Rep. 19, 693–718.

Böck, A., 2000. Biosynthesis of selenoproteins—an overview. Biofactors 11, 77–78.

Böck, A., Forchhammer, K., Heider, J., Leinfelder, W., Sawers, G., Veprek, B., Zinoni, F., 1991. Selenocysteine: the 21st amino acid. Mol. Microbiol. 5, 515–520.

Bou-Resli, M.N., Dashti, H.M., Mathew, T.C., Al-Zaid, N.S., 2001. Pre- and postnatal tissue selenium of the rat in the growing state. Biol. Neonate 80, 169–172.
Brigelius-Flohe, R., 1999. Tissue-specific functions of individual glutathione peroxidases. Free Radic. Biol. Med. 27, 951–965.
Brigelius-Flohe, R., 2006. Glutathione peroxidases and redox-regulated transcription factors. Biol. Chem. 387, 1329–1335.
Brigelius-Flohe, R., Banning, A., 2006. Part of the series: from dietary antioxidants to regulators in cellular signaling and gene regulation: sulforaphane and selenium, partners in adaptive response and prevention of cancer. Free Radic. Res. 40, 775–787.
Burk, R.F., Hill, K.E., 2005. Selenoprotein P: an extracellular protein with unique physical characteristics and a role in selenium homeostasis. Annu. Rev. Nutr. 2, 215–235.
Caban, K., Copeland, P.R., 2006. Size matters: a view of selenocysteine incorporation from the ribosome. Cell. Mol. Life Sci. 63, 73–81.
Capuco, A.V., Keys, J.E., Smith, J.J., 1989. Somatotrophin increases thyroxine-5′-monodeiodinase activity in lactating mammary tissue of the cow. J. Endocrinol. 121, 205–211.
Carlson, B.A., Xu, X.M., Gladyshev, V.N., Hatfield, D.L., 2005. Selective rescue of selenoprotein expression in mice lacking a highly specialized methyl group in selenocysteine tRNA. J. Biol. Chem. 280, 5542–5548.
Castellano, S., Novoselov, S.V., Kryukov, G.V., Lescure, A., Blanco, E., Krol, A., Gladyshev, V.N., Guigo, R., 2004. Reconsidering the evolutionary distribution of eukaryotic selenoproteins: a novel non-mammalian family with scattered phylogenetic distribution. EMBO Rep. 5, 71–77.
Castellano, S., Lobanov, A.V., Chapple, C., Novoselov, S.V., Albrecht, M., Hua, D., Lescure, A., Lengauer, T., Krol, A., Gladyshev, V.N., Guigo, R., 2005. Diversity and functional plasticity of eukaryotic selenoproteins: identification and characterization of the SelJ family. Proc. Natl. Acad. Sci. U. S. A. 102, 16188–16193.
Chambers, I., Frampton, J., Goldfarb, P., Affara, N., McBain, W., Harrison, P.R., 1986. The structure of the mouse glutathione peroxidase gene: the selenocysteine in the active site is encoded by the 'termination' codon, TGA. EMBO J. 5, 1221–1227.
Chittum, H.S., Baek, H.J., Diamond, A.M., Fernandez-Salguero, P., Gonzalez, F., Ohama, T., Hatfield, D.L., Kuehn, M., Lee, B.J., Hatfield, D., Hampton, L., 1997. Selenocysteine $tRNA^{[Ser]Sec}$ levels and selenium-dependent glutathione peroxidase activity in mouse embryonic stem cells heterozygous for a targeted mutation in the $tRNA^{[Ser]Sec}$ gene: selenium induces changes in the selenocysteine $tRNA^{[Ser]Sec}$ population in mammalian cells. Biochemistry 36, 8634–8639.
Combs Jr., G.F., 2001. Selenium in global food systems. Br. J. Nutr. 85, 517–547.
Combs, G.F., Combs, S.B., 1984. The nutritional biochemistry of selenium. Annu. Rev. Nutr. 4, 257–280.
Committee on Medical Aspects of Food Policy, 1991. Dietary reference values for food energy and nutrients for the UK report on health and social subjects No. 41. London: HM Stationary Office.
Contempre, B., Dumont, J.E., Denef, J.F., Many, M.C., 1995. Effects of selenium deficiency on thyroid necrosis, fibrosis and proliferation: a possible role in myxedematous cretinism. Eur. J. Endocrinol. 133, 99–109.
Copeland, P.R., Driscoll, D.M., 1999. Purification, redox sensitivity, and RNA binding properties of SECIS-binding protein 2, a protein involved in selenoprotein biosynthesis. J. Biol. Chem. 274, 25447–25454.
Copeland, P.R., Driscoll, D.M., 2001. RNA binding proteins and selenocysteine. Biofactors 14, 11–16.
Copeland, P.R., Fletcher, J.E., Carlson, B.A., Hatfield, D.L., Driscoll, D.M., 2000. A novel RNA binding protein, SBP2, is required for translation of mammalian selenoprotein mRNAs. EMBO J. 19, 306–314.
Curran, J.E., Jowett, J.B.M., Elliott, K.S., Gao, Y., Gluschenko, K., Wang, J., Azim, D.M.A., Cai, G., Mahaney, M.C., Comuzzie, A.G., Dyer, T.D., Walder, K.R., Zimmet, P., MacCluer, J.W., Collier, G.R., Kissebah, A.H., Blangero, J., 2005. Genetic variation in selenoprotein S influences inflammatory response. Nat. Genet. 37, 1234–1241.
de Jesus, L.A., Hoffmann, P.R., Michaud, T., Forry, E.P., Small-Howard, A., Stillwell, R.J., Morozova, N., Harney, J.W., Berry, M.J., 2006. Nuclear assembly of UGA decoding complexes on selenoprotein mRNAs: a mechanism for eluding nonsense-mediated decay? Mol. Cell. Biol. 26, 1795–1805.
Demelash, A., Karlsson, J.O., Nilsson, M., Bjorkman, U., 2004. Selenium has a protective role in caspase-3-dependent apoptosis induced by H2O2 in primary cultured pig thyrocytes. Eur. J. Endocrinol. 150, 841–849.
Dorea, J.G., 2002. Selenium and breast-feeding. Br. J. Nutr. 88, 443–461.
Driscoll, D.M., Copeland, P.R., 2003. Mechanism and regulation of selenoprotein synthesis. Annu. Rev. Nutr. 23, 17–40.
Duffield, A.J., Thomson, C.D., Hill, K.E., Williams, S., 1999. An estimation of selenium requirements for New Zealanders. Am. J. Clin. Nutr. 70, 896–903.
Dumitrescu, A.M., Liao, X.-H., Abdullah, M.H.S., Lado-Abeal, J., Majed, F.A., Moeller, L.C., Boran, G., Schomburg, L., Weiss, R.E., Refetoff, S., 2005. Mutations in the SBP2 gene produce abnormal thyroid hormone metabolism in man. Nat. Genet. 37, 1247–1252.
Dunand-Sauthier, I., Walker, C.A., Narasimhan, J., Pearce, A.K., Wek, R.C., Humphrey, T.C., 2005. Stress-activated protein kinase pathway functions to support protein synthesis and translational adaptation in response to environmental stress in fission yeast. Eukaryotic Cell 4, 1785–1793.
Dunstan, J.A., Mitoulas, L.R., Dixon, G.L.E.N., Doherty, D.A., Hartmann, P.E., Simmer, K.A. R.E., Prescott, S.L., 2007. The effects of fish oil supplementation in pregnancy on breast milk fatty acid composition over the course of lactation: a randomized controlled trial. Pediatr. Res. 62, 689–694.
Duntas, L.H., Mantzou, E., Koutras, D.A., 2003. Effects of a six month treatment with selenomethionine in patients with autoimmune thyroiditis. Eur. J. Endocrinol. 148, 389–393.
Dylewski, M.L., Mastro, A.M., Picciano, M.F., 2002. Maternal selenium nutrition and neonatal immune system development. Biol. Neonate 82, 122–127.
Eisenmann, C.J., Miller, R.K., 1994. The placental transfer and toxicity of selenite relative to cadmium in the human term perfused placenta. Placenta 15, 883–895.
Ejima, K., Nanri, H., Toki, N., Kashimura, M., Ikeda, M., 1999a. Localization of thioredoxin reductase and thioredoxin in normal human placenta and their protective effect against oxidative stress. Placenta 20, 95–101.
Ejima, K., Koji, T., Nanri, H., Kashimura, M., Ikeda, M., 1999b. Expression of thioredoxin and thioredoxin reductase in placentae of pregnant mice exposed to lipopolysaccharide. Placenta 20, 561–566.
Ekholm, R., Björkman, U., 1997. Glutathione peroxidase degrades intracellular hydrogen peroxide and thereby inhibits intracellular protein iodination in thyroid epithelium. Endocrinology 138, 2871–2878.
European Union Commission, 2004. List of the authorised additives in feeding stuffs published in application of Article 9t (b) of Council Directive 70/524/EEC concerning additives in feedingstuffs (2004/C 50/01). Off. J. Eur. Union. 47 (C50), 1–144.
Fernandez, J., Yaman, I., Mishra, R., Merrick, W.C., Snider, M.D., Lamers, W.H., Hatzoglou, M., 2001. Internal ribosome entry site-mediated translation of a mammalian mRNA is regulated by amino acid availability. J. Biol. Chem. 276, 12285–12291.
Fletcher, J.E., Copeland, P.R., Driscoll, D.M., 2000. Polysome distribution of phospholipid hydroperoxide glutathione peroxidase mRNA: evidence for a block in elongation at the UGA/selenocysteine codon. RNA 6, 1573–1584.
Foster, L.H., Sumar, S., 1997. Selenium in health and disease: a review. Crit. Rev. Food Sci. Nutr. 37, 211–228.
Fowden, A.L., Forhead, A.J., 2004. Endocrine mechanisms of intrauterine programming. Reproduction 127, 515–526.
Fraga, J.M., Cervilla, J.R., Cocho, J.A., Fernández-Lorenzo, J.R., 1988. Selenium intake and serum selenium levels in newborn infants under total parenteral nutrition. In: Cosmi, E.V., Di Renzo, G.C. (Eds.), Proc. XI European Congress of Perinatal Medicine, vol. II. CIC Editioni Internationali, Rome, pp. 427–430.
Fujimoto, N., Watanabe, H., Nakatani, T., Roy, G., Ito, A., 1998. Induction of thyroid tumours in (C57BL/6N×C3H/N)F1 mice by oral administration of kojic acid. Food Chem. Toxicol. 36, 697–703.
Fujiwara, T., Busch, K., Gross, H.J., Mizutani, T., 1999. A SECIS binding protein (SBP) is distinct from selenocysteyl-tRNA protecting factor. Biochimie 81, 213–218.
Gaal, T., Mezes, M., Noble, R.C., Dixon, J., Speake, B.K., 1995. Development of antioxidant capacity in tissues of the chick embryo. Comp. Biochem. Physiol. B 112, 711–716.
Gallegos, A., Berggren, M., Gasdaska, J.R., Powis, G., 1997. Mechanisms of the regulation of thioredoxin reductase activity in cancer cells by the chemopreventive agent selenium. Cancer Res. 57, 4965–4970.
Galton, V.A., Martinez, E., Hernandez, A., St Germain, E.A., Bates, J.M., St Germain, D.L., 1999. Pregnant rat uterus expresses high levels of the type 3 iodothyronine deiodinase. J. Clin. Invest. 103, 979–987.
Gartner, R., Gasnier, B.C., Dietrich, J.W., Krebs, B., Angstwurm, M.W., 2002. Selenium supplementation in patients with autoimmune thyroiditis decreases thyroid peroxidase antibodies concentrations. J. Clin. Endocrinol. Metab. 87, 1687–1691.
Ghezzi, P., 2005. Regulation of protein function by glutathionylation. Free Radic. Res. 39, 573–580.
Gladyshev, N.V., 2006. Selenoproteins and selenoproteoms. In: Hatfield, D.L., Berry, M.J., Gladyshev, N.V. (Eds.), Selenium: Its Molecular Biology and Role in Human Health. Springer, pp. 101–112.
Gladyshev, V.N., Hatfield, D.L., 1999. Selenocysteine-containing proteins in mammals. J. Biomed. Sci. 6, 151–160.
Godfrey, K.M., Barker, D.J.P., 2000. Fetal nutrition and adult disease. Am. J. Clin. Nutr. 71, 1344–1352.
Gronbaek, H., Frystyk, J., Orskov, H., Flyvbjerg, A., 1995. Effect of sodium selenite on growth, insulin-like growth factor-binding proteins and insulin-like growth factor-I in rats. J. Endocrinol. 145, 105–112.
Gross, M., Oertel, M., Köhrle, J., 1995. Differential selenium-dependent expression of type I 5'-deiodinase and glutathione peroxidase in the porcine epithelial kidney cell line LLC-PK1. Biochem. J. 306, 851–856.
Grumolato, L., Ghzili, H., Montero-Hadjadje, M., Gasman, S., Lesage, J., Tanguy, Y., Galas, L., Ait-Ali, D., Leprince, J., Guérineau, N.C., Elkahloun, A.G., Fournier, A., Vieau, D., Vaudry, H., Anouar, Y., 2008. Selenoprotein T is a PACAP-regulated gene involved in intracellular Ca^{2+} mobilization and neuroendocrine secretion. FASEB J. 22, 1756–1768.
Grundner-Culeman, E., Martin III, G.W., Harney, J.W., Berry, M.J., 1999. Two distinct SECIS structures capable of directing selenocysteine incorporation in eukaryotes. RNA 5, 625–635.
Hamal, K.R., Burgess, S.C., Pevzner, I.Y., Erf, G.F., 2006. Maternal antibody transfer from dams to their egg yolks, egg whites, and chicks in meat lines of chickens. Poult. Sci. 85, 1364–1372.
Hatfield, D., Lee, B.J., Hampton, L., Diamond, A.M., 1991. Selenium induces changes in the selenocysteine $tRNA^{[Ser]Sec}$ population in mammalian cells. Nucleic Acids Res. 19, 939–943.
Hatfield, D.L., Gladyshev, V.N., 2002. How selenium has altered our understanding of the genetic code. Mol. Cell. Biol. 22, 3565–3576.
Hattori, H., Imai, H., Furuhama, K., Sato, O., Nakagawa, Y., 2005. Induction of phospholipid hydroperoxide glutathione peroxidase in human polymorphonuclear neutrophils and HL60 cells stimulated with TNF-alpha. Biochem. Biophys. Res. Commun. 337, 464–473.
Hegedus, I.L., Sahai, M.A., Labádi, M., Szori, M., Paragi, G., Viskolcz, B., Bottoni, A., 2005. Selenocysteine derivatives I. Sidechain conformational potential energy surface of *N*-acetyl-L-selenocysteine-*N*-methylamide (MeCO-L-Sec-NH-Me) in its β_L backbone conformation. J. Mol. Struct., Theochem 725, 111–125.
Hill, K.E., Lyons, P.R., Burk, R.F., 1992. Differential regulation of rat liver selenoprotein mRNAs in selenium deficiency. Biochem. Biophys. Res. Commun. 185, 260–263.

Hintze, K.J., Lardy, G.P., Marchello, M.J., Finley, J.W., 2001. Areas with high concentrations of selenium in the soil and forages produce beef with enhanced concentrations of selenium. J. Agric. Food Chem. 49, 1062–1067.
Hintze, K.J., Lardy, G.P., Marchello, M.J., Finley, J.W., 2002. Selenium accumulation in beef: effect of dietary selenium and geographical area of animal origin. J. Agric. Food Chem. 50, 3938–3942.
Hirota, K., Matsui, M., Iwata, S., Nishiyama, A., Mori, K., Yodoi, J., 1997. AP-1 transcriptional activity is regulated by a direct association between thioredoxin and Ref-1. Proc. Natl. Acad. Sci. U. S. A. 94, 3633–3638.
Holcik, M., Sonenberg, N., 2005. Translational control in stress and apoptosis. Nat. Rev. Mol. Cell. Biol. 6, 318–327.
Horibata, Y., Hirabayashi, Y., 2007. Identification and characterization of human ethanolaminephosphotransferase1. J. Lipid Res. 48, 503–508.
Hostetler, C.E., Kincaid, R.L., 2004. Maternal selenium deficiency increases hydrogen peroxide and total lipid peroxides in porcine fetal liver. Biol. Trace Elem. Res. 97, 43–56.
Hostetler, C.E., Michal, J., Robison, M., Ott, T.L., Kincaid, R.L., 2006. Effect of selenium intake and fetal age on mRNA levels of two selenoproteins in porcine fetal and maternal liver. J. Anim. Sci. 84, 2382–2390.
Hohtola, E., Visser, G.H., 1998. Development of locomotion and endothermy in altricial and precocial birds. In: Starck, J.M., Ricklets, R.E. (Eds.), Avian Growth and Development: Evolution Within the Altricial–Precocial Spectrum. Oxford University Press, Oxford, UK, pp. 157–173.
Huang, K., Lauridsen, E., Clausen, J., 1994. The uptake of Na-selenite in rat brain. Localization of new glutathione peroxidases in the rat brain. Biol. Trace. Elem. Res. 46, 91–102.
Hwang, K., Milner, J.A., 1996. Intracellular distribution of selenium and the growth of mammary cells in culture. Biol. Trace Elem. Res. 51, 133–147.
Imai, H., Saito, M., Kirai, N., Hasegawa, J., Konishi, K., Hattori, H., Nishimura, M., Naito, S., Nakagawa, Y., 2006. Identification of the positive regulatory and distinct core regions of promoters, and transcriptional regulation in three types of mouse phospholipids hydroperoxide glutathione peroxidase. J. Biochem. 140, 573–590.
Itoh, K., Chiba, T., Takahashi, S., Ishii, T., Igarashi, K., Katoh, Y., Oyake, T., Hayashi, N., Satoh, K., Hatayama, I., Yamamoto, M., Nabeshima, Y., 1997. An Nrf2/small Maf heterodimer mediates the induction of phase II detoxifying enzyme genes through antioxidant response elements. Biochem. Biophys. Res. Commun. 236, 313–322.
Jameson, R.R., Diamond, A.M., 2004. A regulatory role for Sec tRNA$^{[Ser]Sec}$ in selenoprotein synthesis. RNA 10, 1142–1152.
Jameson, R.R., Carlson, B.A., Butz, M., Esser, K., Hatfield, D.L., Diamond, A.M., 2002. Selenium influences the turnover of selenocysteine tRNA$^{[Ser]Sec}$ in Chinese hamster ovary cells. J. Nutr. 132, 1830–1835.
Jones, H.N., Powell, T.L., Jansson, T., 2007. Regulation of placental nutrient transport—a review. Placenta 28, 763–774.
Juniper, D.T., Phipps, R.H., Givens, D.I., Jones, A.K., Green, C., Bertin, G., 2008. Tolerance of ruminant animals to high dose in-feed administration of a selenium-enriched yeast. J. Anim. Sci. 86, 197–204.
Kang, M.I., Kobayashi, A., Wakabayashi, N., Kim, S.G., Yamamoto, M., 2004. Scaffolding of Keap1 to the actin cytoskeleton controls the function of Nrf2 as key regulator of cytoprotective phase 2 genes. Proc. Natl. Acad. Sci. U. S. A. 101, 2046–2051.
Karimpour, S., Lou, J., Lin, L.L., Rene, L.M., Lagunas, L., Ma, X., Karra, S., Bradbury, C.M., Markovina, S., Goswami, P.C., Spitz, D.R., Hirota, K., Kalvakolanu, D.V., Yodoi, J., Gius, D., 2002. Thioredoxin reductase regulates AP-1 activity as well as thioredoxin nuclear localization *via* active cysteines in response to ionizing radiation. Oncogene 21, 6317–6327.
Kasik, J.W., Rice, E.J., 1995. Selenoprotein P expression in liver, uterus and placenta during late pregnancy. Placenta 16, 67–74.
Kim, H.Y., Gladyshev, N.V., 2004. Methionine sulfoxide reduction in mammals: characterization of methionine-R-sulfoxide reductases. Mol. Biol. Cell. 15, 1055–1064.
Klinger, G., Shamir, R., Singer, P., Diamond, E.M., Josefsberg, Z., Sirota, L., 1999. Parenteral selenium supplementation in extremely low birth weight infants: inadequate dosage but no correlation with hypothyroidism. J. Perinatol. 19, 568–572.
Köhrle, J., Brigelius-Flohe, R., Böck, A., Gartner, R., Meyer, O., Flohe, L., 2000. Selenium in biology: facts and medical perspectives. Biol. Chem. 381, 849–864.
Köhrle, J., Jakob, F., Contempré, B., Dumont, J.E., 2005. Selenium, the thyroid, and the endocrine system. Endocr. Rev. 26, 944–984.
Koopdonk Kool, J.M., De Vijlder, J.J., Veenboer, G.J., Ris Stalpers, C., Kok, J.H., Vulsma, T., Boer, K., Visser, T.J., 1996. Type II and type III deiodinase activity in human placenta as a function of gestational age. J. Clin. Endocrinol. Metab. 81, 2154–2158.
Korotkov, K.V., Novoselov, S.V., Hatfield, D.L., Gladyshev, V.N., 2002. Mammalian selenoprotein in which selenocysteine (Sec) incorporation is supported by a new form of sec insertion sequence element. Mol. Cell. Biol. 22, 1402–1411.
Korpela, H., Loueniva, R., Yrjänheikki, E., Kauppila, A., 1984. Selenium concentration in maternal and umbilical cord blood, placenta and amniotic membranes. Int. J. Vit. Nutr. Res. 54, 257–261.
Kovacic, P., Jacintho, J.D., 2001. Mechanisms of carcinogenesis: focus on oxidative stress and electron transfer. Curr. Med. Chem. 8, 773–796.
Kryukov, G.V., Gladyshev, V.N., 2004. The prokaryotic selenoproteome. EMBO Rep. 5, 538–543.
Kryukov, G.V., Kumar, R.A., Koc, A., Sun, Z., Gladyshev, N.V., 2002. Selenoprotein R is a zinc-containing stereo-specific methionine sulfoxide reductase. Proc. Natl. Acad. Sci. U. S. A. 99, 4245–4250.
Kryukov, G.V., Castellano, S., Novoselov, S.V., Lobanov, A.V., Zehtab, O., Guigo, R., Gladyshev, V.N., 2003. Characterization of mammalian selenoproteomes. Science 300, 1439–1443.
Kumaraswamy, E., Malykh, A., Korotkov, K.V., Kozyavkin, S., Hu, Y., Kwon, S.Y., Moustafa, M.E., Carlson, B.A., Berry, M.J., Lee, B.J., Hatfield, D.L., Diamond, A.M., Gladyshev, V.N., 2000. Structure–expression relationships of the 15-kDa selenoprotein gene: possible role of the protein in cancer etiology. J. Biol. Chem. 275, 35540–35547.
Kuricová, S., Boldižárová, K., Grešáková, L., Bobček, R., Levkut, M., Leng, L., 2003. Chicken selenium status when fed a diet supplemented with Se-yeast. Acta Vet. Brno 72, 339–346.
Kyriakopoulos, A., Rothlein, D., Pfeifer, H., Bertelsmann, H., Kappler, S., Behne, D., 2000. Detection of small selenium-containing proteins in tissues of the rat. J. Trace. Elem. Med. Biol. 14, 179–183.
Kyriakopoulos, A., Bertelsmann, H., Graebert, A., Hoppe, B., Kuhbacher, M., Behne, D., 2002. Distribution of an 18 kDa-selenoprotein in several tissues of the rat. J. Trace Elem. Med. Biol. 16, 57–62.
Lacourciere, G.M., Stadtmanm, T.C., 2001. Utilization of selenocysteine as a source of selenium for selenophosphate biosynthesis. Biofactors 14, 69–74.
Lee, A.M., Huel, G., Godin, J., Hellier, G., Sahuquillo, J., Moreau, T., Blot, P., 1995. Inter-individual variation of selenium in maternal plasma, cord plasma and placenta. Sci. Total Environ. 159, 119–127.
Lei, X.G., Evenson, J.K., Thompson, K.M., Sunde, R.A., 1995. Glutathione peroxidase and phospholipid hydroperoxide glutathione peroxidase are differentially regulated in rats by dietary selenium. J. Nutr. 125, 1438–1446.
Lescure, A., Gautheret, D., Carbon, P., Krol, A., 1999. Novel selenoproteins identified in silico and in vivo by using a conserved RNA structural motif. J. Biol. Chem. 274, 38147–38154.
Letavayová, L., Vlčková, V., Brozmanová, J., 2006. Selenium: from cancer prevention to DNA damage. Toxicology 227, 1–14.
Levander, O.A., Beck, M.A., 1997. Interacting nutritional and infectious etiologies of Keshan disease: insights from Coxsackie virus B-induced myocarditis in mice deficient in selenium or vitamin E. Biol. Trace Elem. Res. 56, 5–21.
Li, G.S., Wang, F., Kang, D., Li, C., 1985. Keshan disease: an endemic cardiomyopathy in China. Hum. Pathol. 16, 602–609.
Linke, K., Jakob, U., 2003. Not every disulfide lasts forever: disulfide bond formation as a redox switch. Antioxid. Redox. Signal. 5, 425–434.
Low, S.C., Berry, M.J., 1996. Knowing when not to stop: selenocysteine incorporation in eucaryotes. Trends Biochem. Sci. 21, 203–208.
Low, S.C., Grundner-Culemann, E., Harney, J.W., Berry, M.J., 2000. SECIS-SBP2 interactions dictate selenocysteine incorporation efficiency and selenoprotein hierarchy. EMBO J. 19, 6882–6890.
Lu, C., Qiu, F., Zhou, H., Peng, Y., Hao, W., Xu, J., Yuan, J., Wang, S., Qiang, B., Xu, C., 2006. Identification and characterization of selenoprotein K: an antioxidant in cardiomyocytes. FEBS Letts. 580, 5189–5197.
Lundqvist, M.L., Middleton, D.L., Radford, C., Warr, G.W., Magor, K.E., 2006. Immunoglobulins of the non-galliform birds: antibody expression and repertoire in the duck. Dev. Comp. Immunol. 30, 93–100.
Mahan, D.C., Kim, Y.Y., 1996. Effect of inorganic or organic selenium at two dietary levels on reproductive performance and tissue selenium concentrations in first-parity gilts and their progeny. J. Anim. Sci. 74, 2711–2718.
Mahan, D.C., Parret, N.A., 1996. Evaluating the efficacy of selenium-enriched yeast and sodium selenite on tissue selenium retention and serum glutathione peroxidase activity in grower and finisher swine. J. Anim. Sci. 74, 2967–2974.
Mahmoud, K.Z., Edens, F.W., 2003. Influence of selenium sources on age-related and mild heat stress-related changes of blood and liver glutathione redox cycle in broiler chickens (*Gallus domesticus*). Comp. Biochem. Physiol. B 136, 921–934.
Maiorino, M., Scapin, M., Ursini, F., Biasolo, M., Bosello, V., Flohe, L., 2003. Distinct promoters determine alternative transcription of gpx-4 into phospholipid-hydroperoxide glutathione peroxidase variants. J. Biol. Chem. 278, 34286–34290.
Maquat, L.E., 2001. Evidence that selenium deficiency results in the cytoplasmic decay of GPx1 mRNA dependent on pre-mRNA splicing proteins bound to the mRNA exon–exon junction. Biofactors 14, 37–42.
Martin III, G.W., Berry, M.J., 2001. Selenocysteine codons decrease polysome association on endogenous selenoprotein mRNAs. Genes Cells 6, 121–129.
Maruyama, T., Sachi, Y., Furuke, K., Kitaoka, Y., Kanzaki, H., Yoshimura, Y., Yodoi, J., 1999. Induction of thioredoxin, a redox-active protein, by ovarian steroid hormones during growth and differentiation of endometrial stromal cells in vitro. Endocrinology 140, 365–372.
Merlot, E., Couret, D., Otten, W., 2008. Prenatal stress, fetal imprinting and immunity. Brain Behav. Immun. 22, 42–51.
Mikkelsen, R.L., Page, A.L., Bingham, F.T., 1989. Factors affecting selenium accumulation by agricultural crops. In: Jacobs, L.W. (Ed.), Selenium in Agriculture and the Environment. SSSA Special Publication, vol. 23. ASA and SSSA, Madison, WI, USA, pp. 65–94.
Milner, J.A., Sherman, L., Picciano, M.F., 1987. Distribution of selenium in human milk. Am. J. Clin. Nutr. 45, 617–624.
Mitchell, J.H., Nicol, F., Beckett, G.J., Arthur, J.R., 1998. Selenoprotein expression and brain development in preweanling selenium- and iodine-deficient rats. J. Mol. Endocrinol. 20, 203–210.
Moghadaszadeh, B., Beggs, A.H., 2006. Selenoproteins and their impact on human health through diverse physiological pathways. Physiology 21, 307–315.
Moreno-Reyes, R., Egrise, D., Boelaert, M., Goldman, S., Meuris, S., 2006. Iodine deficiency mitigates growth retardation and osteopenia in selenium-deficient rats. J. Nutr. 136, 595–600.
Moriarty, P.M., Reddy, C.C., Maquat, L.E., 1998. Selenium deficiency reduces the abundance of mRNA for Se-dependent glutathione peroxidase 1 by a UGA-dependent mechanism likely to be nonsense codon-mediated decay of cytoplasmic mRNA. Mol. Cell. Biol. 18, 2932–2939.
Morrison, D.G., Medina, D., 1989. Time course of selenite metabolism in confluent cultures of mouse mammary epithelial cells. Chem. Biol. Interact. 71, 177–186.
Morrison, D.G., Berdan, R.C., Pauly, D.F., Turner, D.S., Oborn, C.J., Medina, D., 1988. Selenium distribution in mammary epithelial cells reveals its possible mechanism of inhibition of cell growth. Anticancer Res. 8, 51–64.

Motohashi, H., Yamamoto, M., 2004. Nrf2-Keap1 defines a physiologically important stress response mechanism. Trends Mol Med. 10, 549–557.
Nevins, T.A., Harder, Z.M., Korneluk, R.G., Holcik, M., 2003. Distinct regulation of internal ribosome entry site-mediated translation following cellular stress is mediated by apoptotic fragments of eIF4G translation initiation factor family members eIF4GI and p97/DAP5/NAT1. J. Biol. Chem. 278, 3572–3579.
Nordberg, J., Arnér, E.S.J., 2001. Reactive oxygen species, antioxidants, and the mammalian thioredoxin system. Free Radic. Biol. Med. 31, 1287–1312.
Novoselov, S.V., Calvisi, D., Labunskyy, V.M., Factor, V., Carlson, B.A., Fomenko, D.E., Moustafa, M.E., Hatfield, D.L., Gladyshev, V.N., 2005. Selenoprotein deficiency and high levels of selenium compounds can effectively inhibit hepatocarcinogenesis in transgenic mice. Oncogene 24, 8003–8011.
Ortman, K., Pehrson, B., 1999. Effect of selenate as a feed supplement to dairy cows in comparison to selenite and selenium yeast. J. Anim. Sci. 77, 3365–3370.
Panee, J., Stoytcheva, Z.R., Liu, W., Berry, M.J., 2007. Selenoprotein H is a redox-sensing high mobility group family DNA-binding protein that up-regulates genes involved in glutathione synthesis and phase II detoxification. J. Biol. Chem. 282, 23759–23765.
Papp, L.V., Lu, J., Striebel, F., Kennedy, D., Holmgren, A., Khanna, K.K., 2006. The redox state of SECIS binding protein 2 controls its localization and selenocysteine incorporation function. Mol. Cell. Biol. 26, 4895–4910.
Papp, L.V., Lu, J., Holmgren, A., Khanna, K.K., 2007. From selenium to selenoproteins: synthesis, identity, and their role in human health. Antioxid. Redox Signal. 9, 775–806.
Pappa, E.C., Pappas, A.C., Surai, P.F., 2006. Selenium content in selected foods from the Greek market and estimation of the daily intake. Sci. Total Environ. 372, 100–108.
Pappas, A.C., Acamovic, T., Sparks, N.H.C., Surai, P.F., McDevitt, R.M., 2005a. Effects of supplementing broiler breeder diets with organic selenium and polyunsaturated fatty acids on egg quality during storage. Poult. Sci. 84, 865–874.
Pappas, A.C., Karadas, F., Surai, P.F., Speake, B.K., 2005b. The selenium intake of the female chicken influences the selenium status of her progeny. Comp. Biochem. Physiol. B 142, 465–474.
Pappas, A.C., Acamovic, T., Sparks, N.H.C., Surai, P.F., McDevitt, R.M., 2006a. Effects of supplementing broiler breeder diets with organoselenium compounds and polyunsaturated fatty acids on hatchability. Poult. Sci. 85, 1584–1593.
Pappas, A.C., Acamovic, T., Surai, P.F., McDevitt, R.M., 2006b. Maternal organo-selenium compounds and polyunsaturated fatty acids affect progeny performance and levels of selenium and docosahexaenoic acid in the chick tissues. Poult. Sci. 85, 1610–1620.
Park, Y.C., Whanger, P.D., 1995. Toxicity, metabolism and absorption of selenite by isolated rat hepatocytes. Toxicology 100, 151–162.
Payne, R.L., Southern, L.L., 2005. Changes in glutathione peroxidase and tissue selenium concentrations of broilers after consuming a diet adequate in selenium. Poult. Sci. 84, 1268–1276.
Pesti, G.M., Combs, G.F., 1976. Studies on the enteric absorption of selenium in the chick using localized coccidial infections. Poult. Sci. 55, 2265–2274.
Petit, N., Lescure, A., Rederstorff, M., Krol, A., Moghadaszadeh, B., Wewer, U.M., Guicheney, P., 2003. Selenoprotein N: an endoplasmic reticulum glycoprotein with an early developmental expression pattern. Hum. Mol. Genet. 12, 1045–1053.
Przybylska, J., Albera, E., Kankofer, M., 2007. Antioxidants in bovine colostrum. Reprod. Domest. Anim. 42, 402–409.
Rao, L., Puschner, B., Prolla, T.A., 2001. Gene expression profiling of low selenium status in the mouse intestine: transcriptional activation of genes linked to DNA damage, cell cycle control and oxidative stress. J. Nutr. 131, 3175–3181.
Rayman, M.P., 2000. The importance of selenium to human health. Lancet 356, 233–241.
Rayman, M.P., 2004. The use of high-selenium yeast to raise selenium status: how does it measure up? Br. J. Nutr. 92, 557–573.
Rayman, M.P., 2005. Selenium in cancer prevention: a review of the evidence and mechanism of action. Proc. Nutr. Soc. 64, 527–542.
Rebel, J.M.J., Van Hemert, S., Hoekman, A.J.W., Balk, F.R.M., Stockhofe-Zurwieden, N., Bakke, D., Smits, M.A., 2006. Maternal diet influences gene expression in intestine of offspring in chicken (*Gallus gallus*). Comp. Biochem Physiol. A 145, 502–508.
Reed, J.J., Ward, M.A., Vonnahme, K.A., Neville, T.L., Julius, S.L., Borowicz, P.P., Taylor, J.B., Redmer, D.A., Grazul-Bilska, A.T., Reynolds, L.P., Caton, J.S., 2007. Effects of selenium supply and dietary restriction on maternal and fetal body weight, visceral organ mass and cellularity estimates, and jejunal vascularity in pregnant ewe lambs. J. Anim. Sci. 85, 2721–2733.
Reeves, W.C., Marcuard, S.P., Willis, S.E., Movahed, A., 1989. Reversible cardiomyopathy due to selenium deficiency. J. Parenter. Enteral. Nutr. 13, 663–665.
Rundlof, A.K., Arner, E.S., 2004. Regulation of the mammalian selenoprotein thioredoxin reductase 1 in relation to cellular phenotype, growth, and signaling events. Antioxid. Redox Signal. 6, 41–52.
Sahlin, L., Wang, H., Masironi, B., Holmgren, A., Eriksson, H., 1999. Regulation of thioredoxin mRNA in the rat uterus by gonadal steroid. J. Steroid Biochem. Mol. Biol. 68, 203–209.
Scheaffer, A.N., Caton, J.S., Redmer, D.A., Reynolds, L.P., 2004. The effect dietary restriction, pregnancy, and fetal types on fetal weight, maternal body weight, and visceral organ mass in ewes. J. Anim. Sci. 82, 1826–1838.
Schomburg, L., Schweizer, U., Köhrle, J., 2004. Selenium and selenoproteins in mammals: extraordinary, essential, enigmatic. Cell. Mol. Life Sci. 61, 1988–1995.
Schrauzer, G.N., 2000. Selenomethionine: a review of its nutritional significance, metabolism and toxicity. J. Nutr. 130, 1653–1656.
Shen, Q., Leonard, J.L., Newburger, P.E., 1995. Structure and function of the selenium translation element in the 3′-untranslated region of human cellular glutathione peroxidase mRNA. RNA 1, 519–525.
Shennan, D., 1988. Selenium (selenate) transport by human brush border membrane vesicles. Br. J. Nutr. 59, 13–19.
Sievers, E., Arpe, T., Schleyerbach, U., Garbe-Schöberg, D., Schaub, J., 2001. Plasma selenium in preterm and term infants during the first 12 months of life. J. Trace Elem. Med. Biol. 14, 218–222.
Soriano-García, J.F., Torras-Llort, M., Ferrer, R., Moretó, M., 1998. Multiple pathways for L-methionine transport in brush-border membrane vesicles from chicken jejunum. J. Physiol. 509, 527–539.
Soriano-García, J.F., Torras-Llort, M., Moretó, M., Ferrer, R., 1999. Regulation of L-methionine and L-lysine uptake in chicken jejunal brush-border membrane by dietary methionine. Am. J. Physiol. 277, R1654–R1661.
Surai, P.F., 2006. Selenium in Nutrition and Health. Nottingham University Press, Nottingham, UK.
Surai, P.F., Speake, B.K., Noble, R.C., Sparks, N.H.C., 1999. Tissue-specific antioxidant profiles and susceptibility to lipid peroxidation of the newly hatched chick. Biol. Trace Elem. Res. 68, 63–78.
Thompson, K.M., Haibach, H., Sunde, R.A., 1995. Growth and plasma triiodothyronine concentrations are modified by selenium deficiency and repletion in second-generation selenium-deficient rats. J. Nutr. 125, 864–873.
Thomson, C.D., Robinson, M.F., Butler, J.A., Whanger, P.D., 1993. Longterm supplementation with selenate and selenomethionine: selenium and glutathione peroxidase (EC 1.11.1.9) in blood components of New Zealand women. Br. J. Nutr. 69, 577–588.
Thomson, C.D., Packer, M.A., Butler, J.A., Duffield, A.J., O, 'Donaghue, K.L., Whanger, P.D., 2001. Urinary selenium and iodine during pregnancy and lactation. J. Trace Elem. Med. Biol. 14, 210–217.
Thorlacius-Ussing, O., Flyvbjerg, A., Esmann, J., 1987. Evidence that selenium induces growth retardation through reduced growth hormone and somatomedin C production. Endocrinology 120, 659–663.
Thorlacius-Ussing, O., Flyvberg, A., Jorgensen, K.D., Orskov, H., 1988a. Growth hormone restores normal growth in selenium-treated rats without increase in circulating somatomedin C. Acta Endocrinol. 117, 65–72.
Thorlacius-Ussing, O., Flyvbjerg, A., Orskov, H., 1988b. Growth in young rats after termination of sodium selenite exposure: studies of growth hormone and somatomedin C. Toxicology 48, 167–176.
Tilly, J.L., Tilly, K.I., 1995. Inhibitors of oxidative stress mimic the ability of follicle-stimulating hormone to suppress apoptosis in cultured rat ovarian follicles. Endocrinology 136, 242–252.
Trafikowska, U., Sobkowiak, E., Butler, J.A., Whanger, P.D., Zachara, B.A., 1998. Organic and inorganic selenium supplementation to lactating mothers increase the blood and milk Se concentrations and Se intake by breast-fed infants. J. Trace Elem. Med. Biol. 12, 77–85.
Ursini, F., 2000. The world of glutathione peroxidases. J. Trace Elem. Med. Biol. 14, 116.
Utomo, A., Jiang, X., Furuta, S., Yun, J., Levin, D.S., Wang, Y.C.J., Desai, K.V., Green, J.E., Chen, P.L., Lee, W.H., 2004. Identification of a novel putative non-selenocysteine containing phospholipid hydroperoxide glutathione peroxidase (NPGPx) essential for alleviating oxidative stress generated from polyunsaturated fatty acids in breast cancer cells. J. Biol. Chem. 279, 43522–43529.
Vaishnav, R.A., Getchell, M.L., Huang, L., Hersh, M.A., Stromberg, A.J., Getchell, T.V., 2008. Cellular and molecular characterization of oxidative stress in olfactory epithelium of Harlequin mutant mouse. J. Neurosci. Res. 86, 165–182.
Valverde, C., Aceves, C., 1989. Circulating thyronine and peripheral monodeiodination in lactating rats. Endocrinology 124, 1340–4134.
Vanderpas, J.B., Contempre, B., Duale, N.L., Goossens, W., Bebe, N., Thorpe, R., Ntambue, K., Dumont, J., Thilly, C.H., Diplock, A.T., 1990. Iodine and selenium deficiency associated with cretinism in northern Zaire. Am. J. Clin. Nutr. 52, 1087–1093.
Vendeland, S.C., Deagen, J.T., Butler, J.A., Whanger, P.D., 1994. Uptake of selenite, selenomethionine and selenate by brush border membrane vesicles isolated from rat small intestine. Biometals 7, 305–312.
Vonnahme, K.A., Hess, B.W., Hansen, T.R., McCormick, R.J., Rule, D.C., Moss, G.E., Murdoch, W.J., Nijland, M.J., Skinner, D.C., Nathanielsz, P.W., Ford, S.P., 2003. Maternal undernutrition from early to mid gestation leads to growth retardation, cardiac ventricular hypertrophy and increased liver weight in the fetal sheep. Biol. Reprod. 69, 133–140.
Weiss Sachdev, S., Sunde, R.A., 2001. Selenium regulation of transcript abundance and translational efficiency of glutathione peroxidase-1 and -4 in rat liver. Biochem. J. 357, 851–858.
Wek, R.C., Jiang, H.Y., Anthony, T.G., 2006. Coping with stress: eIF2 kinases and translational control. Biochem. Soc. Trans. 34, 7–11.
Whanger, P.D., 2000. Selenoprotein W: a review. Cell. Mol. Life Sci. 57, 1846–1852.
Wilplinger, M., Sima, A., Pfannhauser, W., 1998. Selengehalt in der Nährung und dessen Zusammenhang zum Gehalt im Boden. Lebensmittelchemie 52, 93–95.
Wolffram, S., 1999. Absorption and metabolism of selenium: differences between inorganic and organic sources. In: Lyons, T.P., Jacques, K.A. (Eds.), Proceedings of Alltech's 15th Annual Symposium. Nottingham University Press, Nottingham, UK, pp. 547–566.
Wolffram, S., Arduser, F., Scharrer, E., 1985. In vivo intestinal absorption of selenate and selenite by rats. J. Nutr. 115, 454–459.
Würmli, R., Wolffram, S., Stingelin, Y., Scharrer, E., 1989. Stimulation of mucosal uptake of selenium from selenite by L-cystein in sheep small intestine. Biol. Trace Elem. Res. 20, 75–85.
Xia, L., Nordman, T., Olsson, J.M., Damdimopoulos, A., Björkhem-Bergman, L., Nalvarte, I., Eriksson, L.C., Arnér, E.S.J., Spyrou, G., Björnstedt, M., 2003. The mammalian cytosolic selenoenzyme thioredoxin reductase reduces ubiquinone: a novel mechanism for defense against oxidative stress. J. Biol. Chem. 278, 2141–2214.
Xia, Y., Hill, K.E., Byrne, D.W., Xu, J., Burk, R.F., 2005. Effectiveness of selenium supplements in a low-selenium area of China. Am. J. Clin. Nutr. 81, 829–834.

Yang, M., Sytkowski, A.J., 1998. Differential expression and androgen regulation of the human selenium-binding protein gene hSP56 in prostate cancer cells. Cancer Res. 58, 3150–3153.

Yin, F., Giuliano, A.E., Van Herle, A.J., 1999. Signal pathways involved in apigenin inhibition of growth and induction of apoptosis of human anaplastic thyroid cancer cells. Anticancer Res. 19, 4297–4303.

Zhang, Y., Fomenko, D.E., Gladyshev, V.N., 2005. The microbial selenoproteome of the Sargasso Sea. Genome Biol. 6, 37.

Zimmermann, M.B., Köhrle, J., 2002. The impact of iron and selenium deficiencies on iodine and thyroid metabolism: biochemistry and relevance to public health. Thyroid 12, 867–878.